Characterising oesophageal motility disorders by high-resolution impedance manometry in dermatomyositis patients

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Abstract

Objective

We studied high-resolution impedance manometry (HRiM) findings in dermatomyositis (DM) to detect oesophageal dysmotility, even in asymptomatic patients, and correlated the alterations to clinical and serological disease domains.

Methods

We performed a cross-sectional study of DM patients, enrolled between December 2021 and December 2022. All patients underwent rheumatological, laboratory and HRiM assessment. HRiM findings were compared with different clinical and serological profiles.

Results

The study population consisted of 15 DM patients (13 women and 2 men, age 54±15.2 years). The mean disease duration was 6.6 years. According to HRiM findings, three different groups of oesophageal disease severity were identified (in order of severity G0, G1 and G>1, 5 patients per group). G>1 group was significantly associated with MDA5 antibodies (80% vs. 20%, $p<0.05$). Interstitial lung disease (ILD) did not show any significant association with HRiM findings. However, a diffusing lung capacity for carbon oxide (DLCO) < 80% was present in 100% of G>1 ($p<0.05$). No associations between dysphagia, creatine kinase (CK) level, muscle weakness, skin, articular involvement and treatment were found.

Conclusions

Oesophageal involvement is frequent and should be evaluated in the comprehensive work-up of DM. We used for the first time HRiM in DM, which proved to be an accurate and objective technique in assessing oesophageal disease, even in the subclinical stage. Interestingly, the MDA5-positive group had a higher burden of HRiM pathological findings, suggesting a greater severity of oesophageal involvement, often asymptomatic.

Key words

anti-MDA5, dermatomyositis, dysphagia, oesophageal involvement, high-resolution impedance manometry

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Introduction

Dermatomyositis (DM) belong to the idiopathic inflammatory myopathies (IIM) spectrum and are autoimmune diseases characterised by variable skin, muscle, joint, lung, and gastrointestinal involvement (1). Specifically, oesophageal involvement is common in IIM, with dysphagia being a frequent, often early, symptom in DM, reported by 18-54% of DM patients (2, 3).

Dysphagia may result from the inflammation of the striated muscle that constitutes the first part of the gastrointestinal tract, namely the oropharynx and the upper third of the oesophagus (4, 5). Notably, an altered function of the lower part of the oesophagus, where only smooth muscle fibres are found, has even been described in IIM making this complication more complex than expected (6, 7), and mirroring the oesophageal involvement found in systemic sclerosis (SSc) (8).

Suggested risk factors for oesophageal dysmotility in DM are older age, male gender, muscle weakness, and malignancy (9). The association between autoantibodies and dysphagia remains unclear, however it has been recently pointed out a possible association with anti-TIF1-γ antibody presence (10).

Clinical features of dysphagia include swallowing impairment, regurgitation, nasal speech, hoarseness, malnutrition, dehydration and aspiration with subsequent possible pneumonia. Patients experience a deeply decay in quality of life and present a poor prognosis, with a 1-year mortality rate of 31% (11).

The treatment of oesophageal dysmotility is challenging and encompasses pharmacological and non-pharmacological options. High dose glucocorticoids (GC) are the cornerstone of treatment and in case of refractory or severe disease intravenous immunoglobulins (IVIg) can be used, as well as other immunosuppressive agents (12, 13). Beside drugs, rehabilitation exercises and diet modification can help in controlling dysphagia (14, 15); while in intractable dysphagia surgical procedures, including cricopharyngeal or oesophageal dilation, cricopharyngeal myotomy and botulinum injections may be considered as rescue treatments (9).

Considering the difficult management and the deep impact on quality of life of dysphagia, a prompt diagnosis is of foremost importance. To date, the evaluation of oesophageal dysmotility was mainly performed by videofluoroscopic swallowing study that has the disadvantage of radiation exposure for patients (16).

In the last few years, the high-resolution impedance manometry (HRiM), an evolution of the classical high-resolution manometry (HRM), has emerged as a valuable tool to explore oesophageal motility and has already been applied to rheumatic diseases with promising results (17). This technique assesses oesophageal motility with a topography plotting that incorporates impedance and manometry sensors, providing information on oesophageal peristaltic patterns and pressures, empowering the diagnostic accuracy of the exam (18, 19).

HRiM is a safe, feasible and repeatable exam that can help the rapid detection of oesophageal dysmotility in order to optimize patient treatment and prevent complications. Moreover, constant reassessment may be useful during follow-up to evaluate treatment efficacy and subclinical relapses.

To the best of our knowledge, no studies have so far investigated oesophageal involvement in DM by HRiM. Thus, the aim of the present study is to evaluate, for the first time, oesophageal dysmotility related to DM by the use of HRiM.

Materials and methods

Patients

From December 2021 to December 2022, 15 consecutive patients (13 females, 2 males, age 53±15.2 years) admitted to the Myositis Clinic of our Rheumatology Unit with a diagnosis of DM, fulfilling the classification criteria (20), were enrolled in our cross-sectional study.

A complete rheumatological assessment was performed before the HRiM and the associations between HRiM parameters, serological and clinical features were analysed.

Patients were characterised for clinical involvement at the time of the procedure (oesophageal, muscle, skin, joint, lung involvement). The presence of dysphagia was investigated by screening questions: "Does food get stuck in

your throat? Do you have to swallow repeatedly in order to get rid of food?" (21). Interstitial lung disease (ILD) was established using a multidisciplinary approach that combined clinical and imaging data. Autoantibody profile (myositis-specific and -associated autoantibodies), creatine kinase (CK), diffusing lung capacity for carbon oxide (DLCO) collected closest to the time of the procedure were retrospectively analysed. Data on treatments (GC and immunosuppressive agents) were also recorded (Table I).

HRiM

All DM patients underwent HRiM after >8 hours fasting. All drugs that could interfere with oesophageal motility were discontinued. The HRiM probe (ManoScan 360, Given Imaging Ltd) is equipped with a 36 intraluminal solid-state pressure transducers which interact directly with the recorder, returning the pressure information relating to the motility of the entire oesophagus in a single trace; and five impedance sensors to measure the movement of the bolus in relation to the recorded oesophageal motility. The HRM trace is visualised on the monitor as a colour map in which the warm colours correspond to the high pressures and the cold colours to the low pressures, represented in a path that flows on the temporal plane. The impedance signal is shown on the monitor as a purple area superimposed on the pressure trace.

After proper pressure calibration and thermal compensation, the catheter is introduced through the nostril, after administration of a local anaesthetic spray. Patients are then placed in supine position, with the catheter taped to the nose. Once the gastric cavity has been reached, verifying on the monitor that the upper oesophageal sphincter (UES) and lower oesophageal sphincter (LES) have been clearly identified, the basal pressure of the sphincters is recorded during a 30-second time window without swallowing. Subsequently, 10 boluses of 5cc of physiological saline solution (0.3% saline) are administered to the patient, inviting the patient to perform a single swallow per administered bolus. In accordance with the version of the Chicago Classification 4.0 (19), in case of suspicion of Esophago-gastric Junction Outflow Obstruction (EGJOO), swallows must be performed in two positions, both supine and sitting.

Once the study is finished, the probe is removed and the trace analysis phase begins (ManoView ESO 3.3 analysis software): basal pressure and residual sphincter pressure are analysed for both upper and lower sphincters; on the oesophageal body, distal latency (DL), distal contractile integral (DCI), percentage of peristaltic waves, simultaneous, unsuccessful, fragmented, weak and/or ineffective waves are evaluated.

Oesophageal motility was classified according to the latest version of the Chicago Classification 4.0 (19). By the impedance sensors, the percentage of waves with incomplete bolus clearance and bolus transit time in seconds were evaluated.

Ethics

The study was approved by the Ethics Committee of the Azienda Universitaria Ospedaliera Policlinico "Paolo Giaccone" of Palermo (verb. 02/28.02 Ethics Committee Palermo 1). Written informed consent was obtained from all patients. Before analysis, patient data were anonymised and deidentified. The procedures for this study were conducted in accordance with the Declaration of Helsinki and the Ethics Guidelines.

Statistical analysis

Dichotomous variables were expressed as percentages and absolute frequencies, while continuous parameters were expressed as mean [standard deviation (SD)], as appropriate. Univariate comparisons between groups were made using the Student t-test for continuous variables and Fisher exact tests or chi-squared tests for categorical variables. For three or more groups, we applied the one-way ANOVA. Statistical analyses were performed with Stata v.16 following the recommendations of the STROBE statement to report the results of observational studies (22). A p-value <0.05 was considered statistically significant.

Table I. Demographic, clinical, serological and imaging characteristics of DM patients.

	DM (n=15)
Mean age, years (range)	54.3 (26-71)
Female sex, n (%)	13 (86.6%)
Disease duration, months (range)	80.2 (3-204)
Synovitis, n (%)	3 (20%)
Dysphagia, n (%)	10 (66.6%)
ILD, n (%)	8 (53.8%)
Raynaud's phenomenon, n (%)	12 (80%)
Ulcers, n (%)	5 (33.3%)
Active skin involvement, n (%)	8 (53.3%)
Muscle weakness, n (%)	8 (53.3%)
Autoantibodies	
ANA	15 (100%)
Anti-Mi2	5 (33.3%)
Anti-MDA5	6 (40%)
Anti-Ro52	6 (40%)
Anti-Ku	2 (13.3%)
Anti-NXP2	1 (6,6%)
CK IU/L, mean (range)	90.2 (24-388)
DLCO <80% predicted (%)	75
Therapies	
Glucocorticoids (%)	60
Methotrexate (%)	33.3
Mycophenolate mofetil (%)	33.3
Azathioprine (%)	13.3
Rituximab (%)	20
IVIg (%)	20

DM: dermatomyositis; ANA: anti-nuclear antibodies; CK: creatine kinase; DLCO: diffusing capacity of the lung for carbon monoxide; IVIg: intravenous immunoglobulins.

Results

Demographic, clinical, radiological and functional features of DM patients

The study population consisted of 15 patients diagnosed with DM (13 women and 2 men; age 54±15.2 years). The mean disease duration was 6.6 years from the onset of the first DM symptoms. Dysphagia was reported by 10 patients, while 5 patients did not report any oesophageal complain.

At the time of the procedure, muscle weakness was reported by 8 (53.3%) patients, with mean CK level of 90.2 IU/L. ILD (investigated by lung high-resolution computed tomography (HRCT)) was detected in 8 patients (53.8%) and a DLCO <80% of predicted was found in 75% of patients. Active skin involvement, Raynaud's phenomenon and ulcers were detected in 8 (53.3%), 12 (80%) and 5 (%) patients, respectively. Synovitis was documented in only 3 patients (20%).

All patients were ANA positive, 5 (33.3%) were anti-Mi2, 6 (40%) anti-

MDA5, 6 (40%) anti-Ro52, 2 (13.3%) anti-Ku and 1 (6.6%) anti-NXP2.
All but 3 patients received therapy with disease modifying anti-rheumatic drugs (DMARDs): methotrexate (33.3%), mycophenolate mofetil (33.3%), azathioprine (13.3%), rituximab (20%). IVIg were also administered (20%) and more than half of the patients were taking GC (60%). Detailed patient features are given in Table I.

HRiM findings identify different groups of oesophageal involvement severity in DM and associate with serological features of patients

HRiM findings were categorised into three main groups of alterations belonging to the manometric domain, the impedance domain or satisfying the pathological definitions of the Chicago v4.0 classification. Accordingly, we defined three groups of patients: i) patients presenting no HRiM abnormalities in the three domains (G0); ii) patients presenting alterations in only one of the three above described domains (G1), and iii) patients with alterations within at least two domains (G>1).
Considering such division, when analysing our data we found that each group presented five patients, so 10 patients showed at least one altered domain in oesophageal function.
G>1 group was significantly associated with MDA5 antibodies, as 80% of patients in such group were MDA5 positive (*vs*. 20% in the two other groups, respectively, $p<0.05$). In the same group, we did not find any patient positive for Mi2 antibodies, that were 2 and 3 in G0 and G1, respectively. Ro52 antibodies were equally found in the three groups (2 patients per group), while Ku and NXP2 were positive in 1 patient belonging to G0 and in 1 belonging to G1, respectively.
ILD did not show any significant association with HRiM findings. However, a DLCO <80% was present in 100% of patients belonging to the G>1 group ($p<0.05$).
Interestingly, dysphagia did not associate with any of the group of oesophageal involvement according to HRiM alterations, even if the five patients in the G0 were all complaining for it.

Table II. Clinical, functional and serological features in the different HRiM groups.

	No pathological HRiM domain (G0) (n=5)	1 pathological HRiM domain (G1) (n=5)	>1 pathological HRiM domains (G>1) (n=5)
Anti-Mi2	2 (40%)	3 (60%)	0 (0%)*
Anti-MDA5	1 (20%)	1 (20%)	4 (80%)*
Anti-Ro52	2 (40%)	2 (40%)	2 (40%)
Anti-Ku	1 (20%)	0 (0%)	1 (20%)
Anti-NXP2	0 (0%)	1 (20%)	0 (0%)
High CK	0 (0%)	0 (0%)	1 (20%)
DLCO < 80% predicted	1 (20%)	3 (60%)	5 (100%)*
ILD	2 (40%)	3 (60%)	3 (60%)
Dysphagia	5 (100%)	3 (60%)	2 (40%)
Synovitis	1 (20%)	1 (20%)	1 (20%)
Active skin involvement	3 (60%)	2 (40%)	3 (60%)
Raynaud's phenomenon	4 (80%)	4 (80%)	4 (80%)
Ulcers	2 (40%)	2 (40%)	2 (40%)
Muscle weakness	3 (60%)	2 (40%)	3 (60%)
Prednisone	4 (80%)	2 (40%)	3 (60%)
csDMARDs	2 (40%)	5 (100%)	4 (80%)
Rituximab	1 (20%)	2 (40%)	0 (0%)
IVIg	0 (0%)	2 (40%)	1 (20%)

*$p<0.05$
HRiM: high-resolution impedance manometry; CK: creatine kinase; DLCO: diffusing capacity of the lung for carbon monoxide; ILD: interstitial lung disease; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; IVIg: intravenous immunoglobulins.

No significant associations were found between peripheral muscle involvement, considering both an increase in CK level and muscle weakness, skin involvement, articular involvement and treatment at the moment of HRiM examination (Table II).
When considering the two pathological groups, G1 and G>1, we found significant differences in several domain analysed (Fig. 1). Specifically, for the manometric pattern, high UES pressure was retrieved in 4 *vs*. 2 patients, $p<0.05$, in the G>1 *vs*. G1. For the impedance domain, the G>1 group presented incomplete bolus clearance in 100% of patients ($p<0.05$). Regarding the Chicago v.4.0 classification, we found absent contractility (2 patients) and ineffective oesophageal motility (IEM) (4 patients, $p<0.05$) only in the G>1 group. On the other hand, in the G1 group, 2 patients presented distal oesophageal spasm as the only oesophageal peristalsis disorder retrieved.
No differences in other manometric, impedance features or Chicago v4.0 classification definitions were found.

HRiM findings in DM patients stratified for serological domains

DM patients were stratified according to their serological profile into two groups: anti-MDA5 positive group (6 patients) and anti-MDA5 negative group (9 patients).
We then analysed the 3 pathological HRiM domains described above in the two different serological groups. High UES pressure was observed in 83% of MDA5 positive group compared with 0% of MDA5 negative group ($p<0.05$). In contrast, there were no findings of low UES pressure in both groups.
According to the definitions of the Chicago Classification v4.0, absent contractility and IEM were prevalent in MDA5 positive patients (33.3% vs 0% and 50% vs 11.1%, respectively). Distal oesophageal spasm was described in 22.2% of MDA5 negative patients and in none of MDA5 positive patients. Hypercontractile oesophagus was not observed in any patient. Regarding impedance assessment, incomplete bolus clearance was higher in the MDA5 positive group (66%) than in the MDA5 negative group (22.2%) (Table III).

Discussion

In the present study, we applied, for the first time, HRiM to assess oesophageal function in DM patients. We investigated the prevalence and the features of HRiM abnormalities and associated

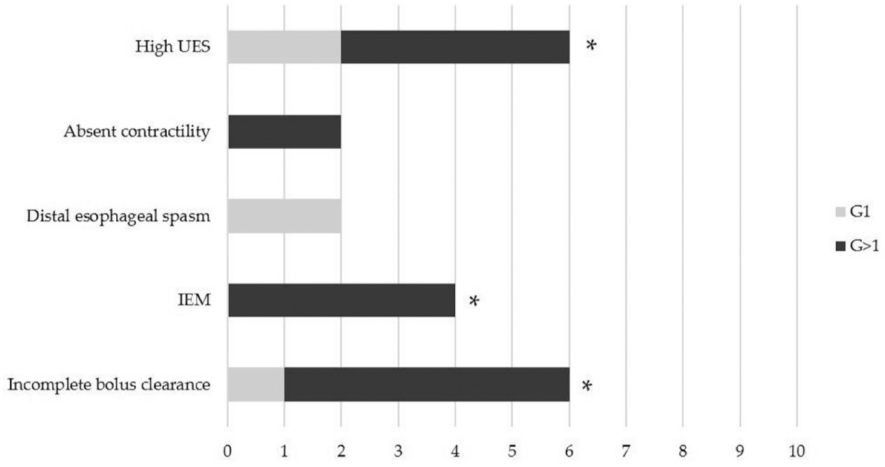

Fig. 1. Pathological features in the HRiM groups. Altered HRiM findings in the DM groups showing at least 1 alteration in one HRiM domain. Statistically significant differences were evidenced for high UES, IEM and incomplete bolus clearance between patients belonging to group G1 and G>1 (one or more than one domain affected).
DM: dermatomyositis; HRiM: high-resolution impedance manometry; IEM: ineffective oesophageal motility; UES: upper oesophageal sphincter.
*p<0.05.

Table III. HRiM features, Chicago classification v4.0 by serological groups.

	Anti-MDA5 positive (n=6)	Anti-MDA5 negative (n=9)
DCI (mmHg/cm/s)	658.9 (0-1878)	1531 (264-4144)
IRP (mmHg)	7.3 (1.6-13.5)	12.4 (5.9-21.1)
DL (s)	5.5 (5-6)	6 (2.5-8.5)
LES pressure (mmHg)	25.3 (8.2-37.4)	34.6 (13.5-66.1)
UES pressure (mmHg)	149.3 (101-274)*	67.7 (48.7-112)
Low LES (%)	16.6	0
High LES (%)	0	22.2
Low UES (%)	0	0
High UES (%)	83.3*	0
Chicago Classification v4.0		
Normal oesophageal motility (%)	50	66.6
Disorders of Peristalsis		
Absent contractility (%)	33.3	0
Distal oesophageal spasm (%)	0	22.2
Hypercontractile oesophagus (%)	0	0
IEM (%)	50	11.1
Disorders of EGJ Outflow		
Achalasia type I, II, III (%)	0	0
EGJ OO (%)	0	0
Altered Bolus flow time (%)	16.6	11.1
Incomplete bolus clearance (%)	66.6	22.2

*p<0.05
HRiM: high-resolution impedance manometry; DCI: distal contractile integral; IRP: integrated relaxation pressure; DL: distance contractile latency; LES: lower oesophageal sphincter; UES: upper oesophageal sphincter; IEM: ineffective oesophageal motility; EGJ: esophagogastric junction; EGJ OO: esophagogastric junction outflow obstruction.

HRiM results with clinical and serological parameters.

First, we demonstrated that DM patients show a high prevalence of oesophageal involvement evidenced by HRiM, even though in a previous report oesophagus disease seemed to be predominant in polymyositis (PM) (23). In addition, HRiM was able to detect alterations in asymptomatic patients, confirming previous data obtained with other techniques (24), underlining that clinical evaluation of oesophageal involvement is not sufficient. Moreover, in 1/3 of patients complaining dysphagia no HRiM alterations were detected, meaning that investigating only symptoms may be misleading in the global evaluation of DM. In particular, the availability of objective assessment of oesophageal disease, as guaranteed by HRiM, may help clinicians in promptly change treatment and in intensifying the follow-up schedule to prevent worsening of upper gastrointestinal tract involvement. The superiority of HRiM was already demonstrated in SSc patients asymptomatic for oesophageal disorders (17), confirming that, even in DM, HRiM could reveal subclinical disease and avoid the overestimation of subjective symptoms.

Our findings clearly point out that the striated component of the oesophagus, comprising the first third of the whole organ, is the main target of disease in DM. In this regard, we found an increase in UES pressure values in the majority of our patients, 6 out of 10, with patients showing a significant increase of such parameter when a stronger burden of alterations, involving both the manometric and impedance domains, was present. This finding is apparently in contrast with what already reported in literature, as damage to the UES is usually related to a decrease in its pressure, as described in PM. However, in our cohort, including only DM patients, the evidence of higher UES pressures seems specific of the MDA5 group, and no previous reports have been published so far. A possible explanation could reside in the fibrotic evolution of striated muscle (24) resulting from a chronic exposure to inflammation and microvascular insults, maybe specific of MDA5 positive DM. To date, no histological study to document oesophageal involvement in MDA5-DM are available to confirm this hypothesis. The absence of LES alterations could be consistent with the absence of antisynthetase syndrome (ASS) in our cohort, notably associated with pathological LES involvement (23).

We did not detect any significant association with clinical characteristics of patients and HRiM abnormalities, except for DLCO. DLCO was decreased in all patients presenting at least two altered

domains in HRiM. Moreover, an ILD pattern was documented in the majority of patients showing a pathological exam (6/10 patients), confirming that in IIM a correlation with ILD severity and HRM finding is present (23). Interestingly, a correlation between HRiM abnormalities and lung disease, comprising both ILD and DLCO reduction, was outlined in SSc, suggesting that oesophageal dysfunction may promote lung disease progression via chronic gastroesophageal reflux and acid microaspiration (17).

In recent years, the diagnosis of IIM has been implemented with the detection of autoantibodies specific or associated to disease, which often correlate with peculiar clinic and histological features. In this regard, knowing the scenario related to the serological status may be important to drive IIM management. In our study we were able to define a cluster of DM, positive for MDA5, that showed specific HRiM alterations. Specifically, the presence of a higher number of HRiM abnormalities was more probable for MDA5 positive patients, possibly underlining a more severe oesophageal involvement, that was in most cases subclinical. MDA5 pattern could be very puzzling and heterogeneous (25) and the development of severe complications, especially rapidly progressive ILD and skin disease, are renown to worsen the clinical course of MDA5-DM. No data on oesophageal disorders are known, so we outline for the first time a possible specific HRiM pattern for MDA5-DM, characterized b y high UES pressure. Our cohort of MDA5 was characterised by a short duration of disease, oesophageal alterations could then be an early sign of disease and should be carefully assessed. Follow-up study by HRiM would be very important to better dissect the evolution of such patients. On the other hand, another subgroup of patients, Mi2 positive, were the only ones showing distal oesophageal spasm, even in this case our findings are a first report, and the number of patients is very low to draw conclusions. Despite that, the result is intriguing as we can speculate that distal oesophageal spasm may be a feature of Mi2-DM, with a shared pathophysiology of the two conditions or a relation of such finding to the inflammatory status characterizing Mi2 patients, renown to present severe muscle involvement (26).

One of the main advantages of HRiM is the inclusion of impedance parameters in the analysis, in our cohort incomplete bolus clearance was evident in 60% of patients with an altered exam, thus corroborating HRM findings. In particular, impedance was pathological in all patients showing a higher burden of oesophageal motility alterations, confirming its accuracy in detecting dysmotility and in empowering HRM diagnostic accuracy (27).

Interestingly, we did not find any association between oesophageal dysmotility and therapies. Importantly, none of our patients experienced severe dysphagia. In line with published data, dysphagia is still one of the more difficult manifestations to treat. No current guidelines nor definitive recommendations from clinical trials are available. The evidence of good response to GC and IVIg is mainly derived from reports and clinical experience. No studies have characterised the response to treatment in DM by HRiM and this will be a future point to address in research.

This study must be regarded as exploratory with some limitations. First, the cohort, even if DM is a rare disease, is small and some analysis could then have been underpowered. Second, no follow up exams were performed, the study is cross-sectional and only describes the presence and the features of oesophageal disorders in our patients, without demonstrating causality or evolution of the encountered pattern. The cohort included heterogeneous patients in terms of disease duration, serological status, and treatment that could have induced further bias in our analysis. Finally, laboratory and imaging data were obtained, in some cases, considerably far away from the date of the HRiM and could explain why there was no significant association between HRiM findings and laboratory parameters or ILD. Only dysphagia was investigated at the same time of HRiM study.

In conclusion, our study demonstrated that oesophageal involvement is frequent in DM and should be explored with an accurate, objective tool, such as HRiM, as it poorly correlates with symptoms of oesophageal impairment. MDA5 positive patients present a higher burden of oesophageal disease with alterations found in every domain analysed: manometry, impedance and in relation to the Chicago Classification v4.0 definitions of oesophageal dysmotility disorder. Further studies, on larger cohorts of patients, are needed to better define the role of HRiM in DM as a technique useful in the diagnostic, prognostic and monitoring work-up, easily performed by well-trained operators, safe (28) and repeatable.

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