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Rīga Stradiņš University

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Magnetic Resonance Enterography in the Diagnosis of Crohn's Disease Using Diffusion-Weighted Imaging with Background Body Signal Suppression (DWIBS) Sequence

Summary of the Doctoral Thesis
for obtaining a doctoral degree (*Ph.D.*)

Sector – Clinical Medicine
Sub-Sector – Radiology

Riga, 2020

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The Doctoral Thesis was developed at the Diagnostic Radiology Department of the Children's Clinical University Hospital of Riga, Latvia

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Abbreviations used in the summary

ADC – apparent diffusion coefficient

ADC-DWI_{SPIR} – ADC based on DWI_{SPIR}

ADC-DWIBS – ADC based on DWIBS

CA – contrast agent

CD – Crohn's Disease

CI – Confidence Interval

DWI – diffusion-weighted imaging

DWI_{SPIR} – DWI with SPIR fat suppression technique

DWI-MaRIA – magnetic resonance index of activity based on DWI

DWIBS – diffusion-weighted imaging with background body signal suppression

ECCO – European Chron's and Colitis Organization

ESGAR – European Society of Gastrointestinal and Abdominal Radiologists

Gd – gadolinium

IBD – inflammatory bowel disease

i/v – intravenous

MaRIA – magnetic resonance index of activity

MRE – magnetic resonance enterography

MRI – magnetic resonance imaging

RCE – relative contrast enhancement

ROI – region of interest

SD – standard deviation

SD-*post*Gd – standard deviation in the T1 weighted images after gadolinium contrast administration

SD-*pre*Gd – standard deviation in the T1 weighted images before gadolinium contrast administration

SNR – signal-to-noise ratio

SPIR – spectral pre-saturation with inversion recovery

STIR – short T1 inversion recovery

WSI – wall signal intensity

WSI-*post*Gd – wall signal intensity after gadolinium contrast administration

WSI-*pre*Gd – wall signal intensity before gadolinium contrast administration

Introduction

Topicality, novelty and practical implications of the study

Crohn's disease (CD) is a chronic idiopathic inflammatory bowel disease which can affect any part of the digestive tract and is characterised by unpredictable periods of exacerbation and remission (Gajendran et al., 2018). Globally, the incidence of CD has increased markedly in both paediatric and adult patients over the past 50 years (Barnes and Kappelman, 2018; Molodecky et al., 2012). Although mortality from CD is relatively low, several manifestations of CD, such as chronic inflammation, fistulae, stricture, and abscess formation, impair patients' quality of life. As a result of CD progression, up to 80 % of cases require surgical resection of the inflamed intestinal zone, and in more than 10 % of cases a stoma is required (Cosnes et al., 2011). The progression of CD can be prevented only by an active therapeutic approach, based on both timely primary diagnosis of the pathology and dynamic follow-up. Today, there is still no common "gold standard" in diagnosis of inflammatory bowel disease (IBD), and CD is diagnosed through a combination of endoscopic, histological, radiological examinations and/or laboratory tests (Panes et al., 2013; Tontini et al., 2015).

In diagnosis of CD, the method of choice is ileocolonoscopy with morphological analysis of tissue specimens. However, its initial diagnosis and follow-up can be complicated, as this method allows limited visualisation of the small intestine and selective evaluation of mucosa. With the help of video capsule enteroscopy in the case of non-obstructive CD, the entire length of the small intestine can be assessed (Wang et al., 2013); however, this method does not allow for obtaining tissue samples for morphological analysis. Relying solely on endoscopic imaging techniques may lead to incomplete diagnosis of full-scale changes, especially due to strong regenerative capacity of the intestinal mucosa

(Okamoto, 2011; Shimizu et al., 2019); inflamed or fibrotically altered subcutaneous mucosa, and deeper localised tissues may be present (Gajendran et al., 2018; Magro et al., 2013; Martin et al., 2012; Sankey et al., 1993; Surawicz et al., 1994). Thus, endoscopic examination methods do not always provide an objective picture of the depth and extent of inflammation in CD. However, accurate assessment of changes is very important. In cases of newly diagnosed CD, it is crucial to start appropriate treatment in time, whereas in cases of pre-diagnosed disease, it is important to make objective judgements about the effectiveness of used treatment. For this reason, a method of visual diagnostics is needed, with the help of which both the relief of the intestinal wall and the transmural changes can be evaluated equally well.

Due to its high resolution and excellent soft tissue contrast, the magnetic resonance imaging (MRI) is the most optimal and promising method for assessment of intestinal wall pathologies, without exposing patients to potentially carcinogenic ionising radiation (Martin et al., 2012; Masselli and Gualdi, 2012; Smith et al., 2012). In 2019, cross-sectional imaging methods including magnetic resonance enterography (MRE), were recognised for the first time as an alternative to endoscopy, for assessment of CD activity in guidelines issued by the *ECCO (European Chron's and Colitis Organization*) and *ESGAR* (*European Society of Gastrointestinal and Abdominal Radiologists*) (Maaser et al., 2019). According to the *ECCO-ESGAR* guidelines on imaging methods for assessment of CD, in intestinal MRI, the T1 dynamic series with intravenous (i/v) gadolinium (Gd) containing contrast agent (CA) is mandatory (Panes et al., 2013), being the basis of the only validated magnetic resonance activity index MaRIA (Magnetic resonance index of activity). However, multiple administrations of Gd CA have been associated with the development of serious complications such as systemic nephrogenic fibrosis (Schlaudecker and Bernheisel, 2009), as well as the formation of Gd deposits in the basal ganglia

and soft tissues of the brain (Daram S. and B., 2005; Gibby W. and A., 2004; Gulani et al. 2017; Koreishi A., Nazarian R., Saenz A., Klepeis V., McDonald A., Farris A., Colvin R., Duncan L., Mandal R., 2009; Quattrocchi and van der Molen, 2017). Thus, it is important to design and develop solutions for clinical abdominal radiology, that would replace the administration of i/v Gd-containing CA during MRI scanning.

With the development of MR technologies, diffusion-weighted imaging (DWI) sequences have been an indispensable part of the MRE protocol over the last decade (Choi et al., 2016; Dohan et al., 2016). In the DWI sequences, the tissue contrast is based on differences in movements of water molecules in different tissues (Chilla et al., 2015). DWI images highlight normal hypercellular tissues and provide information on tissues with diffusion limitation, i.e., inflammatory changes, including abscesses, and benign and malignant formations (Luna, 2012). The DWI sequence is able to identify pathological changes before they appear in conventional MR images (Baliyan et al., 2016). Studies show that limited diffusion in the intestinal wall correlates with areas of active disease in histological preparations (Anupindi, Terreblanche, and Courtier, 2013). DWI is a useful sequence for both identification of inflammatory bowel segments and the evaluation of inflammatory activity and treatment efficacy (Stanescu-Siegmund et al,. 2017). The sensitivity of DWI sequences to differentiate inflammatory changes outperforms the T1 dynamic series with i/v administration of Gd CA (Neubauer et al., 2013; Oto et al., 2011; Sirin et al., 2015). Thus, it can be assumed that in CD diagnosis, the DWI sequence is more informative than the T1 post-contrast series, as it more realistically reflects the actual extent of the inflammatory process and has the potential to replace i/v administration of CA, not only in initial diagnosis of CD, but also when evaluating inflammatory activity in pre-diagnosed CD (Buisson et al., 2013; Hordonneau et al., 2014) using DWI-based MaRIA, called the Clermont score.

The diffusion restriction found in DWI images can be assessed both qualitatively and quantitatively, using the apparent diffusion coefficient (ADC), expressed in mm^2/s. ADC values for inflamed intestinal walls have been shown to be $0.8–2.4 \times 10^{-3}$ mm^2/s, lower than unchanged intestinal wall ADC values (Dohan et al., 2016). Although the addition of a DWI sequence to a range of traditional MRE protocols increases the overall sensitivity and specificity of the method (Kim et al., 2015), the specificity of the DWI sequence, when used alone, is low at 39–61 % (Choi et al., 2016; Qi et al., 2015). To date, there is no single MRE algorithm for patients with suspected IBD, including DWI sequences.

DWI image acquisition is complex and based on difficult physical processes that result in various image distortions (Drake-Pérez et al., 2018; Sánchez-González, Lafuente-Martinez 2012). To prevent them, DWI protocols incorporate one of the fat suppression techniques (Sánchez-González, Lafuente-Martinez 2012). They can suppress the resonant signal from fat both selectively and non-selectively. Spectrally selective fat suppression techniques suppress only the fat resonant frequency spectrum. The examples of fat selective, or spectral techniques, are CHESS (Chemical shift selective fat suppression), SPAIR (Spectral attenuated inversion recovery) and SPIR (Spectral pre-saturation with inversion recovery) (Del Grande et al., 2014; Indrati, 2017). A disadvantage of spectrally selective fat signal suppression techniques is the presence of artefacts caused by magnetic field heterogeneity (Del Grande et al., 2014; Moore et al., 2014).

One of the newest and most clinically relevant derivatives of the DWI sequence is DWIBS – diffusion-weighted imaging with background body signal suppression. It was developed in 2004 by a research team at the Tokai University School of Medicine, led by Taro Takahara, to examine oncology patients and obtain whole-body images to identify tumour recurrences and metastases (Takahara et al., 2004). It is currently widely used in diagnosis of inflammatory

changes, abscesses, and intravascular thrombi, as well as in visualisation of peripheral nerves (Kwee et al., 2009). The DWIBS sequence includes the non-selective fat suppression technique STIR (Short T1 inversion recovery). Unlike spectrally selective fat suppression based on suppression of the fat resonant frequency spectrum, STIR technique is based on the differences between the T1 relaxation times of fat and water protons, as scanning suppresses the signal from the fat tissue with short T1 time (Horger, 2007). The DWIBS sequence is intended for scanning with the patient breathing freely. To compensate for movements, it allows for the simultaneous excitation of multiple scan slices and the reading of signals over a long period of time (Takahara et al., 2004). DWI with the non-selective STIR fat suppression technique provides a sustained and homogeneous fat signal suppression in large areas of the body (Moore et al., 2014; Takahara et al., 2004), including sites located on the periphery of the body (Del Grande et al., 2014), providing higher contrast-to-noise ratio (Kwee et al., 2009). The non-selectivity of the STIR technique may be a disadvantage in cases where tissues contain other substances with a short T1 time, such as methaemoglobin, mucus-containing and viscous substrate, protein, and melanin (Del Grande et al., 2014). Another disadvantage of STIR fat signal suppression is the reduced signal-to-noise ratio (SNR) with partial loss of proton signal during inversion (Kwee, Takahara, Ochiai et al., 2008), which causes noise in the images. There is also literary data on the analysis of ADC values based on DWI with STIR fat signal suppression. The sequence of DWI with STIR has been shown to be superior to DWI with spectrally selective fat signal suppression in diagnosis of malignant and benign breast processes (Stadlbauer et al., 2009). It has also been reported that ADC values of the DWIBS sequence are not affected by motility (Stone et al., 2012), which could be an important factor in the study of peristaltic intestines.

Similarly to the conventional DWI with spectrally selective fat suppression (hereinafter - conventional DWI), the DWIBS sequences can very accurately differentiate the intestinal sections affected by CD, and, despite the noise in the images, DWIBS images can more accurately visualise small structures such as lymph nodes. The contours of the intestinal wall in the DWIBS sequence are sharper (Fig. 1.). Judging by the ability of the conventional DWI sequence to diagnose inflammatory processes in the intestinal wall with high sensitivity, and considering the advantages of the DWIBS sequence (increased contrast-to-noise ratio), it could be promising in the diagnostics of CD. However, there is no literary data on its use in patients with CD and comparison with conventional DWI sequences so far.

There are two directions currently in theory in which, by improving the visualisation capabilities of DWI, the diagnostic capabilities of CD would expand.

1. Primary diagnosis of CD. MRE examination still requires preparation of a patient with an oral CA, which limits the use of this method to patients requiring general anaesthesia. There is literary evidence that MRI without patient preparation in the diagnosis of intestinal wall inflammation cannot replace MRE, but the possibilities of DWI to perform MRI without patient preparation have not been fully explored so far, as the published data is based only on visual evaluation of DWI, without performing quantitative measurements.

2. Evaluation of CD activity. By replacing the post-contrast MR series required to assess CD activity using the Relative Contrast Enhancement (RCE) based CD activity index MaRIA (Dohan et al., 2016; Ordás et al., 2019), the use of the Clermont score, or DWI-MaRIA, is becoming relevant.

To date, there are no publications on selection of specific DWI sequences in MRI diagnostics of CD; however, given the benefits of DWIBS, this sequence may have a greater potential to characterise intestinal wall

inflammation in situations where accurate diagnosis of DWI is not possible, whilst also allowing a more accurate reflection of the activity surrounding the inflammatory process.

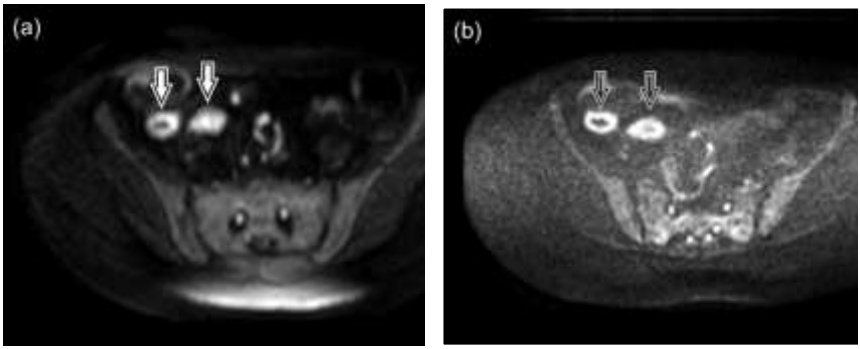

Figure 1**. Tracking images of a conventional DWI sequence with the spectrally selective DWI with SPIR fat suppression technique (a) and DWIBS (b) with a b value of 800 s/mm^2 in a 56-year-old patient with active CD in the distal *ileum* loop**

There is a high signal intensity in the wall of the inflamed intestinal segments, indicating a diffusion restriction within this localisation. Despite the reduced SNR, resulting in grainy images, compared to the conventional DWI sequence (white arrow), the image of the inflamed intestinal wall in the DWIBS sequence is clearer (black arrow). Images from the Author's archive.

Hypothesis of the study

The DWIBS sequence has advantages, and it is superior in the diagnosis of intestinal wall inflammation when compared to conventional DWI sequences with spectrally selective fat suppression.

Aim of the study

To establish whether the DWIBS sequence has advantages in the primary diagnosis of CD without prior preparation of the patient's intestinal tract, and in the evaluation of CD activity.

Tasks of the study

1. To evaluate potential advantages of the DWIBS sequence over conventional DWI for examining patients without prior peroral preparation with osmotically active enteric CA, by studying the ADC values of conventional DWI and DWIBS prior to and post preparation of the patient's intestinal tract in patients without evidence of CD.

2. To evaluate the suitability of the DWIBS sequence used in the Clermont index for the evaluation of CD activity in comparison with the conventional DWI sequence, by evaluation of mutual correlations between the Clermont scores obtained from conventional DWI and DWIBS with the MaRIA, between the ADC values of conventional DWI and DWIBS with the MaRIA, and between the ADC values of the conventional DWI sequence and the ADC values of the DWIBS sequence in patients with radiological features of active CD, localised in the terminal *ileum.*

3. To study the repeatability of ADC measurements of the conventional DWI and DWIBS sequences in patients with active CD in the terminal *ileum.*

Novelty of the research

This is the first research to focus on the DWIBS, in the diagnosis and the evaluation of CD activity. This is also the first research to quantify the effect of prior intestinal tract preparation on the ADC values of bowel walls in diffusion-weighted images.

1. Material and methods

During the development of the Doctoral Thesis, a prospective cross-sectional study was conducted, consisting of three parts:

1) investigation of the effect of preparation of the patient's intestinal tract with oral hyperosmolar CA on ADC values of the conventional DWI and the DWIBS sequences in intestinal and large bowel walls;

2) investigation of the ADC values of the conventional DWI and DWIBS sequences in patients with signs of active CD in MRI, and investigation of the use of these values for the calculation of the Clermont index;

3) evaluation of the repeatability of the component measurements for the MR indices of activity, MaRIA, based on the administration of Gd CA, and the Clermont index based on the ADC-DWI and ADC-DWIBS values.

The dissertation was carried out in the state tertiary care institution Children's Clinical University Hospital of Riga, Latvia, from March 2016 to April 2019. The dissertation summarises data on: 1) false-positive signal hyperintensity in a DWI series of the highest b value without other radiological features of IBD and without clinical or laboratory signs of IBD in patients with dyspeptic complaints; 2) patients with active CD in the terminal *ileum*. The patients included in the study were scanned with a 1.5 T MRI scanner Philips Ingenia (Philips Medical Systems, Best, The Netherlands) using a 16-channel body coil. All patients were fasted for at least six hours prior to the MRE examination and prepared with 1.25 to 1.5 L of 2.5 % mannitol solution orally, prior to scanning. Scanning was performed in the prone position. The MRE protocol included the conventional DWI sequence with the spectrally selective fat suppression technique SPIR (DWI_{SPIR}), and DWIBS sequence. To prevent movement artefacts in DWI_{SPIR} and DWIBS images, intestinal peristalsis was suppressed with butylscopolamine (Buscopan, Sanofi) by i/v administration with 20 ml of 0.9 % saline. In patients who required intravenous CA administration,

the butylscopolamine injection was also performed before the dynamic T1 post-contrast series. Image evaluation and ADC measurements were performed using the Philips Intellispace Portal 5.0 image post-processing server (Philips Medical Systems, Best, The Netherlands). Intestinal wall signal intensity measurements WSI (Wall signal intensity) in T1-weighted images following i/v CA administration and image noise measurements were performed using the Clear Canvas DICOM Viewer, v. 13.2 (Synaptive Medical, Toronto, Canada, 2019). All images were analysed and measured by one radiologist, with experience in abdominal MRI since 2000.

In patients with active CD *ileum* in the distal ileal loop, MaRIA in each inflamed altered segment was calculated according to the formula:

$$MaRIA = 1.5 \times \text{wall thickness (mm)} + 0.02 \times \text{RCE} + 5 \times \text{oedema} + 10 \times \text{ulcers},$$

where the presence or absence of ulcers and oedema was rated as 1 or 0, accordingly. RCE was calculated as per formula 2:

$$\text{RCE} = (\text{WSI-}post\text{Gd} - \text{WSI-}pre\text{Gd}) / (\text{WSI-}pre\text{Gd})) \times 100 \times (\text{SD-}pre\text{Gd} / \text{SD-}post\text{Gd}),$$

where *SD-pre*Gd (standard deviation in the pre-contrast T1-weighted images) and *SD-post*Gd (standard deviation in post-contrast T1-weighted images) correspond to six mean values of standard deviation (SD), for signal intensity measured outside the body in the pre-contrast and post-contrast T1-weighted images (Rimola et al., 2009).

The Clermont score, or DWI-MaRIA, for both DWI_{SPIR} and DWIBS sequences, was calculated per following formula (Buisson et al*.,* 2013; Hordonneau et al*.,* 2014):

$$DWI\text{-}MaRIA = 1.646 \times \text{wall thickness (mm)} - 1.321 \times ADC + 5.613 \times \text{oedema} + 8.306 \times \text{ulcers} + 5.039.$$

Since oedema was one of the inclusion criteria representing inflammation, it was present in all intestinal segments that met the study criteria; therefore, its rating was always equal to 1.

The study was performed in accordance with the Declaration of Helsinki and approved by the statement on compliance with bioethical norms 6/10.09.2015 issued at the meeting of the Ethics committee of Rīga Stradiņš University on September 10, 2015. All patients included in the study or their legal representatives (parents of children) signed a written informed consent form to participate in the study.

1.1. First study. Effect of previous preparation of the patient's intestinal tract with enteric hyperosmolar CA on the ADC-DWI_{SPIR} and ADC-DWIBS values of the intestinal and large bowel walls

The study is reported in the publication by Apine, I., Baduna, M., Pitura, R., Pokrotnieks, J., Krumina G. 2019. "The Influence of Bowel Preparation on ADC Measurements: Comparison between Conventional DWI and DWIBS Sequences", published in Medicina (Kaunas, Lithuania), 55(7): 394, pp.1–13.

1.1.1. Patient population

In this first prospective observational cross-sectional study, the patients underwent MRE examination from March 2015 till March 2018. The study participants were 106 primary care patients (18–76 years old) referred to MRE due to dyspeptic complaints but with no clinical, laboratory, morphological and radiological signs of IBD. The inclusion criteria were: absence of typical IBD symptoms – diarrhoea, bloody and/or mucous stool, severe and/or crampy abdominal pain and rectal involvement (Mazza M*,* Cilluffo MG*,* 2016; Tontini et al*.,* 2015) and absence of any radiological and laboratory evidence of IBD.

The exclusion criteria were: age < 18 years, faecal calprotectin (FC) level > 200 µg/g, acute bowel infection, proven or previously diagnosed IBD, endoscopically proven enteropathy (e.g., coeliac disease, collagenous colitis etc.), radiological signs of IBD, present bowel tumour, and systemic diseases such as cystic fibrosis.

1.1.2. Patient examination

In this study, the first MRI scanning was performed before the preparation of patient's intestines with hyperosmolar oral enteric CA, and the second scanning was performed after the preparation, with filled intestinal loops. ADC of DWI_{SPIR} (ADC-DWI_{SPIR}) and ADC of DWIBS (ADC-DWIBS) values were measured in the intestinal walls in the images acquired. The patients were divided into two cohorts: 1) patients in whom ADC-DWI_{SPIR} and ADC-DWIBS measurements were performed in intestinal walls before and after prior preparation of the patient's intestinal tract; 2) patients in whom ADC-DWI_{SPIR} and ADC-DWIBS measurements were performed in the colonic walls before and after prior preparation of the patient's intestinal tract. The ADC measurements of DWI_{SPIR} and DWIBS images were performed only in the intestinal segments where high SI was observed in the tracking images at b value of 800 s/mm^2 mimicking bowel inflammation. To compare ADC values before and after prior preparation of patients' intestinal tract, only patients with measurements both before and after preparation with oral enteric hyperosmolar CA were included in the subsequent data analysis. To compare ADC-DWI_{SPIR} and ADC-DWIBS values, only patients with ADC measurements performed in both DWI_{SPIR} and DWIBS sequences were included in the subsequent analysis. In both cohorts, the data was grouped and compared according to the prior intestinal preparation status of the patients (unprepared and prepared bowel loops).

For scanning patients, the applied DWI_{SPIR} and DWIBS protocols were obtained from the Philips standard abdominal MRI protocol and included in the protocol repository of the MRI system. To enable ADC-DWIBS measurements, the standard DWIBS protocol was amended by replacing a single b factor b = 1000 s/mm^2 by three b factors 0 s/mm^2, 600 s/mm^2 and 800 s/mm^2, consistent to b values in DWI_{SPIR} protocol.

1.1.3. MRI image analysis: first cohort

The first cohort was formed of patients in whom high SI intestinal walls in DWI_{SPIR} and DWIBS tracking image series at b = 800 s/mm^2, mimicking bowel inflammation, both before and after prior preparation of the hyperosmolar enteric CA, were identified in at least one intestinal site. Such high SI regions in at least one intestinal region were identified in all 106 patients. One collapsed jejunal segment with high SI in the tracking images of b = 800 s/mm^2 in DWI_{SPIR} and DWIBS image series acquired prior to bowel preparation, was identified for each patient. One filled jejunal segment in the tracking images of b = 800 s/mm^2 DWI_{SPIR} and DWIBS image series acquired after bowel preparation was identified for each patient. ADC values were measured in three sites per segment using 10–20 mm^2 oval region of interest (ROI), both before and after preparation (Fig. 1.1).

1.1.4. MRI image analysis: second cohort

The second cohort was formed of patients in whom high SI colonic walls in DWI_{SPIR} and DWIBS tracking image series at b = 800 s/mm^2, mimicking bowel inflammation, both before and after prior preparation of the hyperosmolar enteric CA, were identified in at least one colonic site. Such high SI regions in at

least one colonic region were identified in 78 of 106 patients. One *caecum* or *colon ascendens* segment with high SI in the tracking images of b = 800 s/mm^2 in DWI_{SPIR} and DWIBS image series and with colonic content (faeces) in the lumen prior to bowel preparation, was identified for each patient. One *caecum* or *colon ascendens* segment filled with mannitol substrate, with high SI in the tracking images of b = 800 s/mm^2 in DWI_{SPIR} and DWIBS image series after prior preparation of the patient's intestinal tract was identified for each patient. ADC values were measured in three sites per segment using 10–20 mm^2 oval ROI, both before and after preparation (Fig. 1.2).

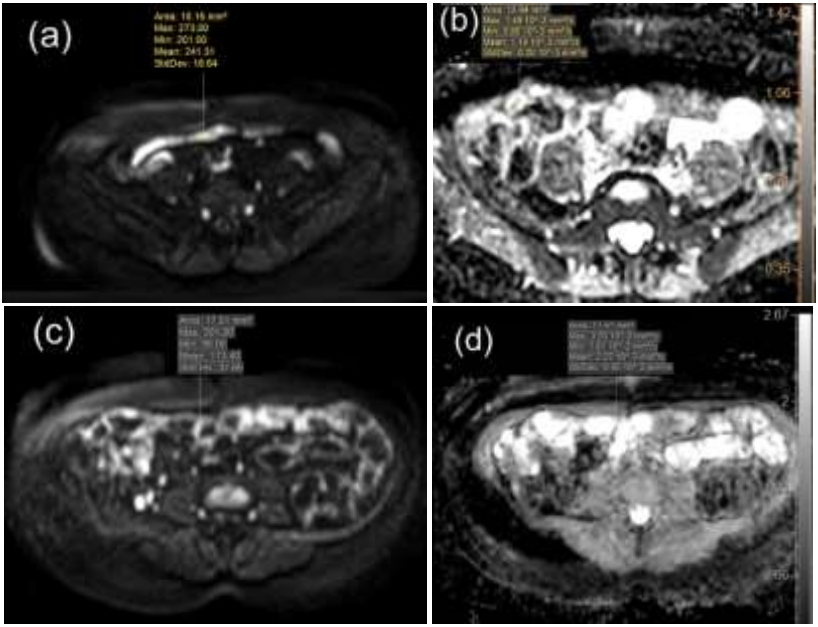

Figure 1.1. **Selecting ROIs for ADC measurements, in localisations of false-positive hyperintensity mimicking inflammation on DWI_{SPIR} tracking images of b = 800 s/mm^2 of collapsed (a) and distended (c) *jejunum***
ADC values appear on the ADC map, (b, for collapsed jejunum, d, for distended jejunum). MRE examination of a 53 y.o. female patient with dyspeptic complaints, with no morphologically proven CD. Images from the Author's archive.

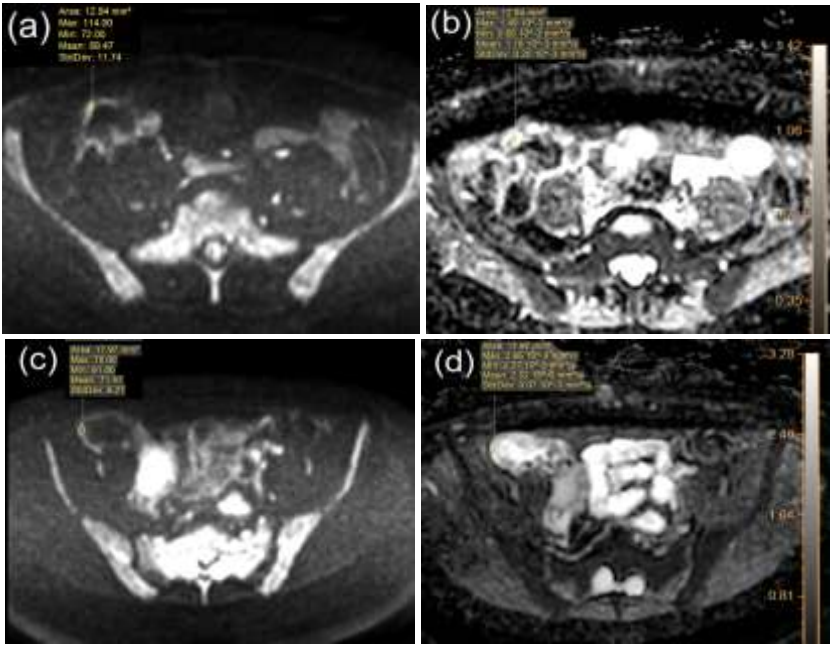

Figure 1.2. **Selecting ROIs for ADC measurements in localisations of false-positive hyperintensity, mimicking inflammation on DWIBS tracking images of b = 800 s/mm2 of the walls of the ascending colon: before preparation of patient with mannitol, at presence of intraluminal faeces (a) and after preparation, at presence of enteric contrast agent (b)**
ADC values appear on the ADC map (b, for non-prepared colon, d, for prepared colon). MRE examination of a 45-year-old male patient with dyspeptic complaints, with no morphologically proven CD. Images from the Author's archive.

1.1.5. Statistical analysis

Statistical analysis was performed using software Stata/IC (StataCorp LLC, Texas, USA). Mean ADC values were compared with a paired t-test. 99% confidence intervals (CI) were calculated for the differences. The statistical significance of differences between mean values within groups was determined

using one-way ANOVA with Bonferroni correction. P values of < 0.05 were considered to be statistically significant.

1.2. Second study. Investigation of ADC-DWI$_{SPIR}$ and ADC-DWIBS values in patients with MRI signs of active CD, and use of ADC-DWI$_{SPIR}$ and ADC-DWIBS values in the calculation of the Clermont index

The study is reported in the publication by Apine, I., Pitura, R., Franckevica, I., Pokrotnieks, J., Krumina, G. 2020. "Comparison between Diffusion-Weighted Sequences with Selective and Non-Selective Fat Suppression in the Evaluation of Crohn's Disease Activity: Are They Equally Useful?", *Diagnostics*, 10, 347, pp. 1–21.

1.2.1. Patient population

This prospective observational cross-sectional study included 17 patients (five adults and 12 children) who had either symptomatic CD, or who were referred to MRE examination for follow-up of already proven CD. The faecal calprotectin levels in all study subjects exceeded 1000 µg/g.

The inclusion criteria were: proven active non-stricturing, non-penetrating CD in the terminal *ileum*, presenting with thickened bowel wall (thickness > 3 mm), presence of mural oedema (hyperintensity of the bowel wall in T2-weighted images compared to the psoas muscle), signs of restricted diffusion in both DWI$_{SPIR}$ and DWIBS sequences presenting with high SI in DWI tracking images of b = 800 s/mm^2 along with low SI in the ADC map, and early mucosal hyperenhancement in the *post*Gd series. The exclusion criteria were: locations of CD other than the terminal *ileum,* bowel thickness less than 3 mm, dynamic blurring in either of the DWI or T1 *post*Gd images, inability to locate active bowel wall inflammation in both DWI$_{SPIR}$ and DWIBS sequences, and post-Gd T1 within one and the same segments.

1.2.2. MRI image analysis

All measurements used in MR image analysis were standardised across the patient groups. The altered locations of the terminal ileum were identified and divided into approximately 3 cm (n = 32 in adults, n = 46 in children). In each segment: 1) wall thickness in mm was measured, 2) presence or absence of ulcers (present or absent) was estimated, 3) six measurements of ADC-DWI_{SPIR} and ADC-DWIBS in the corresponding DWI_{SPIR} and DWIBS tracking images of b = 800 s/mm^2 were performed in each segment in the site of the highest SI, in locations where signs of diffusion restriction were visually observed, 4) six measurements of the wall SI were taken in the same location both before (WSI-*pre*Gd) and after (WSI-*post*Gd) administration of gadolinium contrast medium, in the site with the highest SI in the post-contrast images, 5) six measurements of SD representing the image noise were performed outside the body before (SD-*pre*Gd) and after (SD-*post*Gd) administration of gadolinium contrast medium (Rimola et al*.,* 2009). The ADC, WSI and SD measurements were performed using 4–9 m^2 oval ROI. The MaRIA and Clermont index values were calculated for each altered intestinal segment.

The i/v gadolinium CA used before October 2018 for all adult patients and all but two children was gadodiamide (Omniscan 0.05 mmol/mL, GE Healthcare, dosage 0.2 mL/kg, or 0.1 mmol/kg). Gadobutrol (Gadovist 1 mmol/mL, dosage 0.1 mL/kg, or 0.1 mmol/kg) was used for the two paediatric patients examined after October 2018.

1.2.3. Statistical analysis

The statistical analysis was performed using software SPSS 20.0 (IBM Corporation, Armonk, NY, USA, 2011). The median values with SD for ADC-DWI_{SPIR} and ADC-DWIBS, MaRIA, DWI_{SPIR} based Clermont score, and DWIBS–based Clermont scores were calculated. 95 % CI was calculated for median differences. The statistical significance of differences between the groups was determined using the Wilcoxon signed rank test. Spearman's correlation coefficient was used to assess the correlations between quantitative parameters. P values of < 0.05 (two-tailed) were chosen as a level of statistical significance. The Bonferroni correction was used to control Type 1 errors in multiple comparisons.

1.3. Third study. Evaluation of repeatability of magnetic resonance measurements used to determine CD activity

The study is reported in the publication by Apine, I., Pirksta, I., Pitura, R., Pokrotnieks, J., Pukite, I., Krumina, G. 2020. "Repeatability of magnetic resonance measurements used for estimating the Crohn's disease activity", *Proceedings of the Latvian Academy of Sciences. Section B.* Vol. 74, No 2 (725), pp. 75–82.

1.3.1. Patient population

This prospective observational cross-sectional study included 17 patients (five adults and 12 children) who had either symptomatic CD, or who were

referred to MRE examination for follow-up of already proven CD. The faecal calprotectin levels in all study subjects exceeded 1000 µg/g.

The inclusion criteria were: proven active non-stricturing, non-penetrating CD in the terminal *ileum,* presenting with thickened bowel wall (thickness > 3 mm), presence of mural oedema (hyperintensity of the bowel wall in T2-weighted images compared to the psoas muscle), signs of restricted diffusion in both of DWI sequences (DWI_{SPIR} and DWIBS), presenting with high SI in DWI tracking images of b = 800 s/mm^2 along with low SI in the ADC map, and early mucosal hyperenhancement in the *post*Gd series. The exclusion criteria were: locations of CD other than the terminal *ileum,* bowel thickness less than 3 mm, dynamic blurring in either of the DWI or T1 *post*Gd images, inability to locate active bowel wall inflammation in both DWI sequences (DWI_{SPIR} and DWIBS), and *post*Gd T1 within one and the same segments.

1.3.2. MRI image analysis

The measurements were standardised. The altered locations of the terminal ileum were identified and divided into approximately 3 cm (n = 32 in adults, n = 46 in children). In each segment: 1) one measurement of bowel wall thickness was performed in the location of the largest thickness, 2) presence/absence of ulcers was estimated (1 – yes, 0 – no), 3) three measurements of ADC of the DWI_{SPIR} (Fig. 2.3), and DWIBS (Fig. 2.5) were performed at the site of the maximum SI within the inflamed bowel wall, 4) three measurements of WSI were taken before (WSI-*pre*GD) and after (WSI-*post*Gd) administration of gadolinium contrast medium in exactly the same locations of the highest SI in the bowel wall, in both DWI_{SPIR} and DWIBS sequences, 5) three measurements of the image noise –SD were performed outside the patient's body before (SD-*pre*Gd) and after (SD-*post*Gd) administration of the Gd *(*Rimola et al.*,*

2009). The ADC, WSI and SD measurements were performed using the 4–9 mm^2 oval ROI. The average values of the three measurements of ADC, WSI and SD were used for further calculations.

Identical measurements according to this standard were repeated by the same radiologist after two months.

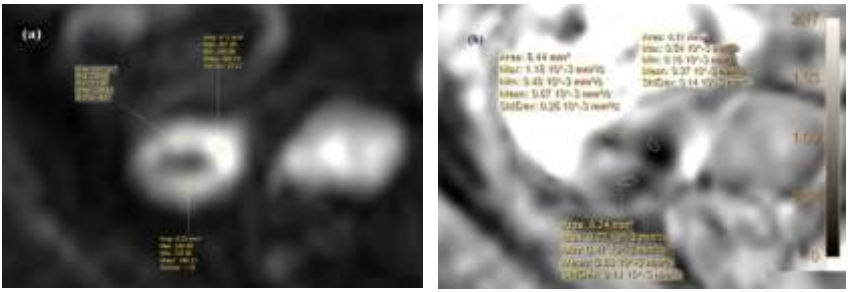

Figure 1.3. **Selecting the ROI for ADC measurements in DWI_{SPIR} images of b = 800 s/mm^2 (a) in a 56-year old male patient with proven CD in the terminal ileal loop**
On the corresponding ADC map (b), the chosen ROI appears automatically. Images from the Author's archive.

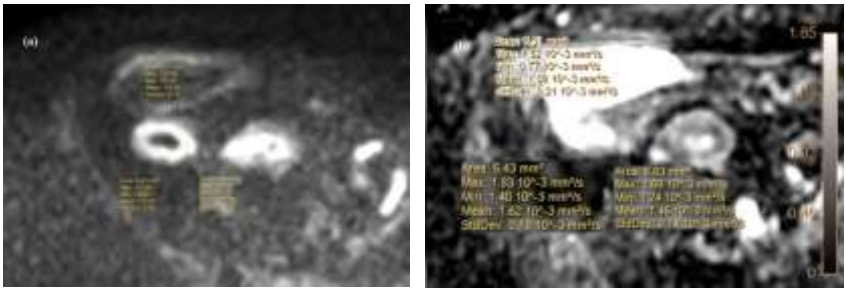

Figure 1.4. **Selecting the ROI for ADC measurements in DWIBS images of b = 800 s/mm^2 (a) in a 56-year old male patient with proven CD in the terminal ileal loop**
On the corresponding ADC map (b), the chosen ROI appears automatically. Images from the Author's archive.

1.3.3. Statistical analysis

Statistical analysis was performed using software Stata/IC (StataCorp LLC, Texas, USA). The mean values and SD were calculated for ADC-DWI_{SPIR} and ADC-DWIBS, as well as RCE, MaRIA and Clermont scores. The mean values of the first and second measurement were compared, and statistical significance of the differences was tested using a paired t-test; 95 % CI were calculated for differences. The statistical significance of differences was determined using one-way ANOVA with Bonferroni correction. A p value of < 0.05 was considered as statistically significant. Differences in the presence/absence of ulcers was evaluated with the Pearson's χ^2 test.

2. Results

2.1. First study. Effect of previous preparation of the patient's intestinal tract with enteric hyperosmolar CA, on the ADC-DWI$_{SPIR}$ and ADC-DWIBS values of the intestinal and large bowel walls

2.1.1. First cohort: Comparison of ADC-DWI$_{SPIR}$ and ADC-DWIBS measurements in unprepared and prepared walls of the small intestines

Amongst the 106 patients, ADC-DWI$_{SPIR}$ values were measured in 91 non-prepared (collapsed) and 106 prepared (filled with the mannitol substrate) jejunal segments. ADC-DWIBS values were measured in 86 collapsed and in 95 distended jejunal segments. To compare ADC-DWI$_{SPIR}$ measurements before and after bowel preparation, 88 pairs of segments were analysed, for comparison of ADC-DWIBS measurements before and after bowel preparation - 83 pairs of segments were analysed. For comparison between ADC-DWI$_{SPIR}$ and ADC-DWIBS measurements before preparation 85 segment pairs were analysed, and 95 pairs were analysed to compare ADC-DWI$_{SPIR}$ and ADC-DWIBS after preparation. The ADC-DWI$_{SPIR}$ and ADC-DWIBS values of the walls of non-prepared and prepared small intestines are presented in Table 2.1.

Table 2.1

The ADC-DWI$_{SPIR}$ and ADC-DWIBS values of the walls of non-prepared and prepared small intestines (*jejunum*).

	Minimum value	**Maximum value**	**Mean value**	**Median value**	**SD**
Non-Prepared (collapsed) *jejunum*, ADC-DWI$_{SPIR}$ value $\times 10^{-3}$ mm^2/s	0.30	2.5	1.09	1.07	0.37
Prepared (filled) jejunum, ADC-DWI$_{SPIR}$ value $\times 10^{-3}$ mm^2/s	0.59	2.71	1.76	1.72	0.41
Non-prepared (collapsed) *jejunum*, ADC-DWIBS value $\times 10^{-3}$ mm^2/s	0.07	2.49	0.91	0.90	0.47
Prepared (filled) *jejunum*, ADC-DWIBS value $\times 10^{-3}$ mm^2/s	0.53	2.97	1.75	1.82	0.51

In both DWI$_{SPIR}$ and DWIBS sequences, the study found marked significant difference between the ADC of non-prepared and prepared bowels. In both DWI$_{SPIR}$ and DWIBS ADC, the values of non-prepared *jejunum* were lower than in prepared jejunum. The ADC difference between the non-prepared and prepared bowel was 38.1 % in DWI$_{SPIR}$ and 48 % in DWIBS. The ADC values are shown in Table. 2.2.

Table 2.2

Comparison of ADC values between DWI_{SPIR} and DWIBS in the walls of non-prepared and prepared *jejunum*

Bowel Preparation State	Non-Prepared (Collapsed) *Jejunum*	Prepared (Filled) *Jejunum*	p Value	Difference between Mean ADC Values of Filled vs. Collapsed Jejunal Loops
Mean *ADC-DWI_{SPIR}* value × 10^{-3} mm^2/s	1.09 (SD = 0.37)	1.76 (SD = 0.41)	< 0.0001	0.67 (38.1 %)
Mean *ADC-DWIBS* value × 10^{-3} mm^2/s	0.91 (SD = 0.47)	1.75 (SD = 0.51)	< 0.0001	0.84 (48 %)

Within the walls of the non-prepared *jejunum*, our data showed a statistically significant ADC difference ($p < 0.0001$) of 16.5 % between DWI_{SPIR} and DWIBS, being lower in DWIBS. No significant ADC difference ($p = 0.84$) between DWI_{SPIR} and DWIBS was observed within walls of prepared *jejunum*.

2.1.2. Second cohort: Comparison of ADC-DWI_{SPIR} and ADC-DWIBS measurements in unprepared and prepared walls of the large bowels

Amongst the 106 patients, ADC-DWI_{SPIR} values were measured in 41 non-prepared (with faeces in the lumen) and 42 prepared (with mannitol substrate in the lumen) colonic segments. ADC-DWIBS values were measured in 25 non-prepared *caecum* or ascending colon segments, and in 18 prepared caecum or ascending colon segments. 41 segment pairs were analysed for comparison between ADC-DWI_{SPIR} measurements before and after preparation, and 18 segment pairs were analysed to compare ADC-DWIBS measurements

before and after preparation. For comparison between ADC-DWI_{SPIR} and ADC-DWIBS measurements before preparation, 25 segment pairs were analysed, and 18 pairs were analysed to compare ADC-DWI_{SPIR} and ADC-DWIBS values after the preparation. The ADC-DWI_{SPIR} and ADC-DWIBS values of the walls of non-prepared and prepared large intestines (*caecum/colon ascendens*) are presented in Table 2.3.

Table 2.3

The ADC-DWI_{SPIR} and ADC-DWIBS values of the walls of non-prepared and prepared large intestines (*caecum/colon ascendens*)

	Minimum value	**Maximum value**	**Mean value**	**Median value**	**SD**
Non-Prepared (with intraluminal faecal content) *caecum/colon ascendens*, ADC-DWI_{SPIR} value × 10^{-3} mm^2/s	0.78	2.68	1.41	1.43	0.31
Prepared (with intraluminal mannitol substrate) *caecum/colon ascendens*, ADC-DWI_{SPIR} value × 10^{-3} mm^2/s	1.19	2.89	2.13	2.16	0.41
Non-Prepared (with intraluminal faecal content) *caecum/colon ascendens*, ADC-DWIBS value × 10^{-3} mm^2/s	0.18	2.49	1.01	1.04	0.41
Prepared (with intraluminal mannitol substrate) *caecum/colon ascendens*, ADC-DWIBS value × 10^{-3} mm^2/s	1.07	3.25	2.04	1.98	0.58

In both DWI_{SPIR} and DWIBS sequences, the study found marked significant difference between ADC in non-prepared and prepared bowels. In both DWI_{SPIR} and DWIBS ADC, values of the non-prepared colon were lower than in the prepared colon. The ADC difference between non-prepared and prepared bowel was 33.8 % in DWI_{SPIR} and 50.5 % in DWIBS (Table 2.4).

Table 2.4

Comparison of ADC values between DWI_{SPIR} and DWIBS in walls of non-prepared and prepared *colon*

Bowel Preparation State	**Non-Prepared (**with intraluminal faecal content**)** ***caecum/colon ascendens***	**Prepared (**with intraluminal mannitol substrate**)** ***caecum/colon ascendens***	**p Value**	**Difference between Mean ADC Values of Prepared vs. Non prepared Colonic Walls**
Mean ADC-DWI_{SPIR} value × 10^{-3} mm^2/s	1.41 (SD = 0.31)	2.13 (SD = 0.41)	< 0.0001	0.72 (33.8 %)
Mean ADC-DWIBS value × 10^{-3} mm^2/s	1.01 (SD = 0.40)	2.04 (SD = 0.58)	< 0.0001	1.03 (50.5 %)

By mutually comparing ADC-DWI_{SPIR} and ADC-DWIBS values within the walls of both the non-prepared and prepared *colon*, the data showed a statistically significant ADC difference ($p < 0.0001$) of 28.4 % between DWI_{SPIR} and DWIBS, being lower in DWIBS. No significant ADC difference ($p = 0.58$) between DWI_{SPIR} and DWIBS values was found.

2.2. Second study. Investigation of ADC-DWI$_{SPIR}$ and ADC-DWIBS values in patients with MRI signs of active CD, and the use of ADC-DWI$_{SPIR}$ and ADC-DWIBS values in calculating of the Clermont index

During the study, 57 patients (20 adults and 37 children) with active Crohn's disease underwent MRE examination. Amongst them, 17 patients – five adults (23, 25, 36, 40 and 57 years old) and 12 children (11 years old; n = 2, 12 years old; n = 3, 13 years old; n = 1, 14 years old; n = 4, 17 years old; n = 2), were enrolled in the study as meeting the research criteria. 15 adults and 25 children did not meet the study criteria: in 14 patients (6 adults and 8 children) CD was localised in the colon, and in 3 paediatric patients it was localised in the jejunum. 9 patients (1 adult and 8 children) with ileal CD had a history of resection of the terminal ileum. 7 patients (2 adults and 5 children) had MR appearance of CD, but the diagnosis was not endoscopically proven. 5 adult patients with the history of known proven CD had no conclusive visual signs of CD. Images of one adult patient showed blurring in the T1 post-contrast images, and images of one paediatric patient showed both blurring in conventional DWI and T1 post-contrast images.

Amongst the enrolled 17 patients, in one adult patient the duration of medical history prior to the MRE examination was more than two years, in three adult patients – from 6 till 12 months, but in one adult patient CD was asymptomatic, of unknown length, and was detected upon performing a set of infertility tests. In one paediatric patient, the duration of CD was slightly less than two years, but in the remaining 11 patients the duration of medical history was less than 6 months.

The overview of measured ADC-DWI$_{SPIR}$ and ADC-DWIBS values, as well as calculated values of MaRIA, DWI$_{SPIR}$-based Clermont score and DWIBS-based Clermont score, is presented in Table 2.5.

Table 2.5

Values of ADC-DWI$_{SPIR}$, ADC-DWIBS, MaRIA as well as ADC-DWI$_{SPIR}$ and ADC-DWIBS-based Clermont scores in the groups of adult and paediatric patients

Measurement	N	Minimum value	Maximum value	Median value	SD
ADC-DWI$_{SPIR}$ (mm^2/s), adults	32	0.66×10^{-3}	2.16×10^{-3}	1.26×10^{-3}	0.29
ADC- DWI$_{SPIR}$ (mm^2/s), children	46	0.18×10^{-3}	2.23×10^{-3}	1.13×10^{-3}	0.31
ADC-DWIBS (mm^2/s), adults	32	0.01×10^{-3}	2.37×10^{-3}	1.15×10^{-3}	0.49
ADC-DWIBS (mm^2/s), children	46	0.20×10^{-3}	2.74×10^{-3}	1.16×10^{-3}	0.44
MaRIA, adults	32	10.65	36.65	24.43	5.31
MaRIA, children	46	9.96	37.67	22.08	6.67
ADC-DWI$_{SPIR}$-based Clermont score, adults	32	12.85	39.23	26.23	4.76
DWI$_{SPIR}$-based Clermont score, children	46	13.59	40.74	23.53	5.42
DWIBS-based Clermont score, adults	32	5.92	38.78	24.28	4.65
DWIBS-based Clermont score, children	46	8.25	39.52	24.39	5.77

There was a statistically significant difference of 10.32 % ($p = 0.02$) between the median values of ADC-DWI$_{SPIR}$ in adults and children, appearing lower in children than in adults. No statistically significant difference ($p = 0.38$) between ADC-DWIBS in adults and children was detected. There was a statistically significant difference of 8 % ($p = 0.03$) between ADC-DWI$_{SPIR}$ and ADC-DWIBS values in adults, appearing lower in DWIBS, but no statistically significant difference ($p = 0.97$) between ADC-DWI$_{SPIR}$ and ADC-DWIBS values was detected in children.

In all patients of both groups, the MaRIA value corresponded to active disease (i.e., ≥ 7) (Rozendorn et al., 2018). Excluding one patient with the score value of 10.65, MaRIA score values in all adult patients also corresponded to

severe disease (i.e., ≥ 11). In the paediatric group, in all but three patients, with the values of 9.95, 10.25 and 10.66, MaRIA values exceeded 11 thus corresponding to severe disease (Rozendorn et al., 2018).

In all patients of both groups, the DWI_{SPIR}-based Clermont score value corresponded not only to active disease (i.e., > 8.4) but also to severe disease (i.e., ≥ 12.5). In two adult patients, the DWIBS–based Clermont score values (i.e., 5.92 and 8.20) were below the threshold of 8.4 for active disease; however, the values of all other patients corresponded both to active and to severe disease. In one paediatric patient, the DWIBS-based Clermont score value (i.e., 8.24) was slightly below the threshold of 8.4 for active disease; two patients with values of 11.26 and 12.38 corresponded to active disease. All other patients corresponded to severe disease (Rozendorn et al., 2018).

The correlation between ADC-DWI_{SPIR} and ADC-DWIBS was weak and statistically unreliable in both adults (rho = 0.27; p = 0.13) (Fig. 2.1.a) and children (rho = 0.22; p = 0.15) (Fig. 2.1.b).

There was a strong and statistically significant correlation between MaRIA and the ADC-DWI_{SPIR}-based Clermont score in both adults (rho = 0.93; p < 0.0001) (Fig. 2.2.a), and in children (rho = 0.98; p < 0.0001) (Fig. 2.2.b). There was also a strong and statistically significant correlation between MaRIA and ADC-DWIBS-based Clermont score in adults (rho = 0.89; p < 0.0001) (Fig. 2.3.a) and in children (rho = 0.95; p < 0.0001) (Fig. 2.3.b). The correlation between ADC-DWI_{SPIR} and MaRIA was moderately negative and statistically reliable in both adults (rho = −0.50, p = 0.004) (Fig. 2.4.a), and children (rho = −0.54, p < 0.0001) (Fig. 2.4.b). There was no correlation between ADC-DWIBS and MaRIA (rho = −0.001, p = 0.99) (Fig. 2.5.a), and a low negative statistically reliable correlation (rho = −0.374, p = 0.01) in children (Fig. 2.5.b).

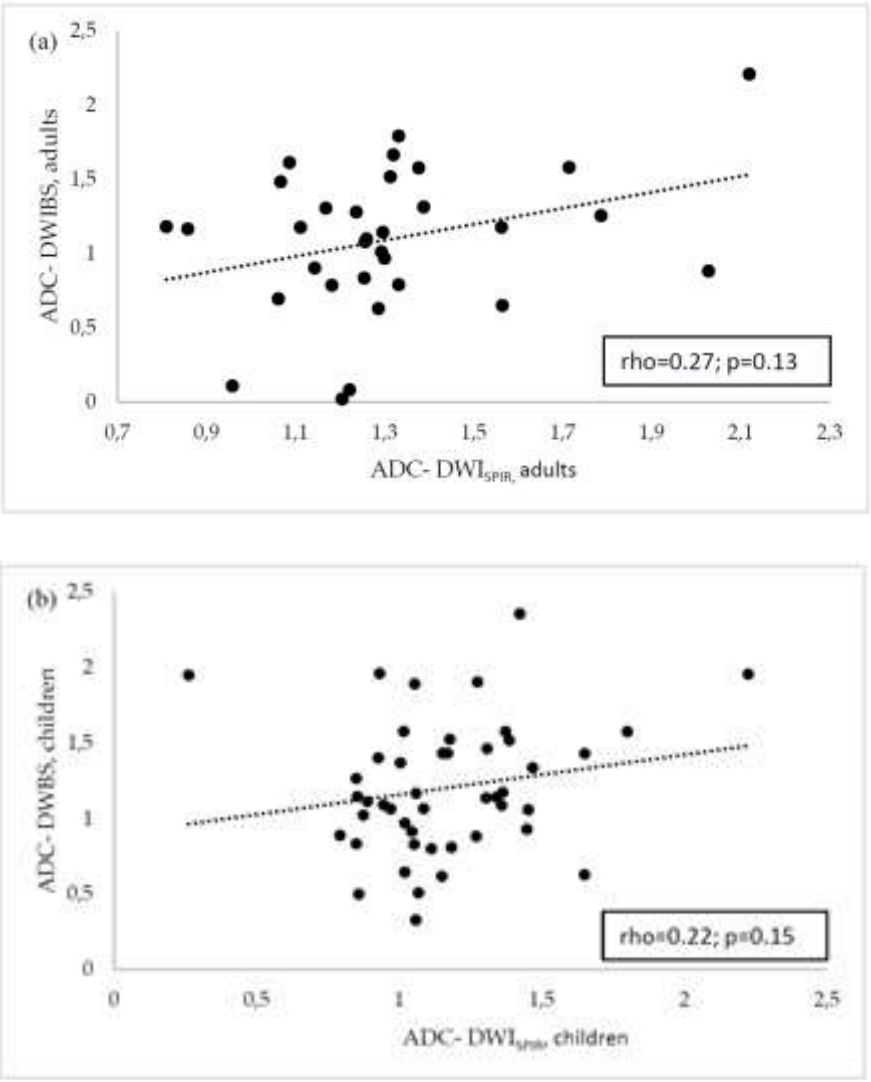

Figure 2.1. **Correlation curve between ADC-DWI$_{SPIR}$ and ADC-DWIBS in adults (a) and children (b) showing no correlation**

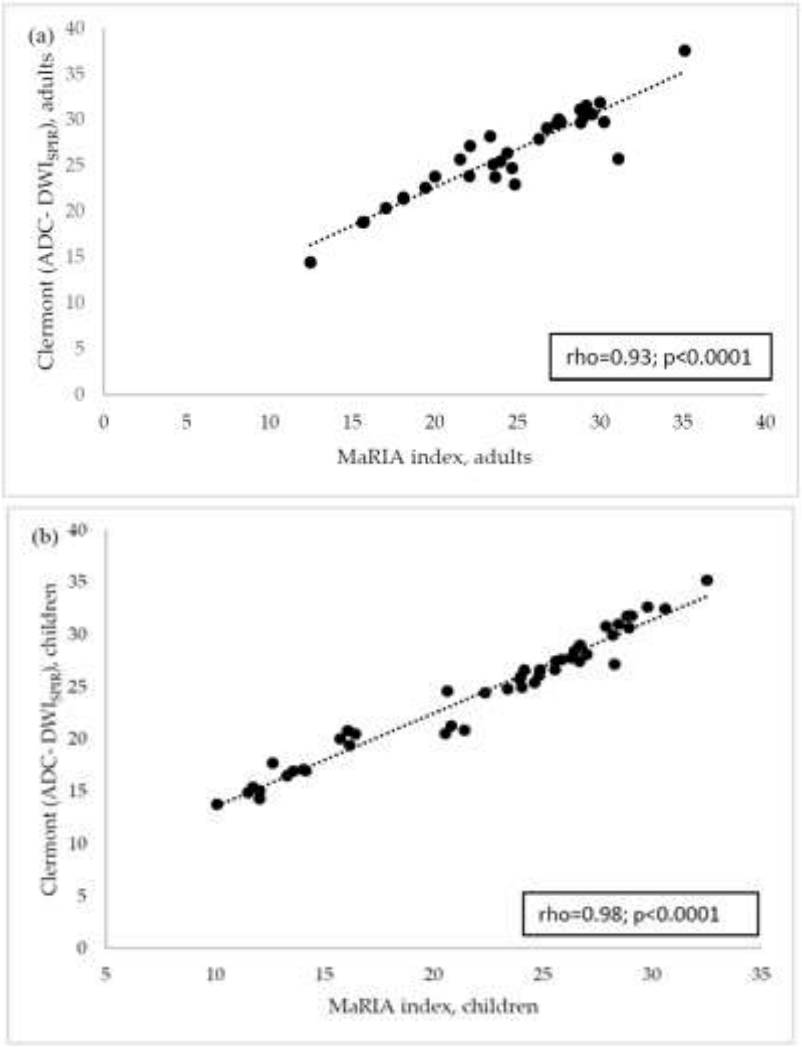

Figure 2.2. **Correlation curve between MaRIA and ADC-DWI$_{SPIR}$-based Clermont score in adults (a) and children (b) showing high correlation**

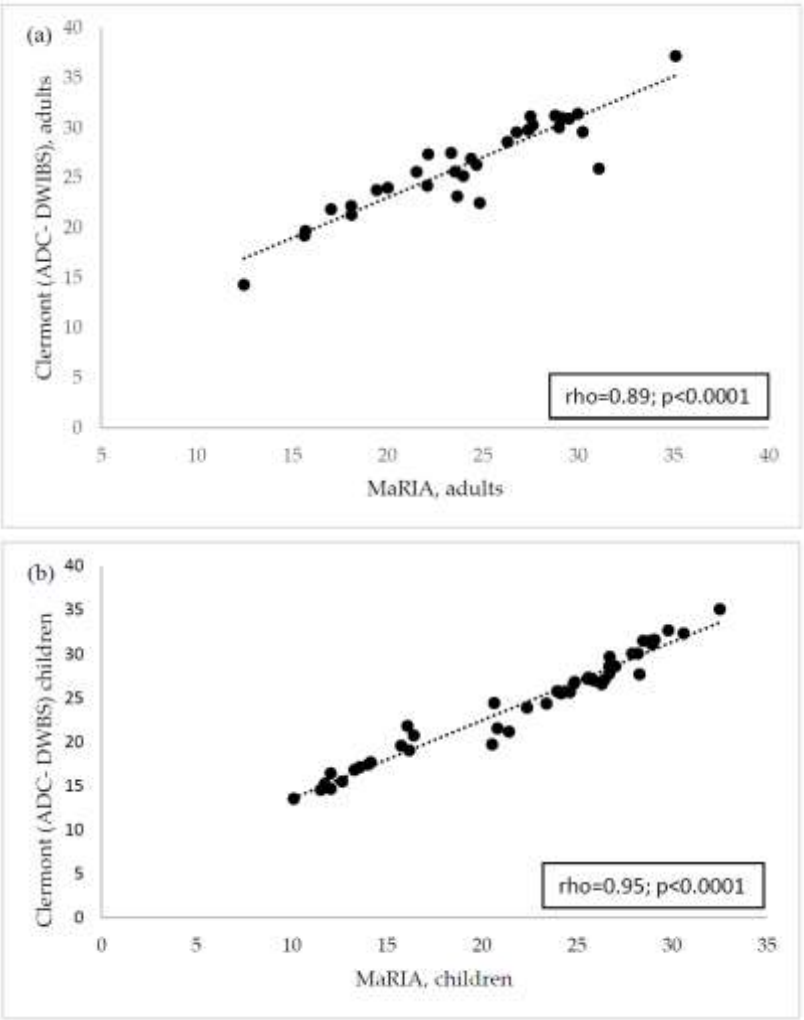

Figure 2.3. **Correlation curve between MaRIA and ADC-DWIBS-based Clermont score in adults (a) and children (b) showing high correlation**

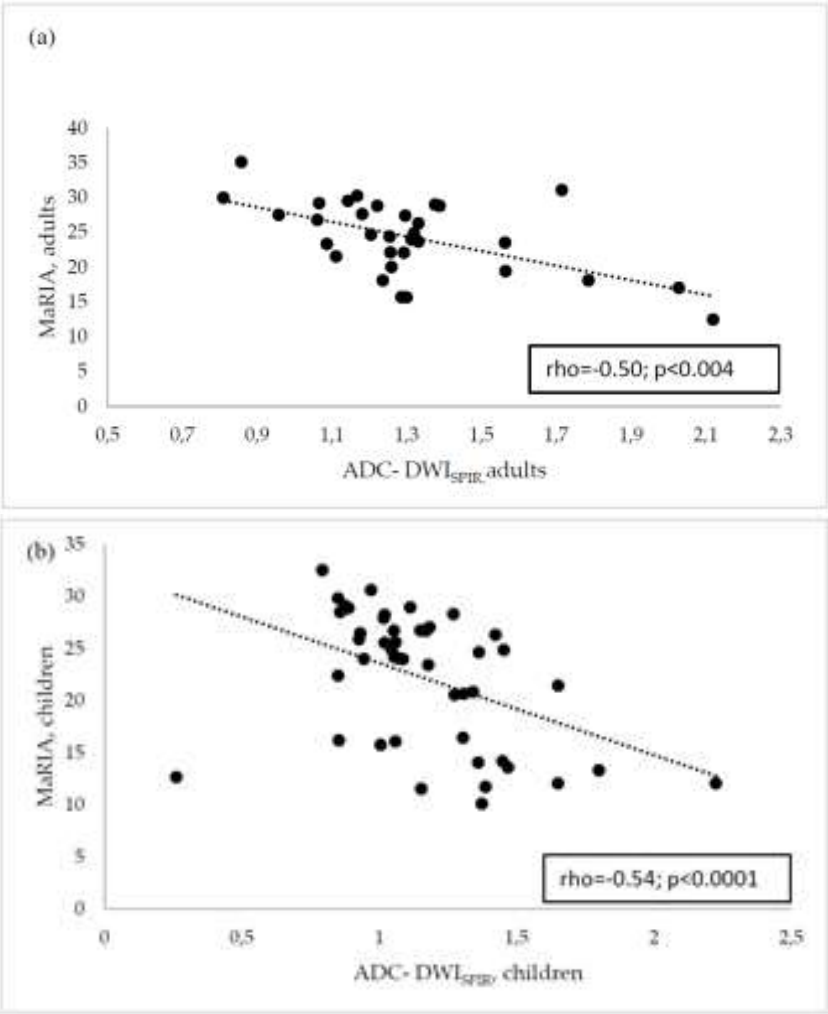

Figure 2.4. **Correlation curve between ADC-DWI$_{SPIR}$ and MaRIA in adults (a) and children (b) showing moderate negative correlation**

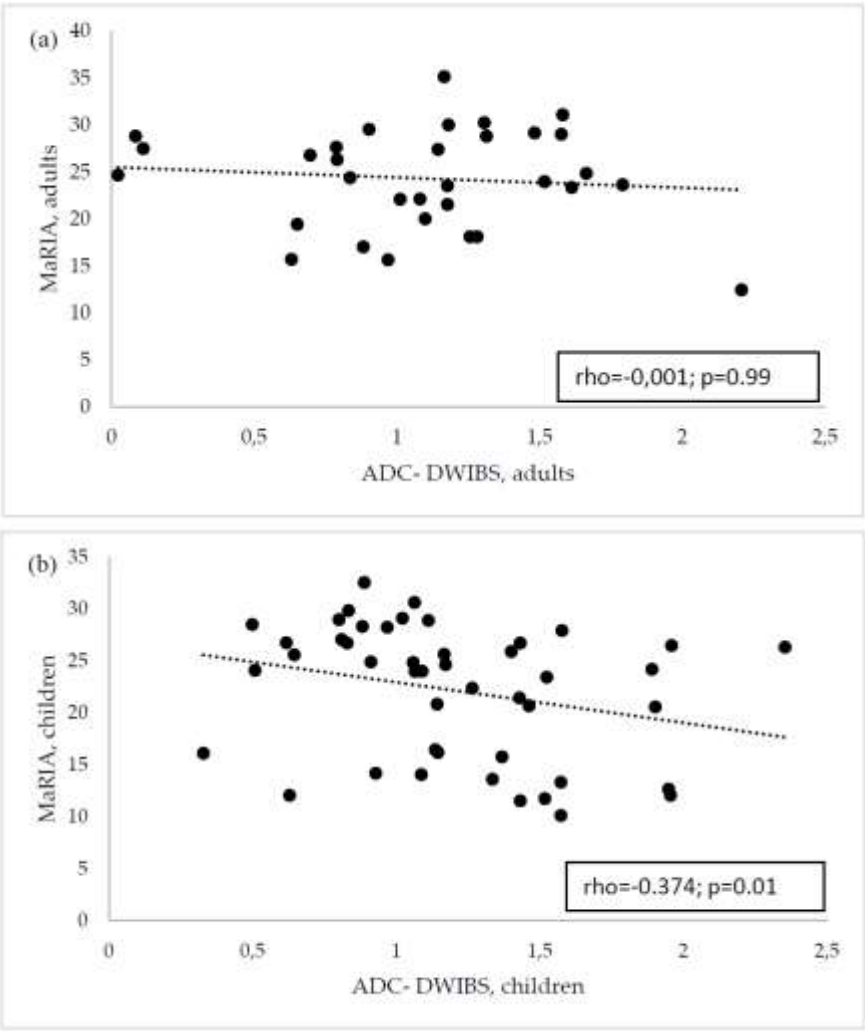

Figure 2.5. **Correlation curve between ADC-DWIBS and MaRIA in adults (a) showing no correlation and in children (b) showing low negative correlation**

2.3. Third study. Evaluation of the repeatability of magnetic resonance measurements used to determine CD activity

No statistically significant difference was observed between the two measurements performed by a single observer, either in the measurement of the bowel wall thickness (p = 0.42), or in the assessment of ADC-DWI$_{SPIR}$ values (p = 0.65) and ADC-DWIBS values (p = 0.23). There was also no statistically significant difference between the two measurements performed by a single observer in assessment of WSI-*pre*Gd (p = 0.06) or WSI *post*Gd (p = 0.57). The highest absolute difference (8 %) between two measurements was observed for WSI-*pre*Gd measurements, and the lowest absolute difference for SPIR-based ADC measurements (1 %) (Table 2.6).

Table 2.6

Numerical values of the first and the second measurements of the bowel wall thickness, ADC-DWI$_{SPIR}$ and ADC-DWIBS, WSI-*pre*Gd, and WSI-*post*Gd

Measurement	First assessment (mean)	Second assessment (mean)	Difference	
			Difference (%)	p value
Wall thickness (mm)	6.4	6.6	0.2 (5 %)	0.42
ADC-DWI$_{SPIR}$ (mm^2/s)	1.219 (*SD* 0.320)	1.227 (*SD* 0.321)	0.008 (1 %)	0.65
ADC-DWIBS (mm^2/s)	1.180 (*SD* 0.505)	1.132 (*SD* 0.478)	0.048 (4 %)	0.23
WSI-*pre*Gd	162.925 (*SD* 127,57)	150.305 (*SD* 99.68)	12.61 (8 %)	0.06
WSI-*post*Gd	336.39 (*SD* 235,35)	316.11 (*SD* 212,90)	20.33 (6 %)	0.57

For analysis of the presence of bowel ulcers between the first and the second assessment, the Pearson χ^2 was 13.70 (p < 0.0005), indicating a systemic

difference between the two assessments for presence of ulcers. The results of the assessment of presence/absence of ulcers are presented in Table 2.7.

Table 2.7

Evaluation of first and the second measurements of the presence/absence of ulcers

Evaluation	Ulcer	Number of Segments	%	Pearson χ^2	p Value
First	Absence	43	55.13	13.70	< 0.0005
	Presence	35	44.87		
Second	Absence	26	33.33		
	Presence	52	66.67		

3. Discussion

3.1. Use of DWIBS sequence in primary diagnostics of CD (first study)

The use of the DWI sequence has been shown to improve the accuracy of CD diagnosis, to assess the disease activity, and to assist in the dynamic follow-up by evaluation of the effectiveness of treatment. It is also able to replace the i/v CA administration. (Dohan et al. 2016). However, despite the sensitivity of the method up to 100 %, its disadvantage is the low specificity of 39–61%. The reason for the low DWI specificity, is the high intensity signal in DWI tracking images with high b value in the intestinal wall. This phenomenon is usually explained by the T2 "shine-through" effect, which is related to the long T2 relaxation time of tissues. Although in this case ADC values should be high (Koh *et al.,* 2012), and in the case of inflammatory changes low, elevated SI in the DWI tracking images in combination with low ADC is observed not only in inflamed, but also in intact intestinal walls. (Jesuratnam-Nielsen et al*.,* 2015).

According to a number of studies, the performance of DWI varies among authors. The range of ADC values in the normal bowel wall was 1.18–3.69 mm^2/s, whereas in inflamed bowel segments 1.24–1.988 mm^2/s, being significantly lower by $0.8 – 2.4 \times 10^{-3}$ mm^2/s than in intact bowels. Several authors have also provided their cut-off ADC values for discriminating between inflamed and intact bowel walls. These values are mutually different and lie between the ADC ranges of inflamed and intact bowel walls, except in one study where the cut-off value lies within the range of the inflamed bowel. According to data from all researchers, ADC ranges of IBD and intact bowels do not mutually overlap (Dohan *et al.,* 2016). Therefore, the theory that DWI could possibly have an advantage in performing MRE examinations without prior preparation of the intestinal tract of patients with hyperosmolar oral CA was explored. This would allow the examination of patients under general anaesthesia, for whom oral

preparation is contraindicated. Therefore, it is important to understand whether the ADC values of the intestinal wall before and after prior preparation with osmotically active oral CA differ, how large these differences are, and whether the ADC range of the intestinal wall does not partially overlap with the ADC range of the inflamed intestinal wall.

Most intestinal wall DWI studies have been performed by preparing patients with large volumes (1000–2000 ml) of hyperosmolar oral CV prior to the MRE examination. To the best of our knowledge, the team of Kiryu et al. is the only research group reporting ADC values in Crohn's disease patients without prior patient preparation using free-breathing DWI as a fat suppression technique. The reported ADC values show a similar trend, with that in prepared bowels being lower in disease-active segments and higher in disease-inactive areas ($1.61 \pm 0.44 \times 10^{-3}$ mm^2/s versus $2.56 \pm 0.51 \times 10^{-3}$ mm^2/s in intestines, respectively) (Kiryu et al., 2009). This difference is large enough to allow for the diagnosis of CD on the basis of ADC measurements, without prior preparation of the patients' intestinal tract. If the differing ADC values in inflamed and unaltered intestinal walls also apply to unprepared intestinal walls, this would allow ADC values to be properly assessed without preparing patients prior to the examination. Therefore, one of the study tasks was to compare the ADC values of unprepared and prepared intestinal walls.

Upon reporting multiple MRE exams, several observations were performed regarding the high SI bowel wall in the DWI tracking images of $b = 800$ s/mm^2. Firstly, it was noticed that intestinal SI was markedly higher in the bowel wall before preparation, i.e., in a totally collapsed bowel, compared to the intestinal wall after preparation, i.e., in a fully distended bowel. In contrast, in the colon SI was markedly higher in the bowel wall after preparation, i.e., in the presence of enteric CA, compared to the colonic wall before preparation, i.e., in the presence of faeces. In both situations, high SI bowel walls in the ADC map

frequently presented low SI. These observations raised a question regarding ADC differences between the bowel wall before and after patient preparation, in both the intestines and colon.

Results from the first cohort comparing ADC values of DWI_{SPIR} and DWIBS between non-prepared (collapsed) and prepared (filled) intestines showed that ADC values in both DWI_{SPIR} and DWIBS in the collapsed bowel sample were markedly lower than in distended bowel samples. As the bowel collapses, the number of cells per volume unit increases; however, the cells are not altered. The measurement results therefore could be explained by the partial volume effect (Scherrer, Gholipour, and Warfield, 2011*)*. In the prepared (filled) jejunal wall, the signal of the very thin bowel wall was contaminated by the high intensity signal from the massive volume of enteric CA, therefore, the ADC value is high. However, in the non-prepared (collapsed) intestinal samples, the amount of high SI intraluminal content is less, therefore, the contamination of the intestinal wall signal is also less. A similar explanation applies to the second cohort comparing ADC values of DWI_{SPIR} and DWIBS between the non-prepared (presence of low SI intraluminal faeces) and prepared (presence of mannitol) colon. The results showed that ADC values in both DWI_{SPIR} and DWIBS were dependent on colonic intraluminal content, and in the presence of low SI faeces, were nearly two times lower than in the presence of high SI mannitol.

By mutually comparing ADC-DWI_{SPIR} and ADC-DWIBS values, no statistically significant difference was observed in the wall of prepared bowels, both regarding the intestines and the colon. On the contrary, ADC-DWIBS values of both the non-prepared small intestine and colon are significantly lower compared to the ADC-DWI_{SPIR} values. This is explained by the large amount of liquid oral CA in the intestinal lumen, which generates the high signal in both the small and large intestinal wall to the same extent, and equally affects the ADC

values of the bowel walls. On the contrary, in the non-prepared bowel, there is a presence of high-viscosity intraluminal content – chyme, in the intestines and faeces, in the colon. The T1 relaxation time of high viscosity content is short, like that of fat. Therefore, STIR, being a non-selective fat signal suppression technique for the DWIBS sequence, suppresses not only the fat signal but also the signal from another type of substrate with a short T1 relaxation time (Krinsky G, Rofsky and Weinreb, 1996; Del Grande *et al.*, 2014). Therefore, the lower ADC-DWIBS values, in the presence of the bowel content, are more likely to overlap the ADC range of the inflamed bowel compared to ADC-DWI_{SPIR}. When comparing the ADC values of the intact intestinal wall in adult patients obtained in the first study, with the ADC values in adult patients with active CD in the terminal *ileum*, obtained in the second study, there was a clear difference in ADC values. In adult patients, the median ADC DWI_{SPIR} value for the previously prepared unaltered small intestinal wall is 1.72×10^{-3} mm^2/s, for the non-prepared unaffected small intestinal wall – 1.07×10^{-3} mm^2/s, while the median ADC value for the terminal loop affected by CD, is 1.26×10^{-3} mm^2/s. The median ADC-DWIBS value for the prepared unaltered small intestinal wall is 1.82×10^{-3} mm^2/s, for the previously unprepared unaltered small intestinal wall - 0.90×10^{-3} mm^2/s, while the median ADC-DWIBS value for the terminal ileum affected by CD is 1.15×10^{-3} mm^2/s. Thus, in both DWI_{SPIR} and DWIBS sequences, the ADC values of the bowel wall affected by CD is higher than the ADC values of the unprepared intestinal wall. Thus, the ADC measurements in both DWI_{SPIR} and DWIBS sequences are unlikely to be suitable for scanning patients without prior intestinal preparation.

The study, however, had several limitations. Measurements were performed by one radiologist not assessing inter-observer agreement, and in such a small volume, ADC values are reported to be hardly reproducible (Dohan et al., 2016; Watson, Calder, and Barber, 2018), as they rest on

subjectivity. Nevertheless, data from ADC measurements in liver imaging suggested better reproducibility of free-breathing DWIBS over respiratory-triggered DWI, (Kwee, Takahara, Koh, et al., 2008) which could be also proven better for bowel walls, but requires further investigation. In intestines, the most uniform luminal distension was present in *jejunum*, which was therefore chosen for intestinal measurements, however, the ileum is the main location of CD. The terminal loop of the ileum also has different morphological patterns, such as the abundance of lymphoid tissues (Gullberg and Söderholm, 2006), which also could influence ADC measurements. In the colon, measurements were performed only in the walls of the *caecum* and the ascending colon, since presence or mannitol was mainly observed in these locations. Location of the sites with high SI signal in DWI tracking images of b = 800 s/mm^2 was not consistent among the series, therefore measurements could not be performed precisely at the same locations. No special attention was paid to the T2 "shine through" effect of bowel walls, and measured ADC values in the DWI tracking images of b = 800 s/mm^2 regardless of SI appearance in ADC map. The goal was to observe properties of ADC-DWI$_{SPIR}$ and ADC-DWIBS in the sites of bowel walls showing high SI at tracking images of b = 800 s/mm^2 resembling bowel inflammation, whereas no other signs of bowel inflammation such as oedema, increased bowel wall thickness, contrast enhancement were considered, which were absent in patients with no presence of IBD as required by the study.

3.2. Use of DWIBS sequence to evaluate CD activity (second and third study)

The primary goal of treatment for CD is to achieve remission. Therefore, the assessment of disease activity is crucial to guide patients' therapeutic decisions regarding the treatment of CD. Although the primary endpoint of

treatment has long been endoscopic remission i.e., mucosal healing (Maaser et al., 2019; Moy, Sauk, and Gee, 2016; Rimola et al., 2009), CD is a transmural inflammation that can persist in patients with long-term mucosal healing (Civitelli et al., 2016; Nardone et al., 2019; Zorzi et al., 2014). It is proven that compared to mucosal healing, transmural healing is related to improved long-term outcomes, including sustained long-term steroid-free clinical remission, less need for rescue therapy, less CD-related hospitalisations and CD-related surgery (Serban, 2018). Therefore, transmural healing has recently been proposed as a new target for CD treatment (Castiglione et al., 2019). To assess transmural changes, imaging techniques are required allowing evaluation of the altered intestinal wall along its entire length and thickness. It has been shown that MRE can replace endoscopy in the assessment of CD activity (Rimola et al., 2009).

The MaRIA score is the only validated index for measuring inflammatory activity in the *ileum* distal loop, tested in large patient populations and multi-centre research (Dohan et al., 2016; Ordás et al., 2019). It requires i/v administration of Gd CA. The Clermont score is based on DWI (therefore called DWI-MaRIA), and it was derived as an alternative for MaRIA, replacing RCE with ADC, thus avoiding the administration of gadolinium contrast media. The authors of the Clermont score state it is not only useful in estimation of ileal CD activity, with excellent correlation with RCE-based MaRIA (Buisson et al., 2013; Hordonneau et al., 2014), but also, in the detection of ulcers (Buisson et al., 2015) and prediction of remission after biological therapy (Buisson et al., 2018). In their reports, the authors cite an outstanding correlation of the Clermont index with MaRIA (Buisson et al., 2013; Hordonneau et al., 2014).

In this study, the correlation between ADC-DWI_{SPIR} and ADC-DWIBS values was calculated. Although ADC-DWI_{SPIR} and ADC-DWIBS values appeared to be comparable visually, virtually no correlation was observed

between ADC-DWI_{SPIR} and ADC-DWIBS values in both adults (rho = 0.27; p = 0.13) and children (rho = 0.22; p = 0.15). Although the DWIBS sequence is performed under free breathing, and availability of both repeated stimulations and acquisitions contributes to improved SNR and both spatial and temporal resolution (Kwee, Takahara, Ochiai et al*.,* 2008), the possibility of respiratory motion in DWIBS, means that slice levels of images obtained with different b-values may not be identical. Since DWIBS employs multiple slice excitations, slice levels of images obtained with the same b-value may be different (Ouyang et al*.,* 2014). The weak correlation between ADC-DWI_{SPIR} and ADC-DWIBS values, may also be impacted by the conceptually different fat suppression mechanisms of SPIR and STIR on ADC values of the intestinal wall, in relation to histopathological characteristics of bowel inflammation, due to differences in gut wall histopathology in adults and children.

Within the study, the ADC-DWI_{SPIR} and ADC-DWIBS values were analysed in two dimensions:

1) ADC values of both adults and children were compared within a single fat suppression technique, and a statistically significant ADC-DWI_{SPIR} difference was observed between adults and children, being lower in children, compared to adults. In contrast, no statistically significant difference was found between the ADC-DWIBS values in adults and children;

2) ADC values obtained with each of the DWI sequences were compared within one patient group, both in adults and children. The analysis showed differences between ADC-DWI_{SPIR} and ADC-DWIBS values in adults, being lower in DWIBS, but did not show a difference between ADC-DWI_{SPIR} and ADC-DWIBS values in the children's group.

To interpret the results, it is necessary to consider the differences in the histopathological picture of adult and paediatric CD, the different physical basis of both DWI_{SPIR} and DWIBS sequences as well as the duration of CD history.

There are three ruling theories considering the exact cause of the restricted diffusion in CD as follows: 1) narrowing of extracellular space caused by presence of oedema and increased cell density, dilated lymphatic vessels as well as formation of lymphoid aggregates, epithelioid granulomas and micro-abscesses (Feakins, 2013; Geboes, 2003; Morani et al., 2015; Zhu et al., 2015); 2) increased perfusion, and 3) mural fibrosis (Morani et al., 2015; Zhu et al., 2015). Although the morphological pattern of CD is generally similar in adult and paediatric patients (Magro et al., 2013), the main difference between the histopathology of paediatric and adult CD, is the more frequent appearance of epithelioid granulomas in the inflamed bowel wall of children (Feakins, 2013; Riddell, 2014; Feakins, 2014).

When analysing the performance of ADC-DWIBS, the non-selectivity of STIR fat suppression must be considered. Unlike the SPIR technique, which uses a spectrally selective radiofrequency pulse, suppressing solely the fat signal, STIR technique uses an inversion recovery technique based on the T1 relaxation time of the tissues examined. Apart from fat having a short T1 time, STIR technique suppresses other substances of short T1 time, thus adding to the decrease of ADC values by suppression of signal from methaemoglobin, melanin, mucoid tissue, and proteinaceous fluid (Del Grande et al., 2014). Although early mucosal lesions in CD can be associated with the damage of small capillaries (Geboes, 2003), there is no literary data on haemorrhagic changes in the intestinal wall, which could lead to the formation of methaemoglobin in the intestinal wall (Riddell, 2014). There is also no evidence that any patient has chronic bowel melanosis associated with the development of melanin deposits, rarely associated with CD. (Lambert, Luk, 1980; Li et al., 2015). The

inflammatory bowel wall tends to contain crypt abscesses, the contents of which could be considered as both mucoid and protein-rich tissues. However, they are occasional and are only observed in 19 % of patients (Riddell, 2014).

A very important consideration influencing the SI of fine and thin structures, such as the bowel wall, is the partial volume effect (González Ballester, Zisserman, and Brady, 2002). Typically, an achievable DWI resolution is in the order of 2 mm × 2 mm × 2 mm (Scherrer et al*.,* 2011). In our DWIBS protocol, the acquisition voxel size is 2.50 mm (RL) × 2.98 AP (AP) × 6 mm (slice thickness), therefore within the single voxel, there will be signal contamination from the adjacent media. The bowel lumen contains the viscous and proteinaceous chyme, and occasionally faecal admixture, so the ADC-DWIBS values will be influenced not only by suppression of the mesenterial fat tissue, but also by saturation of signal from the bowel content with short T1 relaxation time. Therefore, when measured at a short distance from the intestinal lumen as carried out in the group of adults, ADC-DWIBS values are artificially lower, compared to ADC values of DWI with spectrally selective fat suppression, i.e., $DWI_{SPIR.}$

The lower ADC-DWI_{SPIR} values in children, compared to adults are explained by differences in medical history. Although all adult patients had active CD, their medical history prior to the MRE examination was at least six months long (except for one patient whose duration of illness was unknown), whereas all children (except one with an almost 2-year history of CD) were examined no longer than six months after the onset of symptoms. Therefore, the oedema component in the paediatric bowel wall was more pronounced, resulting in a greater diffusion restriction when compared to the adult patients. The presence of epithelioid granulomas may further limit diffusion in the inflamed wall.

In turn, lack of difference in ADC-DWIBS values for adults and children can be explained as follows. The medical history of children included in the study

was shorter and therefore intestinal wall oedema was more severe. The ROIs for performing ADC measurements were positioned at the sites with the highest SI (within the submucosal layer of the bowel wall), therefore the distance to the intestinal lumen was sufficient to prevent the signal contamination caused by the partial volume effect. In turn, since the history of CD was longer in the group of adult patients, apart from oedema, fibrosis was also present. In these locations, the bowel wall was thinner, and ADC-DWIBS values were influenced by the partial volume effect from the bowel content with short T1 time, artificially lowering the ADC values.

The absence of difference between ADC-DWI_{SPIR} and ADC-DWIBS values in the children's group could also be explained with the predominance of the oedematous component, which, by increasing the thickness of the intestinal wall, does not allow the partial volume effect to affect the ADC-DWIBS values measured in the middle of the submucosal layer of the intestinal wall.

In the study, a moderate negative correlation was found between ADC-DWI_{SPIR} and MaRIA in both adults (rho = −0.50, p = 0.004) and children (rho = −0.54, $p < 0.0005$) being weaker than reported by the study group of the Clermont-Ferrand university showing excellent correlation (Buisson et al., 2013; Hordonneau et al., 2014). However, in the systematic review and meta-analysis on using DWI in MRE for evaluating bowel inflammation in CD, Choi et al. states that ADC demonstrates a moderate strength of correlation at best and Clermont score performs better (Choi et al., 2016). This is also consistent with the obtained results, since like the studies by the research group from Clermont-Ferrand University, in the current study there was also observed excellent correlation between MaRIA and both DWI_{SPIR}- and DWIBS-based Clermont scores. However, there may be a methodological error in using correlation between MaRIA and Clermont score, as the data to be correlated should be mutually independent, and should not be used if it includes more than one

observation on any individual (Aggarwal and Ranganathan, 2016). Apart from RCE used in MaRIA and ADC used in the Clermont score, all other three variables (wall thickness, presence of oedema and presence of ulcerations), are used in both equations. The use of correlation analysis opposes the conditions in which correlation can be applied, and in the instances of highest probability, could lead to an overestimation of the similarity between MaRIA and the Clermont score. The accuracy of this statement is supported by the contradiction between correlation of ADC-DWIBS and the ADC-DWIBS-based Clermont score with MaRIA, as despite no apparent correlation between ADC-DWIBS and MaRIA (rho = −0.001, p = 0.99) in the adult group, and low negative correlation between ADC-DWIBS and MaRIA in the paediatric group (rho = −0.37, p = 0.01), the correlation between the DWIBS-based Clermont score and MaRIA remained strong in both adults (rho = 0.89; $p < 0.0005$) and children (rho = 0.95; $p < 0.0005$).

In the study, endoscopy was not selected as the reference standard but the study groups were selected exclusively by visual MRE findings of CD. Lack of an endoscopic picture for comparison can be considered as a limitation of the study, but the possible incomplete correlation of the MR picture with the endoscopic picture should also be taken into account as the endoscopic visual image and the histopathological pattern of the endoscopically obtained tissue samples reflect changes in the intestinal mucosa, whereas the components that form the MR activity indices characterise changes not only in the intestinal mucosa, but also within the entire thickness of the intestinal wall. Both the literary data and our experience at the Children's Clinical University Hospital suggest situations in which intact intestinal mucosa is observed endoscopically in the case of active CD, while MRI examination reveals marked transmural inflammatory changes. However, literature provides a broad picture of the correlation not only between MRE and endoscopic findings, but also between

MRE and surgery specimens of resected intestinal segments with certain defined criteria, along with the conclusion that MRI is an informative and sufficiently accurate method to assess altered bowel walls in CD. Based on these observations, for several years now, when referring patients for MRE examinations, clinicians do not duplicate their results with the invasive endoscopy that is also cumbersome for patients. Consequently, in 2019, for the first time, the *ECCO-ESGAR* guidelines were introduced with a revolutionary statement that radiological cross-sectional imaging methods (and, therefore, MR) can be used as an alternative to endoscopy to assess CD activity (Maaser et al., 2019). Therefore, although CD had been endoscopically confirmed in all patients included in the study, the results of the MRE examination were not duplicated by the endoscopic and histopathological findings in any of cases. The correlation between histopathological and radiological scenes could best be reflected if a representative number of surgically resected intestinal segments were available. However, surgical resection with subsequent histopathological analysis of the specimen, which would provide the most complete picture of intestinal wall changes, was performed in only one patient.

Obtaining high quality and precisely interpretable DWI images requires a uniform magnetic field, very strong gradients and fast image capture, which is not possible with currently available MR equipment. The quality of DWI images is, therefore, lesser than that of conventional MR images, due to low resolution, noise, distortions, and limited morphological interpretability (Chilla et al., 2015). Opinions on reproducibility of ADC-DWI measurements used in the Clermont score varies among authors, and despite good to excellent repeatability reported from certain authors (Yu et al., 2019), contrary concerns on low reproducibility based on research data also exist (Watson et al., 2018). Due to equivocal data on repeatability of measurements that form the MaRIA and Clermont scores, our interest was to assess the repeatability of measurements contributing to both of

these indices, i.e., WSI-*pre*Gd and WSI-*post*GD forming RCE in MaRIA, ADC-DWI used in the Clermont score, as well as bowel thickness and estimation of presence of bowel ulcers, which are common to both MaRIA and Clermont scores.

In the study, the repeatability of both ADC-DWI_{SPIR} and ADC-DWIBS measurements performed by one observer at two-month intervals was good, as no statistically significant differences were found between the mean ADC-DWI_{SPIR} ($p = 0.65$) and *ADC-DWIBS* values ($p = 0.23$). In the case of ADC-DWI_{SPIR}, the differences between the mean values were only 1 %, while in the case of ADC-DWIBS – 4 %.

Several authors found poor repeatability of RCE measurements (Sharman A., Zealley, Bassett, P, Greenhalg R., and Taylor, 2009; Tielbeek et al., 2013). No statistically significant difference was found in WSI-*pre*Gd ($p = 0.06$) or in WSI-*post*Gd ($p = 0.57$) values used in the calculation of RCE. We believe that a strict definition of ROI size and accurate site-by-site WSI-*pre*Gd and *post*Gd measurement in the same bowel segment would result in good inter-observer agreement. It should, however, be noted that the results show high SD in both WSI-*pre*GD (*SD* = 127.57 for the first assessment and *SD* = 99.68 for the first assessment), and WSI *post*Gd measurements (*SD* = 235.35 for the first assessment and *SD* 212.9 for the second assessment), covering 66–78 % of the WSI values. The observations suggest that if WSI-*pre*Gd values were in the tens, the WSI-post Gd values would also be in the tens; if WSI-*pre*Gd values were in the hundreds, this would also be replicated in the WSI-post Gd values. This observation can be explained through individual tissue characteristics of patients, magnetic field inhomogeneity and linearity of gradients yielding wide distribution of WSI values. Detailed analysis of this finding, is however beyond the scope of our current research.

Tielbeek et al. reported moderate repeatability of bowel thickness measurements and excellent repeatability when the thickness measurements were performed by an experienced radiologist (Tielbeek et al., 2013). In the study, no statistically significant difference was found between the first and the second measurements. It should, however, be noted, that wall thickness differed within the same bowel segment, and the maximum thickness was always chosen for the calculations. However, identifying the same exact location of the maximum thickness was not often possible in DWI images due to their low spatial resolution. Similarly, in the pre- and post-contrast series, bowel thickness was always measured in the axial images, but pre- and post-T1 images were acquired in the coronal plane. Therefore, the ROI in these images was not always placed exactly at the site the intestinal wall thickness measurement was performed.

In the study, there was a systematic difference in the assessment of ulcers. The inconsistency of ulcer detection in the study could be associated with lack of strict consensus regarding standardised MR definition of an ulcer. Developers of the MaRIA index defined ulcers as deep depressions in the mucosal surface (Rimola et al., 2009). However, MRI reveals a wide range of ulcers. Even small aphthous ulcers can be seen in MRI images (Ram et al., 2016), and there is no clear definition of the size and appearance of ulcers that should be included in calculation of disease activity indices, or excluded from it. The rating of ulcers could be improved with a 3 T MR scanner, as this provides better spatial and temporal resolution. Literary data indicates that the resolution of 3T MR scanner in diagnosis of ulceration is superior compared to that of the 1.5T device (Fiorino et al., 2013).

It is considered that the strengths of both studies on assessment of ADC-DWI_{SPIR} and ADC-DWIBS values in patients with active CD were: 1) the prospective study design; 2) exact site-by-site comparison in the same bowel segment; 3) exact ROI size that was not defined in other studies on MaRIA and

Clermont scores, except the study conducted by Caruso's team (Caruso et al., 2014) performing measurements with *ROI* size between 12–20 mm^2. However, both studies also faced several limitations: 1) the relatively low number of participants in study groups; 2) patients included in the study were selected according to the visual diagnostic criteria described in the *ECCO-ESGAR* guidelines "Imaging techniques for the assessment of inflammatory bowel disease: Joint *ECCO* and *ESGAR* evidence-based consensus guidelines" (Panes et al., 2013) namely intestinal wall thickening, wall oedema and hyperenhancement following i/v administration of CA, but due to the limited availability of laboratory parameters in the group of adult patients, no correlation of visual finding with laboratory characteristics of disease activity was performed; 3) there was a possible sampling error in the study population, as both adult and paediatric groups were not homogeneous in terms of disease duration. This however, did not affect the repeatability assessment, as all measurements (intestinal wall thickness, WSI-*pre*Gd, WSI-*post*Gd, ADC- DWISPIR and ADC-DWIBS) and ulcer assessment were identical in both adults and children; 4) in both *post*Gd and DWI images, the ROIs were placed on the site of the maximum SI. After administration of gadolinium contrast media, in some cases the most intense contrast enhancement was predominantly observed in ileal mucosa; however, in other cases the enhancement was evenly distributed throughout the intestinal wall. In contrast, in both DWI techniques, bowel wall layers were indistinguishable as the diffusion restriction throughout the intestinal walls was equally intense, which could result in differences of positioning ROI between the T1 post-contrast and DWI sequences; 5) the MaRIA studies are based on a comparison of the visual image with the CDEIS (Crohn's Disease Endoscopic Index of Severity), CD endoscopic activity index in adult patients. Unlike in adults, the estimation of inflammatory activity in children does not rely on endoscopy findings due to its invasiveness, but rather on the Paediatric

Crohn's Disease Activity Index, and the correlation with MaRIA is weak to moderate (rho = 0.42, p = 0.016) (Rozendorn et al., 2018). Its correlation with the Clermont index has not yet been assessed, so the usefulness of the Clermont index for children remains unclear.

Conclusions

1. Compared to conventional DWI sequences, the DWIBS sequence has no advantages and it is inferior for quantitative assessment of bowel walls walls in patients without prior peroral preparation with osmotically active enteric CA. The use of ADC measurements in patients without prior bowel preparation is not appropriate for either DWI or DWIBS sequences.
2. Compared to conventional DWI sequences, DWIBS sequence has no advantages and it is inferior for quantitative assessment of CD activity in patients with already diagnosed disease in the terminal *ileum*. The use of ADC-DWIBS measurements for quantitative assessment of CD activity is not appropriate.
3. By defining a strict measurement standard ADC values of both conventional DWI and DWIBS values are well repeatable, which allows for the opportunity of providing reproducible and equally accurate measurement results in both of the investigated sequences.

Recommendations

1. Neither the conventional DWI, nor DWIBS sequence, has the potential for quantitative diagnostics of primary CD in patients without prior peroral intestinal tract preparation. Therefore, in the diagnosis of Crohn's disease, measurements of ADC values do not give grounds to abandon the preparation of the intestinal tract with a hyperosmolar oral contrast agent, regardless of the fat suppression technique used.
2. According to the results of the study, compared to the DWI sequence with spectrally selective fat signal suppression, the DWIBS sequence is less accurate and is not suitable for use in the Clermont index for quantitative evaluation of CD activity in either adults or children. The DWIBS sequence can only be used for qualitative visual identification of CD changes in the intestinal wall. The conventional DWI sequence remains the choice DWI sequence to be used in the Clermont score to evaluate the activity of CD localised in the terminal ileum.

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