Original Article

Effects of oral contrast agent on the viscoelastic properties of the terminal ileum investigated using magnetic resonance elastography

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Background: While standard clinical magnetic resonance (MR) enterography can detect inflammatory bowel disease, it is of limited value in deciding between medical versus surgical treatment. Alternatively, intestinal MR elastography has the potential to contribute additional information to therapeutic decision-making; however, the influence of bowel distension by oral contrast agent on viscoelastic tissue properties remains elusive. Therefore, we aimed to investigate the influence of oral contrast agent-induced bowel distension on the viscoelastic properties of the terminal ileum in healthy volunteers.

Methods: In this prospective pilot study, 20 healthy volunteers (33.2±8.2 years; 10 men, 10 women) underwent multifrequency MR elastography using a single-shot spin-echo echo planar imaging sequence at 1.5 Tesla and drive frequencies of 40, 50, 60 and 70 Hz. Maps of shear wave speed (c in ms^{-1}) and loss angle (φ in rad), representing stiffness and viscous properties, respectively, were generated using tomoelastography data processing. The volunteers were scanned before and after ingestion of 1,000 mL of 2% mannitol solution as oral contrast agent.

Results: There was no significant difference in terminal ileum biomechanical properties before *vs.* after ingestion of an oral contrast agent (mean c: 1.47±0.24 *vs.* 1.40±0.25 ms^{-1} with P=0.37; mean φ: 0.70±0.12 rad *vs.* 0.68±0.12 rad with P=0.61). Moreover, there was no statistically significant correlation between MR elastography parameters before and after the ingestion of oral contrast (c: r=0.22, P=0.36; φ: r=0.24, P=0.30).

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Conclusions: The results of this study suggest that bowel distension for intestinal MR elastography has no systematic effect on the biomechanical tissue properties of the terminal ileum determined by MR elastography. Therefore, future study protocols appear feasible with or without oral contrast agents.

Keywords: Magnetic resonance elastography (MR elastography); magnetic resonance enterography (MR enterography); inflammatory bowel disease (IBD); terminal ileum; intestine

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Introduction

Although standard magnetic resonance (MR) enterography has been established as a reliable method for the detection of inflammatory bowel disease (IBD), characterization of strictures for therapeutic decision-making remains limited (1-3). While predominantly inflammatory bowel strictures can still be treated with anti-inflammatory medication, predominantly fibrotic strictures require surgical or endoscopic treatment (1,2). Currently, the diagnosis of IBD is based on a combination of clinical, biochemical, histopathological, and imaging tests. Using MR enterography, the identification of active inflammation relies primarily on a qualitative interpretation of T2-weighted fat-saturated images, where high signal intensities are indicative edema. However, there is currently no reliable imaging technique to determine the degree of fibrosis (1,2). Histopathological evaluation of endoscopic biopsy specimens remains the diagnostic gold standard despite limitations such as heterogeneity-based sampling error, lack of biopsy depth, and superficial inspection of the mucosa. The replacement of invasive procedures by imaging biomarkers is warranted. Protocols for standard clinical MR enterography include the ingestion of 450–1,000 mL of a hyperosmolar oral contrast agent such as mannitol, polyethylene glycol, sorbitol or combinations thereof for bowel distention approximately 45 min prior to the magnetic resonance imaging (MRI) scan (2,4-7). It has been shown that insufficient bowel distension degrades diagnostic performance (8,9).

MR elastography is a noninvasive method for the biomechanical assessment of soft biological tissues (10,11). It has become established in routine clinical practice for the staging of hepatic fibrosis (12-16) while more recent work has demonstrated its sensitivity to hepatic inflammation (17-19). As a result of technical advances in the spatial resolution and noise robustness of elastograms, MR elastography has been increasingly used to study smaller organs such as the pancreas (20,21), prostate (22-24) or parotid glands (25). More recently, the feasibility of MR elastography of the intestine has been demonstrated (26-29). It has been shown that (I) IBD-related intestinal lesions have higher viscoelasticity than normal bowel, (II) MR elastography can detect intestinal fibrosis and predict disease outcome, and (III) intestinal MR elastography has demonstrated a good reproducibility (26,27).

Despite these initial efforts, the influence of bowel distension through oral contrast agents on the viscoelastic properties of the terminal ileum remains elusive. Bowel distension may have a systematic impact on the viscoelastic properties of IBD lesions and may influence the design and planning of future studies. Therefore, we conducted a study of healthy volunteers aimed at investigating the effect of bowel distension by performing MR elastography before and after ingestion of an oral contrast agent. We present this article in accordance with the TREND reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-101/rc).

Methods

Subjects

The presented study is not register in the clinical trial platform. This prospective single-center study was approved by the Institutional Review Board of the Charité – Universitätsmedizin Berlin (No. EA1/273/21) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All subjects provided written informed consent. A total of 20 healthy volunteers were studied between May 2022 and July 2022. Healthy volunteers with no history of abdominal surgery or bowel disease and at least 18 years of age were included. Exclusion criteria were bowel diseases as seen on MRI, fecal impaction, increased

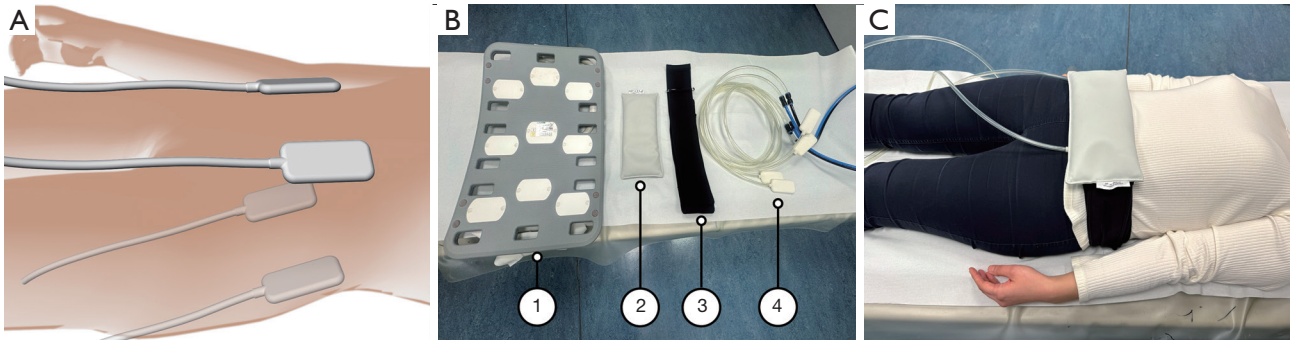

Figure 1 Magnetic resonance elastography driver setup. (A) Two drivers each were placed anteriorly and posteriorly around the lower abdomen. (B) Components: ① magnetic resonance imaging phased-array coil, ② sand-filled cushion, ③ driver belt, ④ four compressed-air drivers with hoses. (C) Placement of components.

peristalsis, and general MRI contraindications. Volunteers were fasted from solid foods for at least 4 hours prior to the examination to reduce bowel activity.

Protocols for MR elastography and MR enterography

Multifrequency MR elastography was performed as previously described in (26). Scans were acquired at 1.5 Tesla (Magnetom Aera, Siemens Healthineers, Erlangen, Germany) with mechanical drive frequencies of 40, 50, 60 and 70 Hz generated by 4 compressed-air drivers. Two drivers each were placed anteriorly and posteriorly around the lower abdomen as shown in *Figure 1*. The drivers were made of 3D-printed polyethylene terephthalate and were held in position using a custom-made belt. The wave transition of the anterior drivers was provided by a sand-filled cushion placed on top of the belt containing the drivers, but below the phased-array coil. A single-shot spin-echo echo-planar imaging sequence was used for 3D wave field acquisition (30). The volunteers breathed freely (31). MR elastography scan parameters were as follows: 25 axial slices, 8-time steps, 12 filter directions, 100×66 matrix, 3×3×5 mm^3 resolution, repetition time of 3,070 ms, echo time of 50 ms, total MR elastography scan time of 5:17 min. Moreover, conventional coronal and axial T2-weighted half-Fourier acquisition single-shot turbo spin-echo sequences were acquired to assess the distribution of the oral contrast agent within the gut and to ensure inclusion of the terminal ileum in the MR elastography scans. All volunteers were scanned twice with the same set of sequences: before and 45 min after the ingestion of 1,000 mL of a 2% mannitol solution as oral contrast agent. Care was taken to place volumes of interests (VOIs) in the same regions of the terminal ileum as representative areas on both scans. As we investigated volunteers solely for the purpose of this study, scans were performed without antispasmodic medication and without intravenous contrast agent. All images including the phase images, magnitude images, wave images and elastograms have been visually assessed by a board-certified radiologist to ensure adequate image quality. Technical success of an MR elastography scan was defined as visually perceptible bowel on the elastograms and bowel distension in the second scan acquired after ingestion of oral contrast.

Data processing

Maps of shear wave speed (c in ms^{-1}), as a representation of stiffness, and maps of loss angle (phase angle of the complex modulus, φ in rad), as a representation of viscous behavior, were generated using the abdominal tomoelastography pipeline with multifrequency processing (open access at https://bioqicapps.charite.de) (32-35). A board-certified radiologist (R.R.S., 5 years of experience in abdominal imaging) drew VOIs based on c-maps in conjunction with magnitude images using ITK-SNAP version 3.6.0 (36). Intestinal content was removed from the VOI using a shear wave speed threshold of 1 m/s, as liquids do not allow shear waves to propagate.

Statistical methods

Continuous variables and group values are reported as means and standard deviation. Groups were compared using a paired t-test. Pearson's correlation coefficient was calculated for MR elastography parameters before and after

Table 1 Individual subject data

No.	Age (years)	Gender	BMI (kg/m^2)	Before oral contrast				After oral contrast			
				c (m/s)	SD of *c* (m/s)	*φ* (rad)	SD of *φ* (rad)	*c* (m/s)	SD of *c* (m/s)	*φ* (rad)	SD of φ (rad)
1	33	M	23.5	1.43	0.29	0.84	0.34	1.05	0.14	0.47	0.10
2	32	W	18.7	1.12	0.16	0.53	0.16	1.04	0.16	0.52	0.12
3	32	M	21.7	1.71	0.51	0.71	0.20	1.19	0.23	0.68	0.20
4	31	W	24.6	1.24	0.25	0.71	0.20	1.77	0.51	0.91	0.33
5	29	W	24.4	1.71	0.26	0.85	0.20	1.48	0.34	0.76	0.25
6	32	M	25.5	1.46	0.23	0.66	0.18	1.62	0.50	0.82	0.25
7	31	M	24.8	1.71	0.37	0.85	0.20	1.65	0.33	0.90	0.21
8	24	W	21.1	1.87	0.46	0.87	0.24	1.53	0.33	0.63	0.17
9	31	M	23.9	1.21	0.28	0.71	0.23	1.39	0.40	0.68	0.28
10	36	M	25.5	1.57	0.32	0.58	0.14	1.51	0.30	0.62	0.15
11	33	W	22.8	1.95	0.43	0.87	0.29	1.36	0.23	0.74	0.18
12	33	M	25.9	1.38	0.34	0.76	0.32	1.09	0.18	0.62	0.15
13	33	M	23.9	1.39	0.28	0.70	0.18	1.26	0.27	0.65	0.19
14	27	M	23.1	1.61	0.43	0.68	0.29	1.19	0.28	0.58	0.17
15	32	M	27.2	1.10	0.22	0.59	0.18	1.24	0.25	0.59	0.15
16	29	W	20.0	1.33	0.25	0.63	0.19	1.25	0.18	0.59	0.13
17	33	W	22.3	1.20	0.22	0.50	0.14	1.21	0.19	0.68	0.19
18	39	W	22.9	1.37	0.31	0.57	0.20	1.77	0.44	0.61	0.18
19	27	W	19.1	1.40	0.26	0.55	0.15	1.78	0.37	0.78	0.21
20	66	W	24.8	1.65	0.40	0.82	0.30	1.63	0.37	0.75	0.23
Mean	33.15	N/A	23.28	1.47	0.31	0.70	0.22	1.40	0.30	0.68	0.19

BMI, body mass index; c, shear wave speed; φ, loss angle; SD, standard deviation; M, man; W, woman; N/A, not applicable.

the ingestion of oral contrast and in relation to age and body mass index (BMI). The significance level was set to 5%. Statistical analysis was performed in Rstudio (R version 4.2.2; R-Foundation, Vienna, Austria) and Matlab (version R2021b; The Mathworks, Inc., Natick, Massachusetts, USA).

Results

In all 20 healthy volunteers (10 men and 10 women), scans were successfully performed without technical failure such as insufficient shear wave amplitudes or apparent breathing-induced motion artifacts both before and after ingestion of oral contrast agent. Individual subject data are shown in *Table 1*. The volunteers had a mean age of 33.2±8.2 years and mean BMI of 23.3±2.2 kg/m^2. Representative viscoelastic maps and conventional MR images are shown in *Figure 2*. There was no statistically significant correlation between MR elastography parameters of the terminal ileum before *vs.* after oral contrast ingestion (*c*: r=0.22, P=0.36; φ: r=0.24, P=0.30). A strong significant correlation was found between *c* and φ before the ingestion of oral contrast (r=0.72, P=0.0004) and after the ingestion of oral contrast (r=0.72, P=0.0004). The mean VOI was 21.25±12.09 cm^3. There was no statistically significant difference in mean VOI before *vs.* after the ingestion of oral contrast (mean VOI before: 18.0 cm^3 *vs.* mean VOI after: 24.5 cm^3; P=0.08). Moreover, a Pearson correlation analysis between the MRE parameters (*c* and φ) and VOI for combined values of both before and after oral contrast showed no significant correlation (*c*: r=–0.12, P=0.45; φ: r=–0.15, P=0.37). For

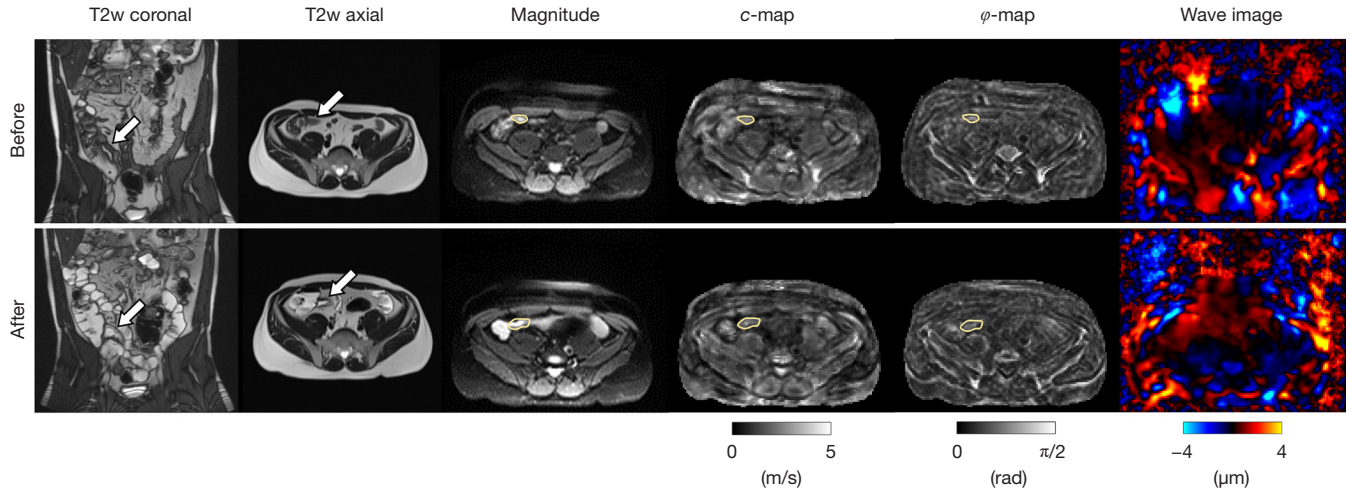

Figure 2 Representative case for illustration. A healthy 31-year-old man before and after ingestion of 1,000 mL of 2% mannitol solution as an oral contrast agent. Before oral contrast (upper row): shear wave speed (c) of 1.21±0.28 m/s and loss angle (φ) of 0.71±0.23 rad. After oral contrast (lower row): c of 1.39±0.40 m/s and φ of 0.68±0.28 rad. The white arrows indicate the terminal ileum on coronal and axial T2w images. Regions of interest are encircled by golden lines on magnitude images, c- and φ-maps. Waves images show the displacement in and out of the axial plane. T2w, T2-weighted.

mean c and φ, there was no significant difference before *vs.* after the ingestion of an oral contrast agent for the terminal ileum (mean c: 1.47±0.24 *vs.* 1.40±0.25 ms^{-1} with P=0.32; mean φ: 0.70±0.12 rad *vs.* 0.68±0.12 rad with P=0.55). Corresponding boxplots are shown in *Figure 3*. No significant correlation was found between MR elastography parameters (c and φ) and age (before oral contrast: P=0.64 and 0.58; after oral contrast: P=0.65 and 0.53; respectively), and between MR elastography parameters (c and φ) and BMI (before oral contrast: P=0.92 and 0.32; after oral contrast: P=0.45 and 0.24; respectively).

Discussion

The results of this pilot study suggest that bowel distension for MR enterography has no systematic effect on biomechanical tissue properties of the terminal ileum in healthy volunteers. Moreover, no dependency of MR elastography parameters on age or BMI was found.

Our results show that some subjects show an increase, and some subjects show a decrease in viscoelastic parameters. Meanwhile, a previous study has demonstrated a good reproducibility of this particular multifrequency MR elastography setup to study the intestine without the use of oral contrast (26). For example, they showed that 5 hourly repeated scans without oral contrast resulted in a low intra-individual standard deviation for both shear wave speed (1.05±0.03 m/s) and φ (0.57±0.03 rad). The unchanged strong significant correlation between c and φ before and after the ingestion of oral contrast in our study further confirms the consistency of the method. Considering these pieces of information, a possible explanation could be an oral contrast-related aggravated bowel movement, especially without the use of antispasmodic medication such as butylscopolamine. From a subjective point of view, this increased intestinal movement has also been observed by the volunteers after the ingestion of oral contrast—the most common side effect of oral contrast is diarrhea. In the context of a pilot study, we refrained from administering intramuscular or intravenous antispasmodic medication for ethical reasons. Nevertheless, it may be advisable to include antispasmodic medication in future study protocols to reduce this effect. Furthermore, only healthy subjects have been investigated in this pilot study. IBD patients may have different physiological reactions to the oral contrast agent that could potentially alter viscoelastic properties and not be observed in healthy volunteers. Moreover, a non-significant trend of slightly increased mean VOI after oral contrast was observed. This trend may be due to bowel distention associated with oral contrast. At the same time, a distension-related thinning of the bowel wall could also be hypothesized. This could be further investigated in future

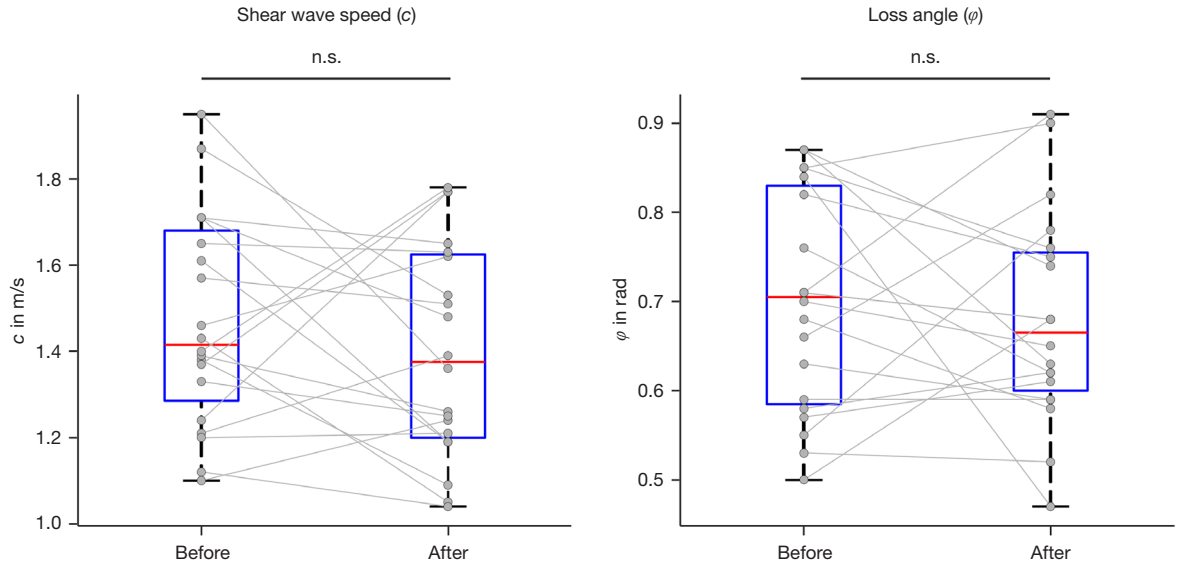

Figure 3 Boxplots displaying median, upper, and lower quartiles of shear wave speed (*c*) and loss angle (φ) for the terminal ileum before and after oral contrast agent ingestion. n.s., not significant.

studies.

Recently, a few studies have investigated the application of MR elastography in IBD. For instance, Reiter *et al.* have demonstrated the feasibility of intestinal MR elastography, showing that the method allows discrimination between healthy volunteers and patients with IBD with an excellent diagnostic performance (area under the receiver operating characteristic curve of 0.90) (26). Moreover, a good interreader agreement was found for MRE parameters investigating volunteers and IBD patients using the same technical setup (intraclass correlation coefficient of 0.78 for shear wave speed, and 0.61 for φ) (26). However, neither healthy volunteers nor patients received oral contrast agents or antispasmodic medications. Avila *et al.* have shown that bowel stiffness correlates with the degree of fibrosis in Crohn's disease and is associated with a higher risk of clinical events (27). All patients drank 1 l of mannitol solution 45 min prior to scanning. Investigating diffusion-weighted imaging, Apine *et al.* found apparent diffusion coefficients to be statistically significantly lower (ranging from 38–48%) in nonprepared bowel compared to prepared bowel in IBD patients (37). Moreover, van Schelt *et al.* reported fibrotic disease involvement of mesenteric adipose tissue in Crohn's disease (38). Standard clinical MR enterography has been investigated in many studies, and several scoring systems for assessing disease activity such as the Magnetic Resonance Index of Activity (39) or the Acute Inflammation Score have been proposed (40-42). These scores are primarily used in the setting of studies and were developed and validated using oral contrast agents, emphasizing the need to study their effect on biomechanical tissue properties of the gut.

Limitations

First, only a small number of subjects were enrolled in this pilot study. Second, for ethical reasons, healthy volunteers were not given any antispasmodic medication. Therefore, the viscoelastic parameters we determined may have been influenced by normal bowel activity. To mitigate this limitation of the study, we ensured that (I) all subjects abstained from solid food for at least 4 hours prior to the examination, (II) that the scan after oral contrast was consistently performed after 45 min with consistent amounts of 1,000 mL mannitol solution as recommended by the current ECCO-ESGAR guideline for diagnostic assessment in IBD (1,2), and (III) that VOIs of the terminal ileum were drawn on the same scan. Third, no breath-holding and no post-processing motion correction was applied. However, each slice of an elastogram in our study was an average of a total of 384 images (4 drive frequencies × 8-time steps × 12 filter directions). This large number of averages improves image quality by reducing the effect of outliers, thereby reducing motion artifacts, as described previously (31).

Furthermore, this is also the reason for the high anatomical resolution, which allows the visual perception of small organs such as the intestine on elastograms without the need to superimpose anatomical images. Finally, despite recent advances in the spatial resolution and noise robustness of elastograms, regions of interest were smaller in healthy subjects with a wall thickness of approximately 1–3 mm compared to IBD patients with increased wall thickness >3 mm (41). To reduce this technical limitation, we evaluated the intestinal wall on multiple slices (VOI).

Conclusions

This study suggests that bowel distension in MR elastography has no systematic effect on viscoelastic tissue properties of the terminal ileum in healthy volunteers. Therefore, future study protocols appear feasible with or without oral contrast agents. Our data provide a basis for the planning of future studies and encourage further investigation of the mechanical properties of the bowel and IBD.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-101/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-101/coif). B.S., A.A.K., B.H., J.B., I.S., and R.R. report that this study was funded by the German Research Foundation. B.H. is Grant recipient from Abbott, AbbVie, Ablative Solutions, Accovion, Achogen Inc., Actelion Pharmaceuticals, ADIR, Aesculap, Agios Pharmaceuticals, INC., AGO, Arbeitsgemeinschaft industrieller Forschungsvereinigungen, Arbeitsgemeinschaft internistische Onkologie, Aktionsbündnis Partnersicherheit e.V., Alexion Pharmaceuticals, Amgen, AO Foundation, Aravive, Arena Pharmaceuticals, ARMO Biosciences, Inc., Array Biopharma Inc., Art photonics GmbH Berlin, ASAS, Ascelia Pharma AB, Ascendis, Advanced sleep research, Astrellas, AstraZeneca, August Research OOF, Sofia, BG, BARD, Basiliea, Bayer Healthcare, Bayer Schering Pharma, Bayer Vital, BBraun, BerGenBioASA, Berlin-Brandenburger Centrum für regenerative Therapie, Berliner Krebsgesellschaft, Biontech Mainz, BioNTech SE, Biotronik, Bioven, BMBF, BMS, Boehring Ingelheimer, Boston Biomedical Inc., Boston Scientific Medizintechnik GmbH, BRACCO Group, Brahms GmbH, Brainsgate, Bistol-Myers Squibb, Calithera Biosciences UK, Cantargia AB, Medicon Village, Cascadian Therapeutics, Inc., Celgene, CELLACT Pharma, Celldex Therapeutics, Cellestia Biotech AG CH, CeloNova BioSciences, and Charité research organization GmbH. B.S. has served as consultant for Abbvie, Abivax, BMS, Boehringer, CED Service GmbH, Endpoint Health, Falk, Galapagos, Janssen, Lilly, Pfizer, Takeda, and Predictimmune; he received speaker fees from: AbbVie, BMS, CED Service GmbH, Falk, Ferring, Galapagos, Janssen, Lilly, Materia Prima, Takeda, Pfizer and grant support by Arena/Pfizer (served as representative of the Charité). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Review Board of the Charité – Universitätsmedizin Berlin (No. EA1/273/21) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All subjects provided written informed consent.

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