Small bowel water content assessed by MRI in health and disease: a collation of single-centre studies

Running title: Small bowel water content by MRI

Neele Dellschaft[1,2], Caroline Hoad[1,2], Luca Marciani[1,2], Penny Gowland[1,2], Robin Spiller[2,3]

1 - Sir Peter Mansfield Imaging Centre, University of Nottingham, Nottingham, UK

2 - NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK

3 - Nottingham Digestive Diseases Centre, University of Nottingham, Nottingham, UK

Summary

Background: New developments in MRI have allowed the non-invasive, accurate measurement of the small bowel water content (SBWC).

Aims: To collate studies measuring small bowel water content following ingestion of a range of foods in both health and disease to provide data for adequately powering future studies in this area.

Methods: This collation brings together 29 studies including 954 participants (530 healthy, 54 diverticulosis, 255 IBS, 53 functional constipation, 12 cystic fibrosis, 15 Crohn's disease, 20 coeliac disease, 15

scleroderma) which have been carried out in a single centre using comparable study designs.

Results: Fasting SBWC (mean 82 (SD 65) ml) shows high variability with a small decline with advancing age (healthy volunteers only; individual patient data). Fasting values are increased in untreated coeliac disease (202 (290) ml, *P*=0.004). Postprandial SBWC shows less intra-individual variability than fasting values in healthy volunteers. SBWC is increased by eating, most markedly by high fat meals but also by fibre, both viscous and particulate. Indigestible residue accumulates in late postprandial period but empties soon after ingestion of a high calorie meal which produces a significant drop (by 50 (52) ml) in healthy volunteers. The associated fall in SBWC is abnormal in people with cystic fibrosis (SBWC reduced by 10 (121) ml, *P*=0.002) and in people with irritable bowel syndrome with diarrhoea (SBWC reduced by 17 (43) ml, *P*=0.007).

Conclusions: SBWC as assessed by MRI is a valuable biomarker indicating the balance of secretion and absorption in health and disease and the impact of treatments.

Key words: MRI, small bowel, water, fibre, secretion, absorption

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Introduction

Small bowel water content (SBWC) is a key parameter for understanding small intestinal function and its disorders, particularly the clinical problems associated with short bowel syndrome and various food intolerances. However, until the development of MRI, small bowel water could not be easily quantified. The factors influencing gastric emptying and pancreatico-biliary secretion and hence input into the small intestine have been extensively studied using a range of techniques including radio-isotopic imaging along with intubation and aspiration.[1–3] Furthermore, factors controlling intestinal absorption from short (25-50cm) perfused segments have been analysed using changes in non-absorbable marker concentration to calculate fluid movements.[4] However, no method had previously existed to quantify the fluid content of the entire, undisturbed, small intestine in intact humans.

Early work used a gradient echo EPI scan to measure the volume of water in the small bowel[5] but subsequently this was replaced with a strongly T2 weighted single shot fast spin echo (RARE) sequence (similar to that used to assessing the pancreatic and biliary ducts showing fluid-containing hollow organs as bright areas in images.[5,6]) This was found to accurately measure small bowel water content with a mean difference between measured MRI volumes and infused volumes of 2% with a standard deviation of 10%.[7] However, not all water present in the small bowel is necessarily observable using this MRI sequence, such as very small pockets of free water as well as water bound in a food matrix or in mucus.

As demonstrated below, we have found SBWC to be a useful, reproducible measure.

Prior studies suggest that small bowel water content will depend on both the underlying motility patterns, whether fasting or fed, the rate of delivery of material from the stomach, and the balance of absorption and secretions (salivary, gastric, pancreatic, biliary and intestinal) in response to luminal contents. It will also depend on the emptying of the terminal ileum SBWC, but this process has rarely been studied since the early barium studies of Ritchie who described increased ileal outflow after meals and named this the gastro-ileal reflex.[8]

Following our initial validation, we performed studies investigating how SBWC varies with fasting and following ingestion of a wide variety of test meals. Here we combine the original data from 29 studies in a meta-analysis to provide the best estimate of these parameters on which to power future studies. This meta-analysis has also allowed further original previously unpublished analyses, in particular examining the gastro-ileal reflex in both health and disease.

Methods

All methods have been previously described in publications of individual studies (see Supplementary Tables for an overview and meta-analyses. Individual data points for all the studies are deposited at https://rdmc.nottingham.ac.uk/handle/internal/9176. For versions of the graphs including error bars please contact the corresponding author). All

studies have in common that volunteers (healthy or patients) had observed an overnight fast. For all studies, participants were asked to refrain from eating foods that were particularly high in fibre or spices, as well as restrict physical exercise and excessive alcohol or coffee on the day before the scans. Depending on the study, participants may have had their normal diet (labelled 'not pre-treated' in Supplementary Table 1), or have already taken specific products for a number of days before the scans, e.g. fibre supplements (labelled 'pre-treated'). All studies were approved by appropriate Research Ethics Committees and all volunteers gave informed consent to participating in the studies. Participants then had an MRI scan including the T2-weighted sequence to determine small bowel water content. This was a single shot turbo spin echo, with 24 contiguous coronal slices with 7 mm thickness, imaged on either a 1.5T GE or 1,5T or 3.0T Philips MRI scanner.[7,9] Regions of interest were then drawn around the small bowel, excluding the gall bladder, bladder, colon and stomach as well as blood vessels. Voxels with an intensity above a threshold, which was determined from that person's cerebrospinal fluid intensity, as seen in cross-section on the abdominal scans, were identified as free small bowel water. The sum of these voxel volumes within the small bowel regions of interest provided an estimate of total SBWC. Segmentation and thresholding were carried out using in-house developed software on the IDL platform (Research Systems Inc., Boulder, CO, USA).

After the initial fasting scan, participants would typically have a breakfast meal, followed by scans at set intervals, and possibly a second meal, depending on each study's hypotheses. In case of cross-over studies, comparing meals or drug treatments etc, a wash-out period of an appropriate length has been observed, usually one week (see Supplementary Table 1).

Analysis of fasted SBWC

For this analysis we only included those studies for which participants with generally healthy digestion were not pre-treated, i.e. no special diet was given before the scan day (the 22 studies included following these criteria are indicated in Table 1 and Supplementary Table 1). If studies took repeated fasted scans of the same participants for cross-over studies, these measurements were averaged within participants before cohort analysis. We included a group of older participants with diverticulosis to provide a better representation of higher age groups. Since diverticulosis is found in approximately 40% of those over 65 years, we assumed that this group represented part of normal ageing. This population (healthy and with diverticulosis) was used to calculate the correlation of fasting SBWC with age (subdivided into age groups of <20, 20-40, 41-60, >60 years) and body surface area (BSA) calculated from the formula BSA=sqrt((weight/kg * height/cm)/3600),[10] on the basis that other organ volumes, such as liver, correlate closely to BSA.[11,12]

Effect of second meal and influence of disease

Some studies had a second, large, high-fat meal which was either 400 g macaroni cheese with 100 g cheesecake and 250 ml water (1000 kcal) or 600 ml of Fortisip (900 kcal). Both meals were given to stimulate the gastro-ileal response. Since timings of scans were different between studies we have used the slope of the SBWC versus time curve to assess the effect of the second meal. Participants included in this analysis were healthy volunteers (n=120), IBS with constipation (n=17), with diarrhoea (n=30) or with both (n=11), and functional constipation (n=15). IBS patients and functional constipation patients all met Rome criteria and those with IBS-D had bile acid diarrhoea excluded. A further 12 participants with cystic fibrosis and their sex and age matched controls were considered separately since they had added cream in their morning meal, causing SBWC before the second meal to be much higher than in the participants described above.

Statistics

For the fasted SBWC measurements, the effect of age and gender on individual patient data was determined with a linear regression analysis. A correlation of individual patient data with BSA was assessed separately with a non-parametric Spearman test as data was not normally distributed. Variability of fasted SBWC was assessed by calculating the coefficient of variation (standard deviation divided by mean of the repeated measurements) in those participants who attended repeatedly for cross-over studies.

For the meta-analysis, individual patient data was analysed for the studies indicated in Supplementary Table 2A by calculating mean and range of fasting SBWC and ages (analysis by health condition, Fig 1B and Fig S2). Overall statistical differences between health conditions were determined by ANCOVA (correcting for potential effects between studies by including the study identifier as a random factor in a hierarchical model)[13] and Tukey HSD post hoc tests used to compare to healthy volunteers. Analysis of same interventions across studies was carried out by calculating mean and standard deviation of fasting SBWC as well as of area under the curve of SBWC over time (Supplementary Table 2B).

When analysing the effect of fibre on the gastroileal response to the second large meal a Mann-Whitney test was used to see if absolute SBWC change (assessed on scans before and after the second meal) was affected by fibre. When analysing the effect of disease on the gastroileal response we assessed if slope of the SBWC change during the meal phase (assessed on scans before and after the second meal, as intervals between scans varied) was different to healthy volunteers, depending on the health condition of participants.

Results

Fasted SBWC

Fasting SBWC varied widely in healthy subjects with a mean (SD) of 81 (65) ml, n=436. As Fig 1A shows, fasting SBWC falls with age and is higher in men than women (linear regression of individual fasted SBWC

with age and gender, n=402 (age information missing for n=15, gender information missing for n=24), $P<0.0001$ with effect of age, $P<0.0001$, and of gender, $P=0.019$), with an average fasted SBWC of 90 (71) ml for men (n=200) and 73 (61) ml in women (n=202). Grouping fasting SBWC by age groups gives average values of 106 (82) ml for those aged under 20 (n=30), 85 (65) ml for those aged 20-40 (n=308), 53 (38) ml for those aged 41-60 (n=39) and 65 (73) ml for those aged over 60 years (n=44). Fasting SBWC was not related to body size, as assessed by correlating to body surface area (Supplementary material, Fig S1, $P=0.654$). The average coefficient of variation between repeated visits, was high at 45% (n=285 participants with two or more scans, across 20 studies).

Within the 29 studies considered we have assessed fasting SBWC for groups with different health conditions (Fig 1B and Supplementary Table 2, listing the studies used in each set; see Table 2 for demographics). Fasting SBWC was significantly lower in IBS-D (44 (35) ml, n=71, P=005), higher in untreated coeliac disease (202 (290) ml, n=20, $P<0.001$) compared to the healthy subjects, including diverticulosis.

SBWC was also higher in our patients with cystic fibrosis (179 (96) ml, n=12, $P=0.001$) but this difference is likely due to their younger age, as their SBWC was not different from age-matched controls ($P=0.7$; range 12-36 years). In contrast, participants with untreated coeliac disease tended to be older (mean 53, range 18-68 years, see Supplementary Fig

S2), which overall was associated with a reduced SBWC. Therefore, it seems likely that the higher SBWC in this patient group is a true effect of disease.

Comparison of postprandial SBWC after liquid meals including water, simple sugars and high fat meals

When small amounts (240 ml) of water devoid of nutrients is ingested there is a rise in SBWC of just 50 ml, peaking at 12 minutes and returning to a steady plateau, slightly elevated from the baseline, within 20 minutes as water is rapidly absorbed[14,15] (Fig 2A). In contrast, ingesting 300 ml of sunflower oil emulsions of different grades of stability led to a steady increase of SBWC above fasting baseline, peaking at around 3-4 hours. The increase was greater for the stable emulsion (fine emulsion with locust bean gum) at 491 ml than the unstable emulsion (coarse emulsion control) which was 329 ml, and remained high throughout the 5 hour study[16] (Fig 2B). Solutions of poorly absorbed low molecular weight substances which are osmotically active (fructose, mannitol, Moviprep), lead to rapid increases of 150-400 ml[9,17–20] (Fig 2C) with a return to baseline by 4 hours after ingestion. In contrast, glucose, a low molecular weight sugar which is rapidly absorbed, and inulin, a high molecular weight fructan which exerts little osmotic force, both show increases of less than 100 ml, rapidly returning to baseline[9,17,18] (Fig 2D).

SBWC response to a complex meal

When the meal is made more complex by adding solids, the varying rate of gastric emptying for different phases causes a biphasic pattern (Fig 3). The initial rapid fall in SBWC is likely to reflect the stimulatory effect of simple sugars on water absorption plus the emptying of the ileum in response to feeding. A meal primarily consisting of bread, both white and wholemeal, produces a striking fall in SBWC compared to roughly equicaloric rice pudding meals.

When supplementing the basic rice pudding meal with a glucose polymer, maxijul, we could still see the typical profile of SBWC with the sharp fall as the orange juice empties from the stomach, similar to the response to glucose ingestion, and the subsequent rise as solids empty. Supplementing it with cream showed an additional increase in SBWC between 90 minutes and 180 minutes after ingestion, similar to that seen when feeding oil emulsions (Fig 2B), likely due to stimulation of pancreatic and biliary secretions.[16] Compared to the plain rice pudding meal, supplementation with bran showed an increased late response from 3 hours, sustained to the end of the study 6 hours after ingestion.

Effect of water binding by various dietary fibres

Dietary fibres exert a laxative effect which starts in the small bowel with both stimulation of fluid secretion and "water trapping". Studies using ispaghula,[21,22] kiwifruit,[23] nopal[22] and bran[9,22] have all shown increases in SBWC compared to the rice pudding meal alone (Fig 4). Kiwifruit showed

the strongest effect compared to a maltodextrin control. Its storage polysaccharides are highly effective in trapping water and kiwifruit also contains proteases and raphides (minute calcium oxalate monohydrate crystals with a needle-like structure), either of which may stimulate small bowel secretions. Both psyllium, a viscous gel-forming fibre, and bran, a particulate one, showed similar effects on SBWC when given at doses providing similar fibre intake as did nopal, a fibre derived from prickly pear cactus, which contains both viscous and particulate fibre.[22]

Effect of second meal and influence of disease

Consumption of a second, large meal was typically associated with a fall in SBWC. The cross-over studies summarised in Fig 4 show an average drop of 72 (60) ml after the second meal in the control arm of each study with a similar drop of 94 (76) ml when their diet contained additional fibre (ispaghula, bran or kiwifruit; P=0.154). Comparing data between different patient cohorts revealed that some cohorts did not have this fall in SBWC in response to a meal (Fig 5). The fall of the SBWC value preceding the 1000 kcal meal was 50 (52) ml or 45%, expressed as a percentage (SD 50, CI 35-54%; n=120), for healthy volunteers. The gastro-ileal response appears to occur within the first 30 minutes as values obtained at intervals varying from 20 to 75 minutes after the second meal are of similar magnitude (see Supplementary Table 3).

This response to a large meal persists in people with constipation (functional constipation and IBS with constipation (IBS-C) combined drop

by 41 (41) ml, slope (ml/min) not different, *P*=0.34 compared to healthy volunteers) or mixed bowel pattern (IBS-M, reduced by 28 (49) ml, *P*=0.52), but is less obvious in people with IBS with diarrhoea (IBS-D, reduced by 17 (43) ml, *P*=0.007 for slope compared to healthy volunteers) see Fig 5. However, the most complete impairment of response was seen in people with cystic fibrosis compared to age matched healthy control.[24] These cohorts received the standard rice pudding meal but with 30 g cream added as the morning meal, leading to a much larger postprandial SWBC, no doubt due to additional stimulation of pancreatic and biliary secretions. The response to the 1000 kcal meal was much reduced in the people with cystic fibrosis (drop of 10 (121) ml) compared to the controls who showed a large effect with a drop of 153 (73) ml (*P*=0.002).

Discussion

In this meta-analysis we combined data on SBWC from 29 different studies with 436 individual data sets to allow more precise assessments of effect sizes. The data provides unique information about the variability between studies and subjects in the processing of complex meals, using a technique which could be available in every large hospital. We found fasting SBWC to be a highly variable parameter, possibly related to the cyclical pattern of gut motility[25] and increased secretions associated with the MMC[26] which regularly passes down the intestine at 1-2 hour interval.[27] The fasting SBWC would be expected to fluctuate with the

phase of the migrating motor complex (MMC) which scans cannot be easily synchronised to, a feature which may account for the high average coefficient of variation between repeated visits.

While fasting SBWC is therefore unlikely to be useful in detecting small changes, we have recently shown that patients with untreated coeliac disease have approximately twice the median SBWC of healthy subjects which can be easily detected and some patients with scleroderma also have elevated levels.[28] Both conditions can be complicated by small intestinal bacterial overgrowth due to delayed clearance of fasting contents by impaired motility[29,30] and the elevated fasting SBWC might be an indicator of this, something worth further study.

There have been very few comparable studies of SBWC by other research groups, which have used only single time points postprandially.[6,31] It is worth noting that absolute values of SBWC do depend on thresholding and precise MRI technique, and some authors have reported different normal ranges.[32] The large variability in the fasting SBWC means that this parameter would only be useful to detect differences between disease groups if the expected difference was large.

There is a significant fall in values with advancing age which is most likely due to the known fall in pancreatic secretions noted with advancing age.[33] Even extreme age does not appear to significantly alter fasting intestinal motility[34] so it seems unlikely that this contributes significantly. The

higher values in men compared to women is likely reflecting difference in body size.

The postprandial profile is less variable than fasting values and shows clear differences between rapidly absorbed sugars like glucose and poorly absorbed ones like fructose and mannitol (see Supplementary Fig S3). The test solutions have a very low sodium concentration leading to initial sodium net secretion down an osmotic and electrochemical gradient across the relatively permeable duodenal and jejunal epithelium.[35] The sodium secretion is rapidly reversed into net absorption by glucose-sodium co-transport which fructose lacks, being largely transported by passive diffusion.[36] This most likely accounts for the rapid rise in SBWC after fructose not seen with glucose. Similarly, other osmotically active, poorly absorbed, non-nutrients like mannitol also cause a rapid rise in SBWC followed by a rapid fall as the distension stimulates intestinal motility leading to rapid passage of fluid into the colon.[37]

The SBWC technique is quite reproducible (see Supplementary Fig S4) so its greatest value is in a cross-over design. Power calculations using the data (n=199) from the response to the standard rice pudding meal with bran (mean AUC (over the time period T-45 to T225 minutes postprandially) 15174 (11567) ml*min; see Supplementary Table 2) show that using just 25 subjects one can show changes of 46% with an 80% power and alpha set at 0.05. While this change may seem large, food and

drug effects reported here are often of this magnitude which is why we have been able to show significant effects using modest subject numbers.

Comparison of solutions of simple sugars with fatty emulsions shows the important role of the pancreatico-biliary secretions. High fat meals showed much larger rises in SBWC[16] (Fig 3B) most likely due to pancreatic and biliary secretions driven by cholecystokinin (CCK) released by the products of fat digestion acting on the enteroendocrine cells.[38]

The mixed liquid / solid meals show a more complex pattern as different components are selectively emptied. The well recognised sieving effect[39] means that liquids empty faster than solids. This causes an initial rapid fall in SBWC when the orange juice, high in glucose and sucrose, preferentially empties ahead of the solid rice pudding component of our standard test meal.[9] Interestingly, the initial fall was much greater with bread meals. While this might reflect the known extremely efficient hydrolysis of starch to glucose and its rapid absorption, the fact that the measured SBWC is less than that seen after simple glucose solutions suggests it may also be related to changes in water mobility due to interaction with starch leading to changes in MR signal. When we compared breads with different gluten content we noted no differences in SBWC[40] so gluten seems not to be critical to this effect.

One of the major findings is the impact of dietary fibre. Whereas previous technologies focused on their effect on the colon and transit, our SBWC measurement has made it clear that fibre exerts a major effect on

absorption of water from the small bowel and hence delivery of fluid to the ascending colon.[21–23] Both viscous and non-viscous fibre show this effect which presumably reflects rather different mechanisms. The particles of bran may exert shear forces, since similar size effects on transit are seen with inert plastic particles.[41] Shear is known to activate mechanosensitive ion channels, Piezo2, whose activation stimulates secretion of serotonin from enteroendocrine cells,[42] which in turn stimulates intestinal secretion of water. By contrast, viscous fibre like ispaghula and that found in kiwifruit trap water by forming a gel which limits water mobility and hence access to the absorptive enterocyte. As our studies show, this unabsorbed residue with its associated water typically rests in the terminal ileum during fasting, only to be propelled into the colon when stimulated by meal ingestion. The averaged data from all our studies on fibre indicate an increase of 75 ml in SBWC over control (viscous fibres 186 (106) ml; controls 111 (59) ml at T345 or T360, the last scan before the second meal; P=0.01). While this increase is modest, this amount of liquid can be expected to significantly increase distension of the ascending colon whose resting volume averages 203 ml.[43]

The rapid fall in SBWC after feeding a large second meal is novel but in keeping with previous observations made using a range of techniques including barium,[8] intestinal perfusion,[44] manometry[45] and scintigraphy.[46] The manometric studies have reported a rapid cessation of fasting patterns after eating, with increased ileal motility lasting at least 2 hours,

some of the patterns being propulsive.[45] The scintigraphic studies showed that the rate of emptying of the terminal ileum is increased following a meal and enhanced by guar gum.[46,47] This presumably reflects increased flow secondary to water trapping by guar. A subsequent scintigraphic study showed that within 15 minutes after a second meal, around 20% of meal residue taken 3h 45 minutes previously had entered the colon, showing that the emptying of the terminal ileum is rapid, and faster still in IBS-D.[48] This is supported by recent MRI studies showing that ascending colon volumes increase by 25-50 ml immediately after a meal,[43] presumed to reflect the transfer of undigested meal residue from the previous meal from the terminal ileum to colon. Our meta-analysis of SBWC shows that this ileal response involved propulsion of around 50 (52) ml of fluid into the ascending colon.

We found that this gastro-ileal response was much impaired in cystic fibrosis (drop of 10 (121) ml). This is in keeping with the known increased viscosity of terminal ileal mucus and its luminal contents in CF[49] most likely due to impaired mucosal bicarbonate secretion.[50] Alternatively, since fat absorption is known to be disrupted in CF[51], this response may be affected by the ileal brake, which inhibits small bowel transit[52].

As before we can calculate that using just 25 subjects, with an alpha value of 0.05 and a power of 80% we can detect a change of 58% (36 ml) which suggests that the technique could detect the normalisation of ileal chyme movements by therapeutic interventions.

We also noted a reduction in the postprandial drop in SBWC in IBS with diarrhoea compared to controls. This is most likely due to the fact that both fasting and postprandial small bowel volumes are reduced in these patients so there is less fluid to transfer when the ileal motility increases immediately after feeding.

Strengths and limitations

In collating studies from a single centre we have a data set with uniquely homogeneous methodology, including study design, patient group definitions, meals and MRI scanners used. There is very limited data from other groups to compare our conclusions, as discussed above. We await studies reproducing the methodology described here as we are confident that SBWC will be a useful tool if it is used widely.

Conclusions: Future uses of MRI assessment of small bowel function

Our new techniques offer great potential for the rapid and economical screening of a range of novel therapeutic agents which act on small bowel function. These target secretion and absorptive mechanisms in the epithelial cells of the small bowel including stimulating membrane bound guanylate cyclase-C (GC-C) receptors(linaclotide, plecanatide),[53] ClC-2 chloride channels (lubiprostone) or inhibiting Na+/H+ exchangers (tenapanor[54]) and Na+/glucose co-transporters (e.g. mizagliflozin[55]). Given the large flows through the small bowel, assessing how these drugs alter small bowel secretion and hence net flow into the colon, will be key in understanding their mode of action and also in the development of

newer related agents, which will need early assessment before committing to expensive large-scale trials.

The value of assessing the postprandial fall in SBWC is well seen when using this parameter in cystic fibrosis patients. Here we were able to clearly show that ileal emptying was impaired, pointing to the role of increased viscosity in causing the syndrome of distal intestinal obstruction syndrome (DIOS). Future studies could use this parameter to judge the effectiveness of different combinations of CFTR modulators now being introduced into clinical practice.

Fluid fluxes through the small bowel are also critically important for managing patients with short bowel syndrome and those requiring enteral nutrition in which diarrhoea is a serious clinical problem. Designing feeds to minimise this requires detailed understanding of how various dietary items alter flow, which until now has been difficult to quantify. The techniques may also be relevant to studying other disease characterised by slow small bowel transit like coeliac disease, scleroderma and small bowel bacterial overgrowth. This new data is additionally of great importance in the modelling drug absorption and food digestion as it provides key inputs for such models.

Finally, it is highly significant that our techniques, which only require standard MRI capabilities found in most large hospitals, could be easily disseminated and being non-invasive and patient friendly could play a

part in a personalised medicine approach with novel therapies now emerging.

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DISCLAIMER

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STATEMENT OF INTEREST

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AUTHORSHIP STATEMENT

Guarantor of the article: Robin Spiller.

Author contributions: Neele Dellschaft created the draft manuscript. All authors contributed to conception of work and data interpretation and writing of manuscript.
All authors, final review prior to submission.

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Figure legends

Fig 1: Variability of SBWC. A) Effect of age and gender on fasting SWBC in healthy volunteers including those with diverticulosis: n=402, linear regression, $P<0.0001$ with both an effect of age, $P<0.0001$, and of gender, $P=0.019$. SBWC was averaged between repeat visits. Age information missing for n=15. B) Fasting SBWC for healthy volunteers (HV, n=382), people with diverticulosis (Div, n=54), irritable bowel syndrome with constipation (IBS-C, n=51), with diarrhoea (IBS-D, n=71), with both constipation and diarrhoea (IBS-M, n=29), functional constipation (FC, n=23), cystic fibrosis (CF, n=12), Crohn's disease (Crohn's, n=15), untreated coeliac disease (n=20) and scleroderma (n=15).

Fig 2: SBWC in ml after ingestion of varied liquid meals including water, simple sugars and fat emulsions by healthy volunteers using identical y-axis scales to facilitate comparison. A) 240 ml water.[14] B) 300 ml fat emulsions of 20% sunflower oil given as either a coarse emulsion, a coarse emulsion stabilised with locust bean gum (LBG) or a fine emulsion with LBG.[16] C) Low molecular weight, osmotically active substances, mainly sugars, evoking a strong SBWC response: mannitol, moviprep, fructose, and glucose and fructose combined. D) Sugars causing little change in SBWC: glucose and inulin. For C) and D), data was compared between studies: FODMAP,[18] FABS,[17] Marciani 2010,[9] Marciani 2014[19] and Murray.[20] All drinks were consumed within minutes before Time 0.

Fig 3: SBWC in response to complex meals. All rice pudding meals consisted of 220 g rice pudding with 34 g jam and 100 ml orange juice (331 kcal),[9] with additional 15 g bran (362 kcal),[9] 50 g glucose polymer maxijul (532 kcal),[56] or 22 g cream (436 kcal).[56] The white bread meal consisted of 150 g white bread with 24 g margarine, 34 g jam and 100 ml orange juice (659 kcal)[40] whilst the wholemeal bread meal consisted of 190 g wholemeal bread with 34 g jam and 100 ml orange juice (542 kcal).[57] Meals were ingested within 15 minutes before Time 0.

Fig 4: Changes in SBWC following ingestion of meal and viscous fibre products. All studies had a first meal, ingested within 15 minutes before Time 0 (grey arrow). Studies compared are containing 1) Two 150 g kiwifruits given twice a day (Wilkinson-Smith *et al;*[23] doses shown by a blue arrow given before the first meal at -40 minutes and then at 160 minutes; second meal at 380 minutes); 2) 7.5 g of particulate fibre (bran or nopal) given once with the first meal, shown by a green arrow (Gunn *et al*);[22] 3) 7.5 g of psyllium fibre given once with the first meal, shown by a pruple arrow (Gunn *et al*);[22] 4) 7 g or 3.5 g doses of psyllium compared to maltodextrin given three times a day shown by an orange arrow (Major *et al*;[21] doses with the first meal at -15, then at 150 and 305 minutes, second meal at 385 minutes). SBWC of control participants are averaged from the above studies, red line, receiving meals at -15 and at 380 or 385 minutes, with the grey field indicating the 95% confidence interval.

Fig 5: Drop in SBWC in reaction to a large afternoon meal, showing the results of two scans before and two scans after a 1000 kcal meal. Participants were scanned after a standard morning rice pudding meal. A) All HV studies, with a meta-analysis superimposed representing the average of all HV cohorts (thicker red line). B) The same HV meta-analysis with IBS and functional constipation groups. HV, total n=120, IBS-C, n=17, IBS-D, n=30, IBS-M, n=11, FC, n=15. Slope of drop (ml/min) in IBS-D group was significantly less than HV, *P*=0.007. Time differences between scans were 45 or 60 minutes. Studies used are Chaddock *et al*,[58] Wilkinson-Smith *et al*,[23] Marciani *et al*,[9] Lam *et al*,[59] Major *et al*.[21]

Tables

Table 1: Summary of studies used in alphabetical order of first author's name. All cross-over studies were randomised. Please see the Supplementary Table 1 for full information. HV, healthy volunteer (*, only the HV cohort was used for collation of fasted SBWC; IBS, irritable bowel syndrome with diarrhoea (-D), constipation (-C), or both (-M); CD, Crohn's disease; FC, functional constipation; SCD, scleroderma; CF, cystic fibrosis; v, versus, AUC, area under the curve.

First author and year of publication	**[Ref]**	**Population, n**	**Design**	**Intervention**	**Used for fasted SBWC**
Alyami 2019	[60]	23 HV	Cross-over	Porridge made of oats v pearl millet	Y
Chaddock 2014	[58]	21 HV	Observational	Meals	Y
Coletta 2015	[40]	12 HV	Cross-over	Bread meals with varying gluten	N
Garsed 2014	[61]	51 IBS-D	Cross-over	Ondansetron v placebo	N
Gunn 2020	[22]	13 HV	Cross-over	Nopal v psyllium v bran	N
Gunn 2021	[62]	9 IBS-C, 10 IBS-D	Cross-over	Inulin v psyllium v inulin+psyllium v dextrose	N
Hussein 2015	[16]	11 HV	Cross-over	Fat emulsions with differing droplet size and stability	Y
Khalaf 2020	[63]	20 HV, 15 CD	Case control	Meal	HV*
Lam 2016	[64]	23 FC, 20 IBS-C	Observational	Moviprep	N
Lam 2017	[59]	34 HV, 30 IBS-D, 16 IBS-C, 11 IBS-M	Observational	Meals	HV*
Lam 2019	[28]	20 Coeliac, 15 SCD	Observational	None	N
Major 2017	[17]	29 IBS, 29 HV	Cross-over	Glucose v fructose v inulin	HV*

Major 2018	[21]	16 HV, 15 FC, 1 IBS-C	Cross-over	Psyllium v maltodextrin	N
Marciani 2010a	[65]	16 HV	Cross-over	Ondansetron v placebo	Y
Marciani 2010b	9	11 HV	Cross-over	Mannitol v glucose	Y
		16 HV	Cross-over	Meal with bran v without bran	Y
		26 IBS-D	Case control	Meal with bran	N
Marciani 2012	[39]	18 HV	Cross-over	Meal whole v as soup	Y
Marciani 2013	[57]	12 HV	Cross-over	Bread v rice pudding	Y
Marciani 2014	[19]	12 HV, 12 HV	Observational	Moviprep	Y
Marciani 2015	[56]	13 HV	Cross-over	Meal with cream v carbohydrates	Y
Marciani 2019	[66]	8 HV	Cross-over	Sport drink with v without alginate and pectin	Y
Mudie 2014	[14]	12 HV	Observational	240 ml water	Y
Murray 2014	[18]	16 HV	Cross-over	Glucose v fructose v inulin v glucose+fructose	Y
Murray 2015	[67]	18 HV	Cross-over	Milk drink with varying aeration and foam stability	Y
Murray 2016	[20]	20 HV	Cross-over	Corticotropin-releasing factor v saline injection followed by fructose drink	Y
Murray 2019	[68]	54 Diverticulosis	Observational	None	Y
Ng 2020	[24]	12 HV, 12 CF	Case control	Meals	HV*
Pritchard 2015	[69]	18 HV	Cross-over	Corticotrophin-releasing hormone v saline	Y
		18 HV	Cross-over	Cold water v warm water stimulus	Y

Wilkinson-Smith 2018	[70]	15 HV	Cross-over	Lettuce v rhubarb v bread meals	Y
Wilkinson-Smith 2019	[23]	14 HV	Cross-over	Meals with kiwi v maltodextrin	N

Table 2: Numbers and demographics of participants from all 29 studies considered, stratified by health conditions. Age is given in years as mean (standard deviation).

Health group	**n**	**Age**	**Male : Female**
Healthy volunteers	530	25 (9) (n=15 no data)	257 : 239 (n=34 no data)
Diverticulosis	54	63 (10)	23 : 31
IBS-C	53	38 (14)	24 : 29
IBS-D	173	42 (14)	58 : 115
IBS-M	29	38 (16)	7 : 22
Functional constipation	53	42 (14)	25 : 28
Cystic fibrosis	12	20 (7)	7 : 5
Crohn's disease	15	37 (12)	8 : 7
Coeliac disease	20	46 (14)	8 : 12
Scleroderma	15	63 (13)	(n=15 no data)
Total	954	34 (16) (n=15 no data)	417 : 488 (n=49 no data)