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Original Article

Abnormalities of the distal terminal ileum in people with cystic fibrosis assessed using magnetic resonance imaging

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ABSTRACT

Background: The terminal ileum (TI) is commonly affected in people with cystic fibrosis (pwCF), but limited quantitative information is available on its appearance and dimensions. This study aimed to use magnetic resonance imaging (MRI) to: 1) measure the diameter of the distal TI in healthy volunteers (HVs) and pwCF; 2) test the hypothesis that the diameter of the TI in pwCF is larger than in HVs.

Methods: Twenty-six adult pwCF (23 on modulators) and 30 HVs participated. A commercial image analysis platform (Entrolytics, Motilent, UK) was used to measure the long and short axes diameters of the TI on cross-sectional images, along the most distal 5 cm before the ileo-caecal valve. The cross-sectional area of the TI was calculated assuming an elliptical shape.

Results: (mean±SD) pwCF had a larger TI compared with HVs: the long axis TI diameter (1.6 ± 0.3 cm for HVs versus 2.7 ± 0.7 cm for pwCF, $p < 0.0001$), the short axis TI diameter (1.2 ± 0.3 cm versus 2.2 ± 0.6 cm respectively, $p < 0.0001$) and the TI cross-sectional area ($1.6 \pm 0.7 cm^2$ versus $4.9 \pm 2.5 cm^2$ respectively, $p < 0.0001$). Sixty-five% of pwCF showed heterogeneous, faeces-like chyme presence in the TI.

Conclusions: This study showed that the TI is enlarged and filled with heterogeneous, faeces-like chyme in pwCF compared with HVs. These findings are in keeping with earlier surgical reports. Increased chyme viscosity and/or impaired motility may lead to accumulation of chyme in the TI in pwCF. New treatments correcting these abnormalities such as secretagogues could be evaluated using the new MRI-derived TI diameter and area endpoints.

Abbreviations: CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; CoV, Coefficient of Variation; CT, Computed tomography; DIOS, Distal intestinal obstruction syndrome; FEV1, Forced expiratory volume in 1 second; GI, Gastrointestinal; GRAMPUS-CF, Gut research advancing a mechanistic and Personalised understanding of symptoms in cystic fibrosis; HVs, Healthy volunteers; IBS-D, Irritable bowel syndrome with diarrohea; MRI, Magnetic resonance imaging; PERT, Pancreatic enzyme replacement therapy; pwCF, People with cystic fibrosis; TI, Terminal ileum.

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1. Introduction

The involvement of the gastrointestinal (GI) tract in cystic fibrosis (CF) has increasingly been recognised. This is reflected in the significant burden of GI symptoms experienced by people with CF (pwCF) which the James Lind Alliance Priority Setting has recently highlighted as one of the 'top ten' research priorities [1,2]. Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) [3] results in reduced chloride, bicarbonate and water secretion, which in turn disrupts mucus hydration, leading to increased viscosity of mucus [4,5] throughout the body, including in the GI tract. Pancreatic exocrine insufficiency, seen in the majority of pwCF, leads to maldigestion which is ameliorated but not fully prevented by pancreatic enzyme supplements, resulting in further abnormalities in small intestinal chyme [6]. Symptoms are also exacerbated by the presence of pancreatic insufficiency.

Distal intestinal obstruction syndrome (DIOS) in pwCF is associated with blockage of the distal terminal ileum (TI) by sticky mucus and faeces-like material [5,7]. Recent UK and US registry data report that DIOS occurs annually in approximately 1.5% of pwCF. It is more common in individuals with previous episodes of DIOS and it is related to several contributing factors, including impaired intestinal secretions, activation of the ileal brake due to malabsorbed fat [8] and possibly related to reduced bile acid induced secretion from the TI [9]. The more acidic luminal environment, characteristic of pwCF [10], leads to an increase in protein-bound carbohydrates, mineral concentrations and luminal albumin. These factors in turn accentuate chyme viscosity and can exacerbate the risk of physical obstruction in the TI. In participants with DIOS, computed tomography (CT) scans showed masses of inspissated material in the distal ileum [11] along with bowel dilation [12]. CF can also cause inflammation in the small intestine with mucosal ulceration, increased permeability and elevated faecal calprotectin albeit less severe than in Crohn's disease [13]. Both these pathologies can lead to an abnormal dilation of the TI. However, the amount of TI dilation in CF is yet to be quantified.

The TI is difficult to reach by endoscopy which requires non-physiological bowel preparation and cleansing. Magnetic Resonance Imaging (MRI), with its excellent soft tissue contrast and cross-sectional imaging capability can provide an ideal tool to investigate the anatomical features of the undisturbed terminal ileum. Bowel diameters have been previously measured by MRI in healthy participants using enterographic methods, involving ingestion of a large amount of oral osmotic laxative preparation to distend the bowel [14]. MRI was also used to demonstrate narrowing of the distal bowel lumen in participants with Crohn's disease [15] and a reduction in TI diameter in 58% of participants with irritable bowel syndrome with diarrhoea (IBS-D) [16]. MRI has also shown increased ileocolonic volumes in 13 pwCF compared to matched controls, with endoluminal imaging showing also pooling of intraluminal contents [17].

Based on the considerations above, we hypothesised that (1) MRI can assess abnormalities of morphology and content of the TI in pwCF, without using any unphysiological preparation of the bowel and (2) the diameter of the TI is larger in pwCF compared to controls.

2. Methods

2.1. Study population

Healthy volunteers (HVs) were prospectively recruited by advertisement from the University of Nottingham campus population as part of two consecutive studies approved by the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee. Eighteen participants were prospectively recruited under the MR LENGTH study (approval FMHS 204–0223) and twelve under the HEALTH CF study (approval FMHS 76–0123). Inclusion criteria for healthy volunteers were age between 18 and 65 years, body mass index (BMI) between 18.5 and 30.0 kg/m^2, absence of known medical conditions or previous gastrointestinal surgery, and ability to provide written informed consent. Standard MRI exclusion criteria applied. pwCF were prospectively recruited to this MRI study as a sub-group of the larger Gut Research Advancing a Mechanistic and Personalised Understanding of Symptoms in Cystic Fibrosis (GRAMPUS-CF) study, approved by the Health Research Authority Research Ethics Committee (approval 23-EE-0092). Eligibility criteria included a confirmed diagnosis of CF, age $\geq$16 years, and attendance at either the Nottingham or Leeds CF centres. Exclusion criteria were the presence of additional gastrointestinal conditions and MRI contraindications. Previous resection of any part of the gastro-intestinal tract apart from appendicectomy or cholecystectomy was also an exclusion criterion. Surgical relief of distal intestinal obstruction syndrome or neonatal ileus was permitted unless clinical records showed excision of intestine >20 cm in length. Recruitment was conducted face-to-face by clinical teams at the Nottingham and Leeds CF centres.

All participants provided written informed consent. The MR LENGTH study was conducted first, whilst the HEALTH CF and GRAMPUS-CF studies run in parallel.

2.2. MRI imaging

The participants attended the MRI centre in the morning, after an overnight fast. They were positioned supine in the MRI scanner. A range of multiplanar imaging was used to locate the terminal ileum. Coronal and axial dual-echo out-of-phase images were used to locate the TI as abdominal tissue borders were best identifiable from this type of contrast. After this, two high resolution T1-weighted coronal-oblique and axial-oblique scans were acquired respectively along and perpendicular to the most distal 5 cm of the terminal ileum, before it connects with the cecum at the ileocecal valve.

2.3. MRI image analysis

In this study the operators were not blind to the disease status of the participants.

2.3.1. Visual appearance of the TI

Firstly, a qualitative assessment of the appearance of the most distal part of the TI, where it joins the ileocaecal valve, was carried out. This was done first in the HVs to appraise the overall appearance of the TI in health. For each participant it was noted: a) if the TI shape was straight or curved; b) if it joined the ileocaecal valve with an upward (feet to head) angle, horizontally or downward (head to feet) angle in a coronal view (supplementary Figure S1); c) whether the TI appeared to have an enlarged diameter; (d) if the TI was filled with material that looked similar to the image appearance and texture of colonic chyme with heterogeneous intensity reflecting a mixture of solid, gas and fluid phases (as observed in [18] and termed here 'faecalised') and (e) if the TI walls appeared thickened (as for example as seen in Crohn's disease).

2.3.2. Terminal ileum diameter measurements

TI diameter measurements were carried out using the Entrolytics platform (Motilent, London, UK). For each participant, the most distal 5 cm segment of the TI, up to where it joins the ileocecal valve, was used for the TI diameter measurement. The axial-oblique or sagittal-oblique cross-sectional images acquired perpendicularly to the long axis of the TI were then used to carry out outer-to-outer wall diameter measurements (Fig. 1). The TI diameter measurements were performed on the Entrolytics platform, involving two clicks of the mouse at the desired edges of the TI's orthogonal long axis and short axis, respectively. These two parameters were selected as they are commonly used in clinical practice to characterise the functional properties of tubular structures within the body, including both gastrointestinal and vascular anatomy [19]. For example, two tubular structures may exhibit identical long-axis diameters while differing substantially in their short-axis

diameters, resulting in markedly different luminal calibres and functional capacity. Noting that the TI lumen is mostly elliptical, an approximate cross-sectional area of the TI lumen was also calculated as area $=\pi \times$ (long axis diameter/2) $\times$ (short axis diameter/2).

2.4. Intra-operator and inter-operator variability assessment

To assess intra-operator variability, the long axis diameter and the short axis diameter of the TI for the first 8 prospective HVs data sets and the first 8 prospective pwCF datasets were measured by the same operator on two separate occasions. To assess inter-operator variability, two different operators carried out one measurement of the long axis diameter and the short axis diameter of the TI for the same 16 datasets as above. Agreement and repeatability were assessed using correlation plots, coefficient of Variation (CoV) and visualised using Bland–Altman plots, with differences plotted against the mean of paired measurements.

2.5. Statistical analysis

PRISM 10.3 (GraphPad, San Diego, California) was used to analyse and plot the data. All measurements were recorded in centimetres and approximated to 0.1 cm resolution. Normality of the data was checked using the Shapiro-Wilk's test. Depending on normality, an unpaired parametric t-test or non-parametric Mann Whitney test was used. Two-tailed statistics were used and a p value threshold of 0.05 was chosen to indicate statistical significance of differences. *Post-hoc* correlations of the TI endpoints with patient characteristics were also explored. The data are reported as mean $\pm$ Standard Deviation. For correlation analysis, the linear regression R^2 and p value were also reported.

3. Results

A total of 56 participants were recruited to the study, comprising 30 HVs and 26 pwCF. Their summary demographics and clinical characteristics are listed in Table 1. The HVs had a mean age of 26 $\pm$ 7 years (range 18–41 years), with a mean body mass index (BMI) of 25 $\pm$ 4 kg/m^2; they were 60% female. The pwCF had a mean age of 36 $\pm$ 13 years (range 17 to 67 years), with a mean BMI of 26 $\pm$ 5 kg/m^2; they were 46% female. The MRI study was generally well tolerated by all the participants, with the exception of one pwCF who was withdrawn from the study due to claustrophobia.

3.1. Visual appearance of the terminal ileum

The results of the initial, visual qualitative assessment of the appearance of the most distal TI are reported in Table 2. The data show that the TI appeared enlarged in 73% of pwCF, with 65% of them showing "faecalised" chyme presence in the TI compared with none of the HVs.

The morphological shape (straight or curved) of the TI where it joins the ileocaecal valve was not markedly different between groups, but some differences in the angle of insertion were noted, whereby only 35% of pwCF had a downward angle of insertion compared with 53% of HVs. None of the pwCF or HVs showed thickened TI walls as seen in inflammation / fibrosis as commonly seen in Crohn's disease. As examples, Fig. 2A shows the TI of a patient that is somewhat larger than that from the HV shown in Fig. 1A, but does not have faecalised material

Table 1
Demographic and clinical characteristics of the healthy volunteers (HVs) and people with cystic fibrosis (pwCF) study participants.

		HVs	pwCF
Number of participants (N)		30	26
Age (y)		26±7	36±13
Sex	Male (N)	12	14
	Female (N)	18	12
Body Mass Index (kg/m^2)		25±4	26±5
Pulmonary dysfunction	Predicted % FEV1 <80% (N)	-	14
F508del genotype	Homozygote (N)	-	13
	Heterozygote (N)	-	10
	Other (N)	-	3
Pancreatic status	Sufficient (N)	-	4
	Insufficient (N)	-	22
PERT use	Yes (N)	-	20
	No (N)	-	6
DIOS history	Yes (N)	-	7
	No (N)	-	19
History of meconium ileus	Yes (N)	-	4[a]
	No (N)	-	21
	Not known (N)	-	1
Modulators therapy	Triple therapy (N)	-	22
	Dual therapy (N)	-	1
	None (N)	-	3

[a] One of the pwCF with history of meconium ileus had a surgical excision < 20 cm in length. DIOS, Distal Intestinal Obstruction Syndrome; FEV1, Forced Expiratory Volume in 1 s; PERT, Pancreatic Enzyme Replacement Therapy.

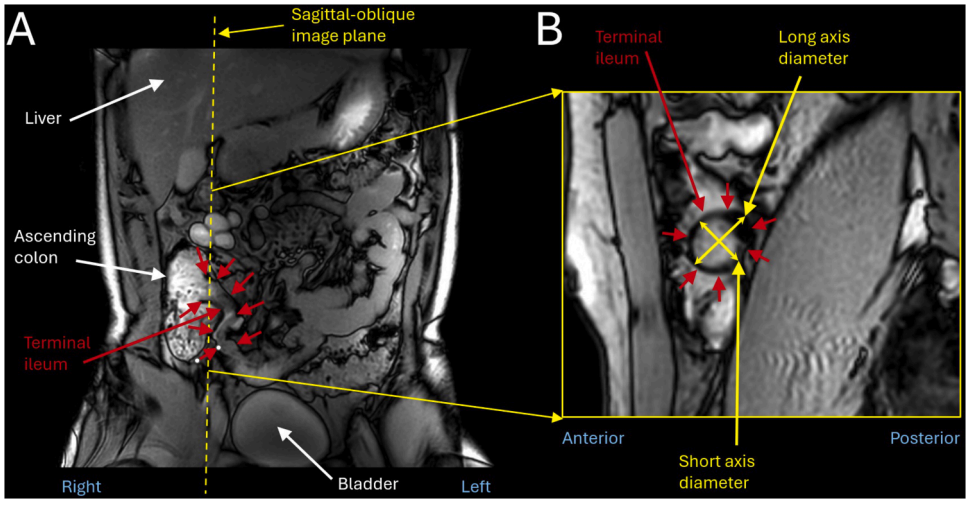

Fig. 1. Example of terminal ileum (TI) localisation and diameter measurement on MRI images from a healthy participant. (A) Coronal MRI image with the liver, bladder and ascending colon labelled for anatomical reference. The TI is indicated by red arrows. Right–left orientation is shown at the bottom of the image. The dashed yellow line indicates the axial-oblique image plane used for subsequent TI diameter measurements. (B) Axial-oblique MRI image at the level of the TI. The TI is indicated by red arrows, and measurements of the short-axis diameter and long-axis are illustrated by the yellow arrows.

Table 2
Visual appearance of the most distal part of the terminal ileum for N = 30 healthy volunteers (HVs) and N = 26 people with cystic fibrosis (pwCF).

		HVs	pwCF
Morphological shape	Straight (N)	12	11
	Curved (N)	18	15
Angle of insertion	Upward (N)	8	8
	Horizontal (N)	6	9
	Downward (N)	16	9
Enlarged diameter	Yes (N)	0	19
	No (N)	30	7
Faecalised contents	Yes (N)	0	17
	No (N)	30	9
Thickened walls	Yes (N)	0	0
	No (N)	30	26

inside it. Fig. 2B shows an MRI image from a different patient who has a markedly enlarged TI that is filled with faecalised material. The image in Fig. 2B is very similar to a cartoon drawn in a surgical paper from 1964, shown for comparison.

3.2. Terminal ileum diameters and area

The individual measurements of the long axis, short axis and area of the TI are shown in Fig. 3A, B and C respectively. The mean long axis diameter was 1.6 ± 0.3 cm in HVs (range 1.0–2.2 cm). By contrast, the mean long axis diameter was 67% larger in pwCF (2.7 ± 0.7 cm, range 1.2–4.2 cm), with the difference between the two groups being highly significant ($p < 0.0001$). Similarly, the mean short axis diameter of the TI was smaller in HVs (1.2 ± 0.3 cm, range 0.6–1.8 cm) compared with the mean of the pwCF group being 76% larger (2.2 ± 0.6 cm, range 1.1–3.8 cm), with the difference between the two groups being highly significant ($p < 0.0001$). The calculated cross-sectional area of the TI was 1.6 ± 0.7 cm^2 (range 0.6–2.8 cm^2) for the HVs group. This was threefold larger in pwCF with a mean of 4.9 ± 2.5 cm^2 (range 1.0–12.5 cm^2), and the difference between the two groups was highly significant ($p < 0.0001$). There was no correlation between TI endpoints and age and BMI (R^2=0.01–0.08, Supplementary Figure S2) for all participants or between TI endpoints and predicted FEV1% for pwCF (Figure S2). No differences between TI endpoints and sub-groups of pwCF male or female, F508del genetic profile, DIOS, pancreatic sufficiency, history of meconium ileus, or PERT use were found *post-hoc* (Supplementary Figure S3).

3.3. Intra- and inter-operator variability

Intra-operator and inter-operator data are shown in Supplementary Figure S1. Intra-operator variability was good with correlation R^2=0.96, $P < 0.0001$ and COV=6% (Figure S4 A). The Bland-Altman plot (Figure S4B) showed good agreement between repeated measurements consistently for the whole range of diameters measured. Inter-operator variability was slightly higher with correlation R^2=0.73, $P < 0.0001$ and COV=8% (Figure S4 C). The corresponding Bland-Altman plot (Figure S4 D) showed reasonably good agreement between operators for the whole range of diameters measured.

4. Discussion

This study found that adults with CF had a significantly larger TI diameter when compared with healthy controls. The quantitative TI diameter data are novel and were acquired using non-invasive MRI imaging in the undisturbed bowel, without using any contrast agent or bowel preparation. The finding of larger TI diameters is in keeping with the larger ileo-colonic volumes in 14 pwCF and matched controls reported by Malagelada et al. [17].

Our study also established a normative range for healthy adults' TI diameters which will allow comparisons in future studies. A previous study using magnetic resonance enterography (MRE) measured retrospectively the mean diameter of the TI without pathology and reported a mean TI diameter of 18.7 mm with a range of 11–26 mm [14]. Our normal values are slightly smaller than these; an explanation for this difference could be that the MRE examination involves administration of oral contrast medium to highlight the bowel, which is not physiological and may distend the TI walls artificially. Another previous MRI study measured the maximum diameter of the distal TI in HVs without using any luminal contrast media, reporting a median diameter for the largest measurement of TI diameter of 17 mm, with a range of 10–18 mm [16]. These values were recorded from coronal images only which would have introduced geometric measurement errors when the TI was oblique to the imaging plane but are nevertheless consistent with the values in HVs found in our study.

The MRI images of the TI showed variation in the shape and angle of insertion of the distal TI into the caecum, across both HVs and pwCF.

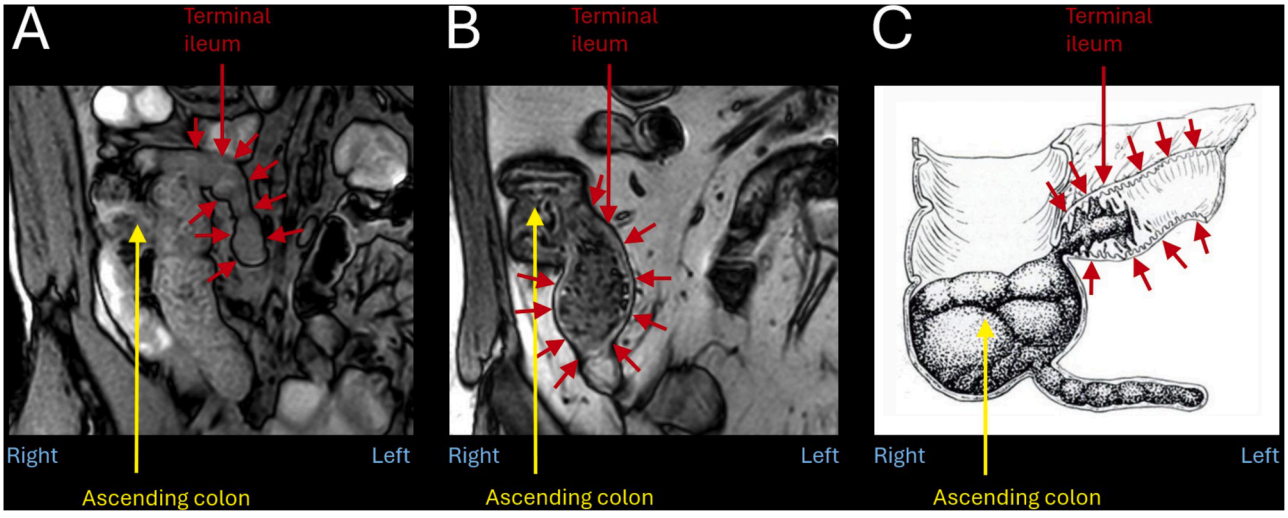

Fig. 2. Coronal MRI images of the terminal ileum (TI) of: (A) a person with cystic fibrosis whose TI is moderately dilated, has a horizontal angle of insertion to the ileocecal valve and does not show faecalised material inside the lumen. (B) a different person with cystic fibrosis showing a markedly dilated TI that is filled with faecalised material. (C) Artist's drawing of the caecum and distal TI resected from a person with cystic fibrosis, showing faecal material extending into the TI and appendix. Reproduced with permission from the 1964 paper [7]. In all three panels the ascending colon is indicated by a yellow arrow and the terminal ileum by red arrows.

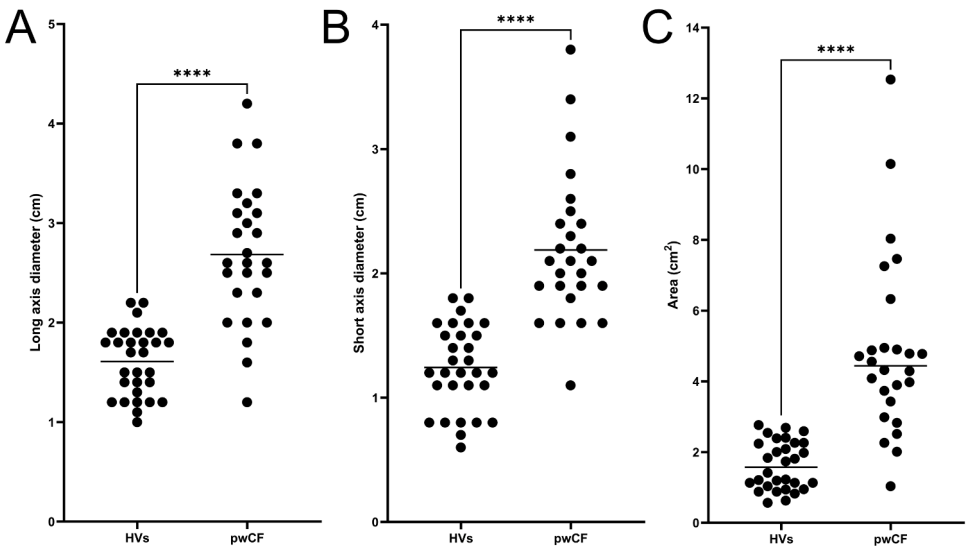

Fig. 3. (A) Long axis diameter, (B) short axis diameter and (C) area of the terminal ileum measured for n = 30 healthy volunteers (HVs) and n = 26 people with cystic fibrosis (pwCF). Each dot represents an individual participant, and the horizontal lines indicate the group means. **** indicates $p < 0.0001$.

One of the key findings here was the detection of the presence of faecalised chyme in the distal TI of 65% of pwCF, with no apparent wall thickening observed in the predefined distal TI segment on our non-contrast images, but subtle mural abnormalities or more proximal small bowel wall changes cannot be excluded. . Malagelada et al. reported thickening of the bowel wall in 10 out of 14 of the pwCF in their study [17], which we have not observed. In our study TI wall abnormalities could not be completely excluded without using administration of oral and intravenous contrast agents for a complete radiological assessment, and this could explain the difference in findings. Other potential contributing factors could be patient selection, and the fact that our cohort was contemporaneous and most of the pwCF studied here were on triple modulator therapy. Some of the MRI images carried a striking resemblance to the 1964 surgical illustration [7] of a resected segment of the caecum and distal TI of a patient, with faecal material extending from the caecum into the TI. Previous MRI studies had already noted the presence of luminal pooling [17] and colon-like textured chyme in the small bowel of pwCF [18] in agreement with the feacalised TI contents finding here.

The pathology behind TI dilatation is not fully understood and could be due to a number of mechanisms. Decreased bicarbonate secretion into the small bowel lumen [3] results in an increased acidic luminal environment which could in turn increase viscosity of mucus through raised protein-bound carbohydrates and mineral concentration [20,21]. The thickened mucus contributes to blockage of the TI [5], as seen in DIOS, resulting in dilation of the small bowel [7,12] from increased pressure and contents. As noted above, a lack of pancreatic enzymes can result in excess fat content reaching the TI [12]. The consequences of this are an exaggerated ileal brake, slowing oro-caecal transit time (OCTT) [12,22] and prolonged residence of chyme in the TI [8]. Indeed. luminal pooling of contents in pwCF had been reported in a previous study [17] and those findings are complementary with the results presented here. Another mechanism could be inflammation in the small bowel [23,24]. The build-up of faecal material in the TI could be a combination of the above factors, ultimately leading to the increase in diameter, though the exact mechanism is yet to be evaluated.

There was some overlap between some of the pwCF with the lower end of TI diameters and the HVs at the higher end of the control range, the significance of which is unclear. The number of pwCF studied does not allow meaningful post-hoc analyses of TI appearance and diameters and clinical characteristics subgroups, therefore this also remains an area to investigate in the future as well as any correlation with measures of GI function, GI symptoms and therapy. By contrast, early MRI work in irritable bowel syndrome with diarrhoea showed that people with IBS-D have significantly reduced diameter of the distal TI compared to HVs [16].

Historically, the distal small intestine has been clinically difficult to evaluate due to its anatomical features and location [25,26]. The distal small intestine is difficult to reach by endoscopy, which can only provide luminal views and cannot assess cross-sectional anatomy. These considerations led us to choose MRI for this investigation, due to its lack of ionising radiation, excellent soft tissue contrast and cross-sectional ability. From the imaging point of view, the TI was easily identifiable on most of the participants and its identification became easier with more practice and experience. In a few cases identification of the TI was harder, particularly when the ascending colon / caecum extended deeper in the pelvis, and also when scarcity of intra-abdominal fat made the distinction of small bowel adjacent loops more difficult. We were interested to qualitatively appraise the angle of insertion of the TI into the caecum as previous MRI studies showed differences in the angle of insertion of the oesophagus to the stomach with disease and linked that to function [27]. Here the proportion of pwCF with a downward angle on insertion was somehow lower than in HVs, but the subgroups were too small in numbers to make meaningful inferences on the possible relevance of this. More quantitative measurements of the angle of insertion can be carried out [27] as well as image texture analysis of the luminal contents [18]; carrying out these measurements was beyond the scope of this work focussing primarily on TI diameters, however they could be considered for future studies.

The additional MRI scans used in this study take only a few short breath-holds, the intra- and inter-operator agreement were good and the measurement itself takes only a few minutes, therefore the TI diameter endpoints could be easily added to MRI studies in pwCF and used as an objective measure within a multi-factorial patient evaluation.

Abnormalities of the terminal ileum can affect motility and TI motility assessment can clearly add value to an MRI exam in pwCF as shown in the previous Malagelada paper [17] using capsule endoscopy. TI motility can be quantified using cine MRI methods as has been shown for the small bowel in pwCF [18] and for the terminal ileum in Crohn's disease [28,29]. Those studies used MRI enterography, which involved ingestion of large volumes of oral contrast, hyperosmotic mannitol solution, which can add to patient burden and would distend the small bowel artificially. Cine MRI assessment of small bowel motility using a meal stimulus rather than of large volumes of oral contrast has been

shown [30], and could represent a more physiological and patient-acceptable way to assess TI motility in pwCF.

A strength of this work was that the TI was imaged in a physiological, undisturbed condition without the use of luminal (orally or rectally administered) contrast media. There were also limitations. The study was not formally powered to test the main hypothesis and the numbers did not allow meaningful sub-group analyses which could have generated interesting new research questions. The average age of the HVs was 10 years younger than that for pwCF, however no correlations between TI diameters and age was found. Another limitation is that the pwCF group comprised only adults and no children. The manual image analysis method took only a few minutes but could introduce some errors and in the near future this could be automated using artificial intelligence. Additionally, whilst not carried out sequentially, the data analysis was not blind to the disease status and this could have introduced bias in the results. In the future it will be important to blind the operator to the disease status.

5. Conclusions

In conclusion, this study demonstrated that pwCF had a significantly larger TI diameter when compared against healthy adult controls, with faecalised chyme identified in the majority of pwCF on undisturbed MRI. The findings advance understanding of the physiopathology of the TI in CF and provide a normative dataset for future comparative studies. MRI-derived TI diameter and cross-sectional area represent reproducible, non-invasive endpoints that could support evaluation of novel therapies and longitudinal disease monitoring in pwCF.

CRediT authorship contribution statement

Faiz Alqarni: Conceptualisation, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualisation. **Soma Kumasaka:** Conceptualisation, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Review & Editing. **Madeleine Taylor:** Validation, Formal Analysis, Investigation, Resources, Writing – Review & Editing. **Arantxa Recto:** Investigation, Resources. **Darren Sills:** Investigation, Resources, Writing – Review & Editing. **Hisham Saumtally:** Investigation, Resources, Writing – Review & Editing. **Charlotte Hamann:** Formal Analysis, Investigation, Resources, Writing – Review & Editing. **Grace Lim:** Methodology, Writing – Review & Editing. **Jan Paul:** Methodology, Investigation, Resources, Writing – Review & Editing. **Alexander Yule:** Conceptualisation, Methodology, Validation, Investigation, Writing – Original Draft, Writing – Review & Editing. **Caroline Hoad:** Methodology, Data Curation, Writing – Review & Editing. **Daniel Peckham:** Investigation, Resources, Writing – Review & Editing, Funding Acquisition. **Iain Stewart:** Investigation, Resources, Writing – Review & Editing, Funding Acquisition. **Tanya M. Monaghan:** Investigation, Resources, Writing – Review & Editing, Funding Acquisition. **Christopher van der Gast:** Investigation, Resources, Writing – Review & Editing, Funding Acquisition. **Katie Gathercole:** Investigation, Resources, Writing – Review & Editing, Funding Acquisition. **Penny Gowland:** Methodology, resources, Writing – Review & Editing. **Robin Spiller:** Supervision, Writing – Review & Editing, Funding Acquisition. **Alan Smyth:** Supervision, Resources, Writing – Review & Editing, Project Administration, Funding Acquisition. **Luca Marciani:** Conceptualisation, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualisation, Supervision, Project Administration, Funding Acquisition.

Data statement

Requests should be addressed to the chief investigator via the study email address (grampuscf@nottingham.ac.uk). Requests will be assessed on a case-by-case basis. Applications should state the research question being addressed and include a link to the researcher's published protocol. This will be reviewed by the research team and a final decision to share data will be the responsibility of the chief investigator. Data sharing is specifically mentioned in the participant information sheet and consent for this has been obtained. Applications will be considered from the time that our own data analysis is complete (expected to be 31/12/26), for a maximum of 7 years after study completion.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2026.07.009.

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