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288th ENMC International Workshop. Towards better diagnosing, understanding and treating gastrointestinal symptoms in myotonic dystrophy: extended insights and practical recommendations. 16-18 May 2025, Hoofddorp, the Netherlands

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ABSTRACT

The 288th ENMC workshop (16–18 May 2025) brought together a group of 26 healthcare professionals, researchers, and patient representatives to advance understanding and clinical management of gastrointestinal (GI) manifestations in individuals with myotonic dystrophy (DM). GI symptoms are common in DM but are not systematically addressed in clinical care and are frequently left untreated or treated incorrectly. This workshop highlighted the breadth and impact of GI manifestations in DM, addressing symptoms in the oropharynx, oesophagus, liver, gallbladder, stomach, small and large intestines, and pelvic floor muscles. Attention was given to nutritional, cognitive, and behavioural influences on these symptoms and differences across males and females. Developments in genetic and animal studies that contribute to an increased understanding of the pathophysiology and potential treatment of GI manifestations were discussed, and recommendations are provided for their use. Building on these discussions, this report extends and substantiates the workshop content by incorporating additional literature and expert interpretation. Practical clinical recommendations to optimise the care and treatment of GI symptoms in DM were provided and, together with patient representatives, a list of 10 questions has been developed that can be used in the consultation room to identify whether a patient is experiencing GI symptoms. Next steps include the development of a DM-specific assessment instrument for GI symptoms and the selection of outcome measures to monitor changes in symptoms over time, during treatment, or in clinical trials.

1. Introduction

Myotonic dystrophy (DM) is a complex, multisystemic disorder that affects a broad range of organ systems beyond skeletal muscle, including

the heart, lungs, endocrine system, gastrointestinal (GI) tract, and central nervous system [1–3]. DM is classified into two genetically distinct subtypes: type 1 (DM1), caused by a CTG repeat expansion in the *DMPK* gene, and type 2 (DM2), resulting from a CCTG repeat expansion in the

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CNBP gene [4]. Prevalence estimates for DM1 and DM2 vary widely across different geographic regions and (ethnic) populations, but are overall suggested to be around 9 per 100,000 and 2 per 100,000, respectively [5]. Whereas DM1 manifests across the lifespan, with clinical features present in both paediatric and adult populations, DM2 typically presents in adulthood [1,6]. Despite differences in molecular aetiology and certain aspects of clinical presentation, both subtypes share the characteristic feature of multisystem involvement, which contributes to DM's diagnostic and management challenges [7].

Involvement of the GI tract is a frequent and clinically significant feature of DM, observed across all age groups and both disease subtypes [8–10]. Symptoms may range from mild to debilitating and can involve any part of the GI tract, including (oropharyngeal) dysphagia, gastro-oesophageal reflux, delayed gastric emptying, constipation, and anal (as well as urinary) incontinence [9,11]. However, these manifestations are often non-specific, underrecognised, sometimes counter-intuitive, and underreported, leading to delays in diagnosis and suboptimal management. The impact of GI symptoms is profound; not only for affected individuals but also for their family members, who often play a central role in daily care and support.

From 16–18 May 2025, the 288th European Neuromuscular Centre (ENMC) workshop brought together 26 healthcare professionals, researchers, and patient representatives to address GI impairments in individuals with DM1 and DM2. The central focus of the workshop was to advance understanding and clinical management of GI manifestations in DM. Four key objectives guided the discussions:

- 1) To assess the frequency, nature, severity and impact of GI impairments in DM;
- 2) To explore underlying pathophysiological mechanisms, diagnostic approaches, and potential therapeutic targets;
- 3) To develop a guideline to support healthcare professionals in the recognition and management of GI symptoms as part of routine care;
- 4) To design a practical and straightforward questionnaire for symptom monitoring and treatment evaluation.

4) To design a practical and straightforward questionnaire for symptom monitoring and treatment evaluation.

2. Overview of currently available knowledge on GI manifestations of DM

This section summarises the content presented during the workshop, which covered GI involvement in DM across the entire GI tract (Fig. 1). Presentations addressed the underlying pathophysiology, genetic and animal model insights, symptom patterns, modifying factors, screening strategies, outcome measures, and treatment approaches. In addition, this report extends beyond the workshop presentations by incorporating evidence from the broader literature and integrating supplementary information to provide a more comprehensive overview and to further elaborate on topics that were introduced during the meeting.

GI manifestations in DM appear to be the result of distinct pathophysiological mechanisms and symptom patterns that reflect the disorder's multisystemic nature. Previous studies have revealed that GI symptoms affect approximately 80 % of individuals with DM, and occur in every part of the GI system, indicating dysfunction of both striated and smooth muscle components of the digestive tract [12]. Striated muscle involvement, particularly in the upper GI tract, contributes to dysphagia, which is reported more frequently in DM1 than in DM2 [12]. In contrast, gastro-oesophageal reflux and symptoms indicative of smooth muscle dysfunction, such as constipation, abdominal pain, and alternating bowel habits, seem to be slightly more common in DM2 [12].

In children affected by DM1, a majority (approximately 75 %) experience at least one GI symptom, with up to 26 % facing associated (psycho)social consequences [9]. Parents frequently report that GI and urological symptoms interfere with daily life, with issues related to bowel and urinary control, as well as GI issues in general, described as having the most significant impact in a large survey study [9,13]. According to data from a large cohort study and several retrospective

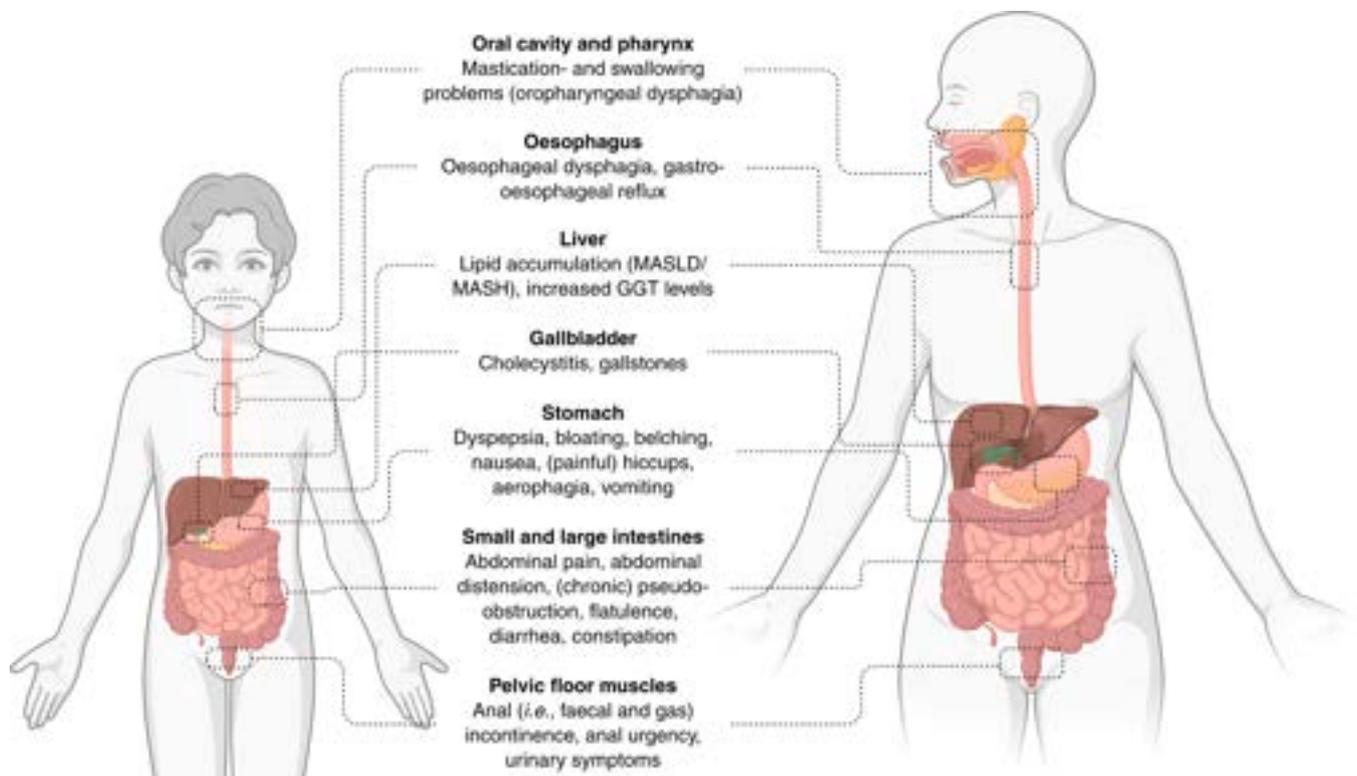


Fig. 1. Gastrointestinal symptoms among individuals with DM. Adapted with permission from "Clinical and Molecular Insights into Gastrointestinal Dysfunction in Myotonic Dystrophy Types 1 & 2" by J.A.M. Peterson and T.A. Cooper, 2022, *International Journal of Molecular Sciences*, 23, 14779. Created in BioRender. Orriëns, L. (2025) <https://BioRender.com/q1n2bpt>.

studies, the five most frequently reported symptoms are abdominal pain, dysphagia, diarrhoea, encopresis, and constipation [9,14,15]. Urological symptoms (e.g., difficulty with toilet training, urinary incontinence or nocturnal enuresis) often co-occur with GI symptoms. In fact, 28 % of children present with a combination of at least one symptom in both categories [9].

At the molecular level, studies indicate that previously established mechanisms of disease, such as dysregulated alternative splicing resulting from muscleblind-like (MBNL) protein sequestration on expressed expanded CUG repeat RNAs, have widespread downstream impacts on the transcriptome and proteome that are likely to affect multiple tissues of the GI tract and contribute to GI dysfunction. This broad and multifaceted involvement distinguishes DM from other neuromuscular diseases in clinical practice— such as inflammatory myopathies, inclusion body myositis, limb-girdle muscular dystrophies, and dystrophinopathies – where symptoms are typically less pronounced and often confined to oropharyngeal dysphagia and constipation compared to the complex spectrum of GI manifestations found in DM [16,17].

To complement published evidence, a cross-sectional survey – using the Gastrointestinal Symptom Rating Scale (GSRs) to assess symptom burden – was conducted through the German Myotonic Dystrophy Registry and presented during the workshop. Among 374 respondents, 34 % were diagnosed with DM1 and 64 % with DM2. A significant burden of GI symptoms was evident, including dysphagia, bloating, and constipation, with GSRs total scores elevated in both cohorts. Dysphagia was more prominent in DM1 (62 %) compared to DM2 (52 %).

Findings from a recent United Kingdom (UK)-based community survey, presented during the workshop, further emphasise the gap between symptom burden and clinical care. Among children with DM1, approximately 75 % experience GI symptoms, yet fewer than 40 % have ever been evaluated by a (paediatric) gastroenterologist. Similarly, while 62 % of adults with DM1 report GI issues, only 25 % have received

specialist care. While this survey focussed on individuals from the UK, we assume that similar statistics are likely across the board.

Personal accounts shared by patient representatives (Textbox 1) vividly illustrate the profound impact of GI symptoms on quality of life, independence, and emotional well-being. These narratives underscore the urgent need for improved clinical recognition, targeted management strategies, and research efforts that address the full scope of GI involvement in DM.

2.1. Mastication and swallowing

Mastication and swallowing difficulties – referred to as oropharyngeal dysphagia (OD) – are common in both DM1 and DM2, although their prevalence and severity differ between the two types. Among children with DM1, OD is a common issue, with its occurrence influenced by the age of onset of symptoms – showing a prevalence of 100 % in the congenital form vs 64 % in the childhood-onset form [3]. In adult-onset DM1, OD also remains a frequent concern [12]. In contrast, OD in DM2 is less prevalent and tends to be milder, rarely resulting in serious complications [18].

In DM1, muscle weakness impairs mastication, leading to poor bolus preparation, while swallowing is frequently affected by pharyngeal residue and delayed clearance. These issues often go unnoticed by the patient, partly due to cognitive traits such as low self-awareness and poor self-directedness, which increase the risk of aspiration [19]. Furthermore, anterior or posterior drooling may occur: anterior drooling refers to unintentional spilling of saliva from the mouth [20], whereas posterior drooling is the uncontrolled spilling of saliva toward the oropharynx (e.g., symptoms such as coughing, gagging, gurgling breath sounds, all related to difficulty in adequately clearing saliva) which may increase the risk of aspiration and respiratory complications [21,22].

OD in individuals with DM can be diagnosed by a Speech and

Textbox 1

Personal accounts from patient representatives.

Stepfather of a child with congenital DM1

As a parent of a child with congenital DM1, you quickly learn that what most would consider a medical emergency is, for us, simply part of everyday life.

Our child has faced nearly every GI complication imaginable – swallowing difficulties that turn every meal into a risk, choking on secretions, stomach pain, acid reflux, bacterial overgrowth, incontinence, constipation and diarrhoea that disrupt daily life. There have been life-threatening episodes of pseudo-obstruction, perforated bowel, a ruptured appendix, mucus plugs in the lungs, and aspiration causing pneumonia and three episodes of collapsed lung in a single year. Such emergencies are often aggressively treated in hospital, leading to unnecessary operations and the increased risks that these bring in congenital DM.

Now he is 25, and managing daily life requires a complex regimen of medications, tube feeding, medical equipment, house adaptations and employing six carers. Hospital visits are frequent. It has such a profound impact that my wife and I had to give up work to provide full-time care. This condition affects every part of life. Education, holidays, and social events are complicated and often out of reach. Isolation becomes a constant presence – not only for the child, but for the entire family.

Mother of two children with childhood DM1

As a mother of two children with DM1, I witness the daily struggles they face, especially with GI complications. These issues are often invisible to others but deeply affect every aspect of their lives.

My eldest, now 35 years old, showed GI issues since infancy, including encopresis and painful reflux that led to recurrent bronchitis. At the age of eleven, he underwent emergency surgery for acute appendicitis, followed just days later by his first intestinal obstruction. Since then, he has had at least one obstruction annually. His condition has worsened over the past decade, with aspiration episodes during obstructions. Last year, a massive aspiration nearly cost him his life and led to three weeks in the Intensive Care Unit, with a long recovery. My younger son, now 28, lives with constant abdominal pain, cramps, and diarrhoea – up to ten times a day. Holding a job is nearly impossible due to unpredictable absences, and the fear of urgently needing a toilet keeps him from leaving the house. Managing his diet is a constant challenge.

As a mother, it is heartbreaking to witness life-threatening situations and constant pain. As a nurse, I am frustrated that these issues are not systematically addressed in clinical care. Greater awareness, clinical guidance, and targeted research are urgently needed. Patients and family deserve support, not just for the muscular symptoms of DM1, but the full scope of challenges of this multisystem disorder they face every day.

Language Therapist (SLT) through a thorough case history, clinical assessment with objective measures, and, if needed, instrumental evaluations such as fiberoptic endoscopic evaluation of swallowing (FEES) or videofluoroscopy [18,19,23–25]. OD has been more extensively studied in adults than in children with DM. Several studies have identified specific characteristics of OD in DM. For example, Umemoto *et al.*, found that a reduced bite force, decreased occlusal, and increased masticatory muscle activity contribute to masticating difficulties [26, 27]. Furthermore, both myopathic weakness and myotonia of the oropharyngeal muscles significantly affect the oral and pharyngeal stages of swallowing [25]. This was demonstrated through measurements using a laryngeal sensor and electromyography, which revealed prolonged laryngeal movement time, extended activation of the submental muscles during swallowing, delayed initiation of the swallowing reflex, and irregular muscle activity in the cricopharyngeal muscle [25]. Additionally, increased echo intensity and atrophy of the masseter muscle have been observed in adults with DM1 and DM2 [28].

In a cohort study conducted at the outpatient clinic of Eginition Hospital in Athens, 23 individuals with DM1 (mean age 49.8 ± 13 years) and 13 with DM2 (mean age 63.1 ± 13.9 years), all with adult-onset diagnosis, were assessed for voice, mastication and swallowing, cognition and cough reflex strength. One of the most notable differences was that the total duration of mastication of solid textures was significantly longer in DM1 compared to DM2. Furthermore, around 50 % of individuals with DM1 failed the standardised and validated screening tool for dysphagia, the Timed Water Swallow Test (100 ml), compared to 30 % of those with DM2 [29].

In children with DM1, clinical observations, caregiver questionnaires and functional assessments have provided valuable insights into OD, including the consistent finding that children with congenital DM1 experience more difficulty with solid foods than with liquids. Sjögreen *et al.*, reported symptoms such as drooling, food leakage, prolonged mastication, and coughing during meals, based on structured clinical evaluations and parental questionnaires [30,31]. Echenne *et al.*, described early swallowing difficulties in congenital DM1, often present from birth, which may improve after infancy, but can persist or reappear later in life [32]. These findings were further supported by Berggren *et al.*, who used both caregiver reports and swallowing assessments to demonstrate that children with congenital DM1 show significantly more impairment when ingesting solids compared to liquids [33].

Although several studies have described clinical features of OD in both adults and children with DM, knowledge about its long-term course remains limited. Therefore, the Radboudumc Centre of Expertise for Neuromuscular Disorders in the Netherlands conducted a three-year retrospective longitudinal chart review study to investigate the progression of mastication and swallowing difficulties in children with DM1 and explore underlying mechanisms [34]. Data were extracted from annual multidisciplinary evaluations, including SLT assessments consisting of a clinical interview, observations (face, jaw, lips, tongue, and dental occlusion), clinical measurements of mastication and swallowing, grading of OD severity, and quantitative muscle ultrasound of orofacial muscles.

Preliminary analysis of the first documented SLT evaluations during the study period for 39 children showed that OD is common, with frequent complaints of pharyngeal residue and mastication issues. Nearly two-thirds of the children require adjustments while eating or drinking. Dental malocclusions are prevalent, and clinical tests reveal reduced bite force and inefficient mastication and swallowing. Quantitative muscle ultrasound findings indicate altered muscle structure and thickness, particularly in the masseter muscle and the intrinsic tongue muscles.

2.2. Oesophagus

Oesophageal symptoms in DM1, although still underexplored, represent a clinically significant aspect of GI involvement. Findings from

a Milan cohort, presented during the workshop, offered insight into this domain. The cohort consisted of 29 patients (mean age, 36.9 ± 11.3 years; 20 females, 9 males) who neurologists referred to a gastroenterologist for various GI complaints. Dysphagia was observed in nine patients; four with dominant OD and five with combined oropharyngeal and oesophageal symptoms. In the latter group, instrumental evaluations such as oesophageal X-ray and high-resolution manometry revealed ineffective oesophageal motility or an achalasia-like pattern. Although a few cases of achalasia have been reported in patients with DM1, the optimal management approach remains uncertain, particularly regarding whether DM1-associated achalasia should be regarded and treated as primary achalasia observed in the general population. These findings underscore the need for further investigation to guide clinical decision-making in this context.

In addition, gastro-oesophageal reflux is a frequent symptom, present in 38 % of adults with DM1 [11,12], and at a somewhat higher rate in DM2 (46 %) [12]. Gastro-oesophageal reflux has been reported in 15 % of children with DM1, with higher rates observed in children with the congenital form (23 %) [9,14]. In addition to reflux of gastric contents into the oesophagus, heartburn, acid regurgitation, chest pain, cough, globus sensation, laryngitis, and erosion of dental enamel can also indicate gastro-oesophageal reflux. Proposed mechanisms include reduced resting tone, impaired competence (*i.e.*, the ability to maintain a pressure barrier), and decreased area vector volume of the lower oesophageal sphincter, along with smooth muscle abnormalities [8]. Nevertheless, current evidence remains inconclusive on the exact cause.

2.3. Liver and gallbladder

Disruption of metabolic pathways in DM has severe effects on hepatic and biliary health, predisposing individuals to liver steatosis, impaired drug metabolism, and gallbladder dysfunction. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) – formerly termed non-alcoholic fatty liver disease – emerges as a critical complication in DM1, affecting up to 45 % of patients [35]. Insulin resistance, a hallmark of DM1, plays a central role in MASLD. Research indicates that patients with DM1 often have higher fasting insulin levels and Homeostatic Model Assessment (HOMA) scores, which are strongly associated with the accumulation of lipids in the liver. Importantly, even non-obese individuals with DM1 can develop MASLD, indicating that there are disease-specific mechanisms at play that go beyond traditional risk factors such as obesity [36,37].

Preclinical studies in mouse models show that toxic CUG repeat expansions in hepatocytes sequester MBNL proteins, disrupting RNA splicing. This dysregulation upregulates acetyl-CoA carboxylase 1, a key enzyme in fatty acid synthesis, resulting in pronounced steatosis [38]. Mice from this study also show that lipid accumulation worsens with high-fat diets [38]. Accordingly, 65 % of patients with DM1 exhibit elevated gamma-glutamyl transferase (GGT), correlating with muscle disease severity assessed by Muscular Impairment Rating Scale (MIRS) score [39]. Ultrasonography detects hepatic steatosis in 34 % of cases, while fibrosis markers like FIB-4 (*i.e.*, Fibrosis-4 Index for Liver Fibrosis) scores indicate advanced disease compared to non-DM1 MASLD cohorts [35]. Aberrant bile acid profiles further complicate hepatic health in DM1 [38]. Concurrently, 60 % of patients with DM1 who have chronic diarrhoea exhibit bile acid malabsorption, attributed to defective ileal reuptake mechanisms [38,39]. These disruptions contribute to cholestatic liver injury and intestinal inflammation, creating a vicious cycle of metabolic dysfunction.

DM1 significantly impacts gallbladder function, with a cholecystectomy prevalence of 17 % – three times higher than age-matched controls. Disruption of contractile pathways cause bile stasis and gallstone formation; gallbladder smooth muscle shows hallmark colocalisation and sequestration of MBNL1 proteins with expanded CUG RNA foci, suggesting that expression of the mutant allele may affect gallbladder function [40]. The classic symptoms of gallbladder disease are

intermittent severe pain in the right upper quadrant after eating a fatty meal. Gallstones can already cause serious complaints in childhood, although patients – including children – often remain asymptomatic until acute cholecystitis develops, necessitating urgent interventions [15]. Gallbladder surgery in DM1 requires tailored approaches. Anaesthetic protocols avoiding neuromuscular blockers reduce postoperative myotonic crises, while pneumoperitoneum pressures often require adjustment to overcome abdominal wall rigidity. Preoperative cardiac and respiratory assessments are crucial, given DM1's multisystemic nature.

To summarise, emerging data indicate that hepatic and biliary involvement in DM1 may represent a direct manifestation of the disease. Integrating hepatologic assessment in the clinical management of DM1 is warranted to detect subclinical liver injury, prevent progression to advanced fibrosis, and mitigate drug-related risks.

2.4. Stomach, intestines and gastrointestinal motility

GI motility is a tightly regulated, segmental process that is essential for the digestion of food, the uptake of water and nutrients, and the storage and excretion of waste. These processes rely on the proper coordinated contraction of the smooth muscle layer that lines the GI tract, which consists of circular and longitudinal layers that modulate gut lumen diameter or segment length, respectively. Coordinated contractions are achieved through neurogenic inputs from the autonomic and enteric nervous systems, as well as hormonal and immunological factors, coupled with the proper response by smooth muscle cells [41,42]. Disrupted function of any cell type in this process can lead to GI dysmotility, impacting the generation of peristaltic waves in the stomach or intestines. Impairment of GI transit not only leads to constipation and/or diarrhoea but can also lead to serious secondary issues such as bacterial overgrowth and chronic intestinal pseudo-obstruction (CIPO), both of which have been observed in patients with DM.

Several clinical studies have identified significant delay in gastric emptying in DM1 affected adults by ultrasound, ¹³C-acetate breath test, or radiolabelled test meals [43–46]. Defects in gastric function are often detected, regardless of a patient's reported symptoms or symptom history [45]. In both adults and children affected by DM1, delays in gastric emptying, also called gastroparesis, can lead to a severely bloated stomach that can impact feeding or cause nausea, pain, severe hiccups, and weight loss. Gastric function has yet to be evaluated in DM2-affected individuals, although reported symptoms would indicate a high likelihood of gastric dysfunction [12].

Small and large intestine motility are shown to be greatly impacted in DM and contribute to symptoms of severe abdominal pain and distention, nausea and vomiting, and constipation and diarrhoea. Past studies using radiological assessment, manometry, or X-ray identified dilated bowels, low amplitude contractions, altered contraction duration, and delays in transit time in patients with DM [10,47–50]. A key manometric study of 10 controls and 10 patients with DM revealed severe disruption of the Migrating Motor Complex of the jejunum during fasting, with a shorter quiescent phase (phase 1), increased duration of irregular activity (phase 2), and an overall decrease in contractile amplitude that impacted motility [47]. Taken together these findings are consistent with neuromyopathic CIPO, which can present clinically similarly to a mechanical small bowel obstruction. Additionally, migrating motor complex dysfunction impairs the ability of the small intestine to clear out luminal contents and can contribute to bacterial overgrowth, leading to diarrhoea and bloating.

From the presented Milan cohort of 29 patients with DM1, previously highlighted in section 2.2, individuals also experienced many symptoms resulting from intestinal dysmotility. Patients complained of abdominal pain (65 %), diarrhoea (55 %), bloating (48 %), alternating bowel habits (14 %) and constipation (14 %). Causes of diarrhoea in DM1 have been explored in the past and several mechanisms hypothesised, such as bile acid malabsorption, intestinal neuroendocrine hormone overexpression

and bacterial overgrowth [51,52].

Interestingly, in the Milan cohort, 23 patients with symptoms compatible with bacterial overgrowth (abdominal pain, diarrhoea and/or bloating) were empirically treated with systemic or non-absorbable antibiotics. Follow-up is available only for 13 patients, but among those a partial response was seen in three, whereas a complete response was seen in eight; often, responses were temporary, requiring re-treatment.

Of the four patients affected with constipation, three had severe constipation, refractory to different lines of laxatives and with both slow-transit and outlet obstruction components, and one had CIPO-like features. CIPO is a rare but serious complication resulting from GI dysmotility, and for patients with DM, early recognition and conservative treatment are necessary to prevent explorative laparotomy or colectomy, which can worsen outcomes [53–55].

2.5. Pelvic floor

Because DM affects both smooth and striated muscle tissue, it may also impair the pelvic floor muscles (PFM), including the puborectalis, external anal sphincter, and internal anal sphincter. These structures play a major role in maintaining anorectal closing pressure and defecation. Dysfunction can lead to an increased risk of anal incontinence and anal urgency, with or without urinary incontinence. Defecation requires coordination of abdominal muscle contraction and relaxation of the of puborectalis which is made of striated muscle fibres. Impaired coordination and increased anal pressures, suggesting hypertonia of the striated muscles, can lead to both incontinence and constipation.

The International Continence Society's 2023 report recommends PFM training as an early intervention for both faecal (level 1, grade B) and urinary (level 1, grade A) incontinence [56]. Perineal rehabilitation for GI symptoms includes lifestyle and bowel habit education, bowel training, exercises aimed at strengthening the external anal sphincter, and PFM. Emerging evidence from studies conducted in both men [57] and women [58] with DM1 has shown that supervised lower-limb muscle strength training can increase muscle fibre size and enhance muscle strength, which translates into a better functional performance and mental well-being.

A recent literature review on GI and genitourinary manifestations in DM1 highlighted that most studies did not use clear definitions of symptoms nor standardised questionnaires to assess the prevalence of symptoms [59]. This finding may explain the great variability reported between studies and limit the possibility of comparing DM1-specific results to those obtained from the general population using standardised questionnaires [59]. A recent prevalence study on pelvic floor disorders in 80 childhood, adult and late-onset DM1 women also demonstrated a higher prevalence of urinary, anal and prolapse symptoms than in the general population [60]. Anal symptoms were reported as the most bothersome, though urinary symptoms were also very common and impactful. Notably, urinary or gas incontinence often preceded faecal incontinence, suggesting that urinary symptoms may serve as early indicators of pelvic floor dysfunction and allow for early intervention in the clinic. Given the premature ageing phenotype in DM1, it is essential to investigate whether pelvic floor disorders emerge earlier in this population, thereby facilitating timely identification and intervention.

To explore the feasibility of PFM training in DM1, a Canadian pilot study included five women with childhood, adult, or late-onset DM1 in a 12-week program that included a home-based regimen and weekly physiotherapy sessions combining education, electrical stimulation, and biofeedback. Three women completed the study and reported reductions in both urinary and anal incontinence, as well as improvements in the impact of symptoms on quality of life and participation. These initial findings suggest that PFM training is feasible in DM1. However, studies to determine the metrological qualities of the outcome measures used in the DM1 population and to assess the effect of perineal rehabilitation on

continence in this population will be necessary.

2.6. Modifying factors

Additional factors that influence GI function, such as nutrition, sleep, mobility, cognition, the enteric nervous system, autonomic nervous system, immune system function and biological sex, can impact symptom presence and severity. Presentations in this workshop highlighted the added complexity of these factors on GI involvement in DM, beyond the functional impact of the disease. Patient representatives also recognised the impact of anosognosia – a lack of awareness of one's symptoms – in assessing symptoms in DM1. Because patients may not realise that they have symptoms, or that their symptoms may be unusual, problems are frequently underreported both at the individual level and across the wider DM population. The benefit of involving caregivers in assessments was stressed.

2.6.1. Nutrition and the gut microbiome

Nutritional assessment – a comprehensive, systemic evaluation that includes both objective and subjective measurements to determine a person's nutritional status – is an important component of care for individuals with DM. Inadequate or deficient intake of energy, protein, and other nutrients can negatively impact body composition and physical function. Since most individuals with DM experience altered body composition and reduced functional capacity, careful evaluation of dietary intake is particularly important. The Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) is a practical triage tool to assess nutritional status and to identify those at risk of malnutrition [61]. It incorporates assessments of weight changes, Nutritional Impact Symptoms, including diarrhoea, dysphagia and obstipation, food intake, and functional status (*i.e.*, activity level).

Weight management can be challenging in DM. Resting energy expenditure can be lower than in unaffected individuals because of lower muscle mass, and physical activity levels are significantly reduced, resulting in a markedly decreased total energy expenditure [62]. This lower total energy expenditure increases the risk for malnutrition in patients with DM, even when overweight, as a lower calorie intake automatically means lower protein and micronutrient intake. Patients who experience fatigue often tend to eat easy-to-use, ultra-processed, unhealthy foods, which have low nutrient density and high calorie content, leading to inadequate and unbalanced nutritional intake. Patients who eat like this can present with obesity, which masks the malnutrition and leads to an undesirable body composition with disproportionately high fat mass and risk for metabolic syndrome [63]. A diet high in fibre, rich in protein, and low in sugar may help support nutritional balance and metabolic health.

Dietary interventions for GI problems are highly dependent on the type of symptoms and their underlying cause. In general, a balanced diet with adequate fibre and fluid intake remains important for managing or alleviating both constipation and diarrhoea. When indicated, the use of laxatives may be appropriate, with different strategies applied for individuals with normal colonic transit time (<72 hours) and those with slow transit. Evidence supporting the effectiveness of probiotics for constipation in DM remains limited. Diarrhoea may also respond to nutritional modifications, depending on the underlying cause. While organic diarrhoea often requires medical treatment, a balanced diet, or diet interventions – such as lactose restriction or low-FODMAP (*i.e.*, Fermentable Oligosaccharides Disaccharides Monosaccharides And Polyols) diet – can be helpful. Despite the lack of supporting evidence, multispecies probiotics may be used to manage diarrhoea.

Certain dietary components can impact the composition and activity of the gut microbiota. Gut microbiota, gut microbiome, or gut flora are the microorganisms, including bacteria, archaea, fungi, and viruses, that live in the digestive tracts. Fermentable fibres, or prebiotics, are broken down by gut bacteria into short-chain fatty acids, such as butyrate, which support gut health and serve as a key energy source for cells lining

the colon. Non-fermentable fibres, in contrast, are not broken down in the gut. Instead, they help to promote intestinal motility and increase stool bulk, contributing to regular bowel movements. Probiotics, which are live beneficial bacteria, can be taken as supplements. They may help modulate the microbiome and reduce symptoms such as diarrhoea. Fermented foods (*e.g.*, yoghurt, kefir, sauerkraut) may also positively influence the gut microbiome [64].

Emerging evidence highlights the gut microbiome as a significant factor in both health and disease [65], including autism spectrum disorder (ASD), diabetes mellitus, inflammatory bowel disease, cardiac arrhythmia, and attention deficit hyperactivity disorder (comorbidities commonly present in DM1). A recent pilot study explored the gut microbiota profiles of children with DM1 and their unaffected siblings [66]. This revealed a significant reduction in the relative abundance of *Faecalibacterium* in children with DM1 compared to their unaffected siblings. *Faecalibacterium*, a key gut bacterium, has been associated with disorders related to DM1, including inflammatory bowel disease. Currently, it is unclear whether this shift contributes to DM1 pathogenesis or is a result of the disease. If further studies confirm its role, targeting *Faecalibacterium* relative abundance could become a potential therapeutic strategy for alleviating GI and neurodevelopmental symptoms in DM1 [66].

Ultimately, a tailored approach is essential, considering the individual's nutritional status, functional capacity, symptoms, dietary intake, and medical history. Regular evaluation and timely adjustment of the treatment plan are key to effective management.

2.6.2. Cognition and behaviour

Cognitive impairments are present across all forms of DM1, forming a continuum of neurocognitive dysfunction. In congenital and childhood-onset DM1, intellectual disability (ID) is often a central feature [67,68]. Dysfunction in the central nervous system significantly reduces quality of life [67]. Research also indicates a strong overlap between DM1 and ASD, suggesting shared neurodevelopmental mechanisms [69].

GI disorders are frequently reported among individuals with ASD and ID [70]. Symptoms vary but commonly include constipation, diarrhoea, abdominal bloating, pain, and selective eating behaviours [70]. These issues arise from a complex interaction of sensory, emotional, cognitive, and communicative factors. Atypical interoception – the perception of internal bodily signals – is a key contributor. In ASD, interoception can be heightened, blunted, or inconsistent, complicating the ability to detect or communicate discomfort. A child may express abdominal pain through behaviour rather than words, such as irritability or withdrawal. Sensory sensitivities to food texture, smell, and taste often lead to restricted diets, which can result in nutritional deficiencies and exacerbate GI symptoms, such as constipation or irritable bowel syndrome. Rigidity in food preferences (*e.g.*, only eating specific brands or textures) is also common.

Emotion dysregulation, prevalent in ASD, is closely linked to GI issues [71]. Individuals may somatise stress or anxiety, which can appear as stomach aches or changes in bowel habits. These symptoms may be genuine or psychologically mediated, complicating diagnosis. Alexithymia, or difficulty recognising and describing emotions, is also common. This can blur the line between emotional and physical discomfort, leading to underreporting of pain and delayed identification of GI issues. Additionally, communication difficulties in individuals with ASD and/or ID pose challenges for accurate symptom reporting. Patient groups report difficulties in swallowing frequently being related to concentration, finding decreased distraction at mealtimes can help to reduce choking. Standardised GI questionnaires may be unreliable unless paired with structured interviews or direct observation. Parents and caregivers may unintentionally underreport symptoms, highlighting the need for clinician-led assessments [72].

A multidisciplinary approach involving medical, psychological, and behavioural professionals is essential. Assessments must be tailored to

the individual's developmental and cognitive level to ensure accurate understanding and intervention.

Summarised, GI symptoms in individuals with a diagnosis of ASD, ID, and DM1 share overlapping features, including altered interoception, emotion dysregulation, and selective eating. Diagnosing and treating these problems requires individualised tools and expert teams familiar with neurodevelopmental and somatic symptom presentations. The paediatric DM1 population is highly heterogeneous, ranging from individuals with profound ID and ASD requiring extensive support, to those with mild learning or attentional difficulties. This spectrum necessitates flexible diagnostic strategies to fully address the brain-body interaction underlying GI problems in these groups.

2.6.3. Enteric nervous system

The enteric nervous system, a subdivision of the autonomic nervous system, plays a critical role in regulating a wide range of GI processes, including bowel motility, transmucosal fluid exchange, immune surveillance, and local perfusion. It comprises a complex network of millions of neurons and glial cells organised into interconnected ganglia located within the gut wall.

Together with the intestinal epithelium, immune system, enteroendocrine signalling pathways, and the gut microbiota, the enteric nervous system facilitates the absorption of nutrients, water, and electrolytes while simultaneously maintaining mucosal barrier integrity to prevent the translocation of luminal pathogens and toxins. Disruption of these tightly regulated interactions may contribute to the pathogenesis of various GI disorders. This highlights the enteric nervous system as a key regulator of GI homeostasis and a potential contributor to the pathophysiology of GI symptoms observed in DM [73].

Autonomic nervous system function in DM was evaluated in two studies which reported frequent symptoms and signs consistent with autonomic dysfunction, including GI involvement [74,75]. Nevertheless, one of the two studies suggested that these manifestations were more likely due to altered function of the target organs rather than primary autonomic neuropathy. Histological examinations of (resected) GI tissues from individuals with DM [49,76,77] revealed mild inflammatory changes in the mucosa, alterations of the myenteric nerve plexus, or atrophy of smooth muscle [50,77]. However, distinguishing primary versus secondary histological pathologies remains a challenge [11].

2.6.4. Sex-related differences

Sex-related differences in GI manifestations in both DM1 and DM2 have recently been highlighted. To better understand the factors underlying these differences, data from the general population are relevant. Recent studies and meta-analyses report a significantly higher prevalence of GI symptoms in females, both in the general population and in individuals with DM [78–80].

Sex hormones appear to play a relevant role in the pathophysiology of several GI manifestations, either through direct physiological effects or due to hormonal fluctuations. They also modulate the gut-brain axis, the disruption of which contributes to the development of irritable bowel syndrome, a condition that frequently affects patients with DM. In DM1, the primary factor contributing to gut-brain axis dysfunction is likely impaired gut motility, resulting from the involvement of smooth muscle and the myenteric plexus [11].

A review of the literature on sex-based differences in DM reveals a consistent female predominance, along with a higher prevalence of various GI symptoms compared to the general population. Hilbert *et al.*, assessed a large cohort of patients with DM through a national registry in the United States of America, including 913 with DM1 and 178 with DM2 [12]. They found female sex to be associated with constipation (odds ratio [OR]: 2.14) and gallbladder problems (OR: 1.59) in DM1, and with constipation (OR: 3.12) and gastro-oesophageal reflux (OR: 2.35) in DM2. Similarly, Dogan *et al.* assessed the influence of sex on the prevalence of specific clinical manifestations in the largest DM1 cohort

studied to date, including 1,409 adult patients with DM1 from the DM-Scope nationwide registry, with comparisons to the general French population [81]. Regarding GI involvement, OD emerged as a DM1-specific feature with a higher prevalence in females (52 % vs 44 %). Other GI symptoms (46 % vs 35 %) and anal incontinence (8 % vs 4 %) also showed a female predominance, though at rates comparable to those in the general French population. Conversely, in a cohort of 152 adult patients with DM1 from the UK, a high frequency of anal incontinence was observed, but without significant female predominance [82]. A recent review on sex-related differences in DM1 discusses similar findings, including the higher prevalence of GI symptoms in females, as reported in the studies above [83].

Perna *et al.*, assessed the presence and severity of GI manifestations among 61 Italian adults with DM1 using both subjective and objective diagnostic measures [39]. They observed a higher overall frequency (89 % vs 60 %) and greater severity of lower GI symptoms in females, whereas pathologically elevated GGT levels were twice as common in males (80 % vs. 44 %). In a subsequent analysis of the same cohort, the group also documented a high prevalence of metabolic-associated fatty liver disease in DM1, with a notable male predominance (63 % vs 10 %), correlating with established risk factors such as body mass index, insulin resistance, and type 2 diabetes [35]. Finally, a study of 302 patients with DM2 by Montagnese *et al.*, identified a fourfold higher occurrence of gallstones among females [84].

In summary, both DM1 and DM2 exhibit a similar sex disparity, with a higher prevalence of specific GI manifestations compared to the general population. This may be attributed to the multisystemic nature of DM, which variably affects the endocrine system, smooth and striated muscle, body weight and composition, and the central nervous system, thereby increasing exposure to known risk factors and promoting the development of related GI disorders.

2.6.5. Immune system function

Although it has been known for many years that individuals with DM1 typically have lower levels of circulating IgG than unaffected individuals [85], the clinical significance of this observation has been unclear. Larger controlled studies are required to determine if low IgG predisposes to increased infections, and if IgG supplementation reduces this risk. Of note, immunoglobulin deficiency is known to be a risk factor for recurrent small intestinal bacterial overgrowth [86,87] and at least one case report suggests that intravenous immunoglobulin treatment may protect against recurrent infections and small bowel obstruction [88]. IgG supplementation may be considered in DM1 individuals with especially low IgG and recurrent infections and/or recurrent small bowel obstruction.

2.7. Genetics and molecular pathology

The predominant molecular mechanism by which the CTG or CCTG repeat expansions in DM1 or DM2, respectively, cause disease is in large part due to the loss of function of the MBNL family of RNA binding proteins by sequestration on the expanded CUG or CCUG RNAs transcribed from the mutant allele [89,90]. The result is mis-regulated pre-mRNA processing of hundreds of genes, many of which revert to expressing foetal protein isoforms that are unable to completely fulfil their functions in adult tissues. This mechanism has been substantiated using MBNL knockout animals that recapitulate many features of DM, with a predominate focus on skeletal muscle, heart, and brain [91–95]. For example, the failure to express the adult isoform of the skeletal muscle-specific chloride channel (CLCN1) causes the myotonia for which the disease is named. Mis-regulation of alternative splicing is a predominant effect of MBNL loss of function and the focus in the field. However, MBNL proteins also regulate the selection of polyadenylation sites that impact protein translation of mRNAs. MBNL also regulates intracellular localisation of specific mRNAs, which could have a major impact on neuronal functions. These additional molecular effects are an

important area for future investigation. Another future area of inquiry for mechanistic insight is the impact of the expanded CUG repeat RNA on mis-expression of other RNA binding proteins including STAUFEN, CELF1 and HNRNPA1, among others. While paradigms for the molecular disruptions are established, it remains unclear how the mis-regulation of pre-mRNA processing in hundreds of genes leads to multiple severe features of disease in affected tissues. A major goal of molecular and cellular studies is to identify the genes for which mis-regulation contributes to tissue dysfunction. Disease features could result from small effects of many genes, which would be challenging to unravel.

DM1 and DM2 pathogenesis is further complicated by the continued somatic expansion of the CTG or CCTG repeat throughout the lifetime of an affected individual [6,96]. Notably, repeat lengths in skeletal muscle are typically thousands of repeats larger than those in blood DNA [97]. The limited post-mortem data available suggest that the repeat is similarly highly somatically expanded in tissues of the GI tract, such as the oesophagus, small intestine, and colon [98]. Tissue-specific somatic expansion almost certainly contributes to the tissue specificity of the symptoms. Still, more data on cell-type-specific repeat lengths and cellular dysfunction are needed, particularly to understand better the role of somatic expansion in mediating aspects of GI tract dysfunction.

In support of a role for somatic expansion in mediating DM1 disease onset, individuals in whom the repeat expands more rapidly than expected develop symptoms earlier than expected [96]. Such variation in expansion rates is associated with variation in the *MSH3* DNA mismatch repair gene which is required to generate expansions [99,100]. DM1 is further modified by variant repeat interruptions within the CTG array, which slow the rate of somatic expansion and delay age at onset [101]. DNA mismatch repair-driven somatic expansion is also recognised as a key driver of disease onset in other repeat expansion disorders, and much effort is ongoing to develop therapies aimed at suppressing somatic expansion.

In addition to modifying the age at onset, the inherited allele length, presence of variant repeats, and rate of somatic expansion also modify many progressive DM1 phenotypes, including skeletal muscle strength, cognitive function, and overall health [101]. The age at onset of GI problems is closely associated with the overall age at onset [1]. Thus, it seems very likely that the overall degree of severity and rate of progression of GI problems in DM1 are similarly modified by genetic factors. However, objective quantitative measures of GI dysfunction in DM1 have not been recorded in any of the genetically well characterised DM1 cohorts. Further delineation of the genetic determinants of GI problems in DM1 and the potential identification of tissue-specific genetic modifiers await the attainment of such data. Given the high value of genetic modifiers as therapeutic targets and the potential utility of molecular genetic stratification in clinical trials, gathering such data should be a very high priority for future research studies.

2.8. Animal studies

Animal studies have significantly increased our ability to investigate the genetic determinants of DM and identify key mechanisms of disease pathogenesis. Mouse models with tissue-specific expression of CTG repeats or knockout of *Mbnl* recapitulate DM disease features, which have enabled identification of transcripts affected by disease mechanisms that likely contribute to DM symptoms [92,102]. Recent work showed that the skeletal muscle features of DM1 are reproduced in a mouse model that combined mis-expression of the *Cln1* chloride channel and the *Cacna1s* calcium channel, demonstrating that the combinatorial effects of two genes can be sufficient for pathology [103]. Furthermore, the authors demonstrated that a calcium channel blocker improved the pathology, suggesting that identifying the determinative genes may lead to potential therapeutic approaches. These results establish a paradigm for investigating the mechanisms that lead to tissue dysfunction throughout the GI tract in DM1 and DM2.

Two mouse models are currently under development to investigate the mechanisms of DM1 and/or DM2 diseases in the GI tract. To study the impact of the DM1 CTG repeat expansion in a tissue-specific and dose-dependent manner, a new TurboDM^{XL} mouse model expressing large, uninterrupted CTG repeats is under development. By replacing the *DMPK* promoter from the well-established DMSXL transgenic mouse model [104] with an inducible TRE3G promoter, mice can be crossed with a tissue-specific rtTA driver that will express CUGexp-DMPK transcripts upon doxycycline administration. Expression of CUGexp-DMPK transcripts was successfully achieved in striated muscles using an ACTA1-rtTA driver and doxycycline feed. ACTA1-turboDM^{XL} mice display molecular DM1 features such as nuclear RNA foci colocalising with MBNL1 and robust splicing defects and exhibit severe myotonia and muscle weakness. Removal of doxycycline leads to reversal of disease symptoms. To investigate the role of smooth muscle dysfunction and associated molecular mechanisms in DM1 GI disorders, TurboDM^{XL} mice will be crossed with Myh11-rtTA mice that are currently under development.

To understand the impact of MBNL loss of a function on GI smooth muscle function, another mouse model with conditional, smooth muscle-specific knockout of *Mbnl1* and *Mbnl2* has been developed. These mice carry Cre recombinase with the modified oestrogen receptor binding domain (CreER^{T2}) driven by smooth muscle myosin heavy chain (*Myh11*) and floxed *Mbnl1* and *Mbnl2* alleles. *Mbnl* loss of a function is induced by tamoxifen injection. Phenotyping assays of the small and large intestines showed that mice with *Mbnl* loss of a function exhibited impaired motility of the upper and lower GI tract. *Ex vivo* force transduction experiments revealed an increased contractile tone in GI segments, likely to cause impaired motility *in vivo*. *Mbnl* loss of a function also significantly decreased small intestine length and increased the thickness of the smooth muscle layers without histopathological changes to the tissue, suggesting a potential intrinsic smooth muscle defect. Protein analysis identified increased phosphorylation of regulatory myosin light chain (Mlc20) in animals with *Mbnl* loss of a function, indicating hypercontraction of smooth muscle tissue. RNA sequencing was also performed on mouse and human DM1 GI tissues, revealing conserved dysregulation of MBNL-sensitive alternative splicing events that provide key mechanistic pathways for further investigation.

While mouse models offer promising mechanistic and therapeutic insight into DM GI pathologies, small model organisms like *Caenorhabditis elegans* (nematode worm), *Danio rerio* (zebrafish), and *Drosophila melanogaster* (fruit fly), provide unique biological and genetic advantages, including well-conserved intestinal architecture and host-microbe interactions that are suitable for gut physiology studies. These small model organisms have gained traction in DM research as complementary tools, given their easy and less expensive management in research laboratories and shorter life cycles, allowing for quicker data generation that is essential for studying adult-onset and progressive diseases. In turn, small animal studies have already enabled meaningful translational research pathways in the DM field [95,105–107].

A *Drosophila melanogaster* model has been developed that enables tissue-specific expression of large CTG repeats, allowing for the study of the effects of DM1-associated GI dysfunction. Current studies are investigating the impact of ubiquitous, visceral muscle, or epidermal CTG repeat expression on GI motility and have already shown alterations in fly food excretion and intake rates. Preliminary molecular characterisation of splicing dysregulation is underway. Ongoing studies with this fly model aim to measure functional changes, refine the timing of interventions, and test the effects of different repeat lengths and genetic backgrounds on GI function (*i.e.*, MBNL deficiency). These approaches will facilitate the identification of tissue-specific dysfunction, novel biomarkers, and therapeutic targets in the GI tract under DM backgrounds. Drug repurposing efforts and evaluation of molecules in current clinical trials will be underway later to outline treatment options for alleviating GI symptoms in DM.

Overall, the development and use of multiple animal models offer a

promising platform for dissecting GI pathophysiology in DM, and efforts are currently underway. Findings from each model will contribute to a broader effort to incorporate underexplored clinical features into DM research, ultimately aiming to improve mechanistic knowledge and therapeutic strategies regarding the GI system.

2.9. Screening and outcome measurement

Despite the clinical relevance of GI involvement in DM, there is currently no scientifically sound, disease-specific questionnaire to assess GI symptoms in this population. Both screening tools – which help identify individuals in need of further evaluation – and outcome measures – which assess symptom severity and track treatment response – are critically needed for clinical care and research.

One commonly used patient-reported assessment tool for GI symptoms is the GSRs, which has been widely applied across various conditions [108]. However, it has not yet been clinimetrically evaluated in patients with DM1 using modern test theory.

To address this gap, GSRs data collected from a Dutch patient registry (n = 401; a collaboration between the university hospitals of Maastricht and Nijmegen, the Netherlands) were analysed using Rasch modelling, to develop the first interval-level, DM1-specific GI symptom outcome measure [109]. The original GSRs data did not meet the expectations of the Rasch model. After evaluating parameters such as disordered thresholds, misfit statistics, item bias, local dependency, and unidimensionality, three items – hard stools, urgent defecation, and constipation – were initially removed. In addition, the item nausea was split by age category (< 40 years vs ≥ 40 years) due to evidence of differential item functioning. These modifications resulted in the Rasch-Transformed GSRs-DM1 (RT-GSRs-DM1), which met all Rasch model criteria. After this, remodelling of all items will be addressed to publish a more applicable linear Rasch-transformed GSRs metric as a ruler.

While this represents an important step toward a DM1-specific, interval-level GI assessment tool, further work is needed. Methodological limitations, including the lack of cross-cultural validation and the absence of data on responsiveness to clinical change, must be addressed before the adapted RT-GSRs-DM1 questionnaire can be widely implemented in clinical trials or routine care.

2.10. Effect of pharmacological DM therapies on GI symptoms

No DM-specific medications have been developed or have been found to alleviate GI symptoms across individuals consistently. Current treatments have centred around ameliorating skeletal muscle phenotypes, such as myotonia; however, some treatments have had secondary effects on GI tract function, both beneficial and adverse. These observations are important not only for their potential therapeutic implications but also for the mechanistic insights they may offer into the underlying pathophysiology of GI involvement in DM.

For example, metformin, primarily used to improve skeletal muscle function and mobility in DM1, has been reported to alleviate GI manifestations in some individuals [110]. However, it is also associated with short-term onset, reversible GI side effects in others. Similarly, mexiletine, a sodium channel blocker commonly prescribed to manage myotonia in DM, is associated with GI side effects (e.g., nausea, diarrhoea, upper GI discomfort) in 29 to 55 % of patients [111]. However, similar symptoms have also been observed in control groups [112]. According to a retrospective long-term evaluation, treatment is discontinued in approximately 16 % due to intolerable GI effects (i.e., nausea and gastro-oesophageal reflux) [112]. While reduced myotonia may indirectly facilitate swallowing, direct therapeutic effects of mexiletine on primary GI dysfunction have not been demonstrated, and its role in modulating GI function remains poorly understood.

Looking ahead, there are ongoing efforts to develop antisense oligonucleotide (ASO) and/or siRNA therapies that directly target the

expression of toxic CUG repeats. While improvements have been made in ASO/siRNA delivery, it remains unclear how effectively GI tract tissues are targeted and whether these treatments can improve GI symptoms. Systematic evaluation of GI outcomes in future *DMPK* lowering trials will be essential.

Taken together, these pharmacological insights suggest a complex interplay between skeletal muscle treatments and GI function. Some therapies may offer dual benefits, while others may uncover shared pathological mechanisms; both avenues warrant further investigation.

3. Discussion

At the end of the workshop, the participants discussed implications for clinical care, research priorities, and opportunities for translational work. GI involvement in DM remains underrecognised despite its substantial burden on patients' daily functioning and quality of life. The group reached consensus on the need for immediate action in clinical practice, better integration of GI endpoints into research, and the development of more refined preclinical models to support discovery. Building on these discussions, the present report extends the recommendations by embedding them in the current literature and by further elaborating on points raised during the workshop. The resulting recommendations are presented across clinical care, clinical research, and animal research.

3.1. Recommendations for clinical care

The workshop participants identified several priorities to improve clinical care for individuals with DM and GI involvement. A central message was that “what we do not ask, we do not know”, underlining the importance of proactively screening for GI symptoms. To support this, a one-page leaflet (Fig. 2) was co-developed with patient representatives after the workshop, designed for use by general practitioners to initiate these relevant conversations. Additionally, the Rasch-modified version of the GSRs is under further development as a potential standardised screening tool to identify potential GI manifestations early in care pathways both in adults and children.

Beyond initial detection, participants stressed the need for practical clinical guidance tailored to the unique challenges in DM. While a formal guideline has yet to be developed, there was consensus on the necessity of one. Such a guideline should eventually cover diagnostic tools appropriate for each GI domain, criteria for specialist referral, and a framework for treatment strategies. As a first step toward this goal, the workshop produced a set of preliminary recommendations, informed by expert opinion and the group's collective clinical experience. These are summarised in Table 1 and reflect the best available guidance at present, while acknowledging the need for further research and validation before a comprehensive clinical guideline can be established.

In the presence of GI symptoms, early consideration should be given to whether cognitive and behavioural issues may be contributing factors. Evaluation should follow the recommendations developed during the 284th ENMC International Workshop on the assessment of cognitive and behavioural abnormalities [113].

Preventing harmful interventions emerged as another clinical priority, particularly the mismanagement of pseudo-obstruction. In response, participants proposed introducing an SOS card to complement existing anaesthesia guidelines for patients with DM. Lastly, the value of dedicated gastroenterologists familiar with neuromuscular conditions was emphasised, given the complexity and multisystem nature of GI involvement in DM.

3.2. Recommendations for clinical research

The group emphasised the urgent need to incorporate GI symptoms more systematically into clinical research. Given their high prevalence and impact on quality of life, GI outcomes should be integrated into DM



Gastrointestinal symptoms questionnaire

Patient name: _____ Date: _____

Diagnosis: Confirmed DM1 (Steinert disease)
 Confirmed DM2 (PROMM disease)
 Another situation (suspected, genetic test pending, misdiagnosed, ...)

I. General

1. Do you feel, or has anyone suggested, that you eat more slowly than others, or eat smaller portions?
 Yes No

II. Swallowing and stomach

2. Do you (sometimes) have difficulty chewing or swallowing, or have you changed what or how you eat or drink to make it easier?
 Yes No

3. Do you choke or cough while eating or drinking, or shortly afterward?
 Yes No
 If yes, how often? Every time Several times a week Once a week or less

4. Do you have heartburn (a burning pain or discomfort in the chest), especially at night?
 Yes No
 If yes, how often? Every night Several nights a week Once a week or less

5. Do you feel bloated or have gas in your stomach?
 Yes No
 If yes, how often? Every day Several times a week Once a week or less

6. Do you vomit?
 Yes No
 If yes, how often? Every day Several times a week Once a week or less

III. Bowel movements

7. How often do you have a bowel movement (either solid or liquid)?
 Less than 3 times a week 3 times a week to 3 times a day More than 3 times a day

8. Do you have difficulty holding your bowel movements?
 Yes No

9. Do you feel bloated or have intestinal cramps?
 Yes No
 If yes, when? After meals Outside of meals
 And how often? Every day Several times a week Once a week or less

IV. Impact on life

10. Do these symptoms affect your life (work, school, travel, eating out, or other activities)?
 Not at all A little (Very) much

Version 1.0 – last updated 18 September 2025

Fig. 2. Brief GI symptoms questionnaire for patients with DM. Developed together with patient representatives based on the workshop and used with permission from Euro-DyMa.

Table 1
Recommendations for screening/assessment and treatment of GI manifestations in DM discussed during the workshop.

GI manifestation	Screening/assessment	Treatment approaches
Oral cavity and pharynx Mastication- and swallowing problems (OD)	<ul style="list-style-type: none"> ● Ideally annual SLT-evaluation consisting of thorough case history, clinical assessment with objective measurements ● Be alert on symptoms like coughing, a wet or gurgling voice after eating or drinking, or recurrent lower respiratory tract infections ● If there is suspicion of (silent) aspiration and more certainty is needed, consider instrumental assessments such as FEES (fibreoptic endoscopic evaluation of swallowing) [23,24] or videofluoroscopy [19] ● Be alert for signs of anterior or posterior drooling [20] <p>If annual SLT evaluation is not feasible:</p> <ul style="list-style-type: none"> ● In children, use the validated Screening list for Physicians [119]. Add the question: "Does the child require food to be cut because they cannot chew properly?" If any item on the list or the additional question is answered positively, refer the child to an SLT. ● In adults, existing questionnaires like the EAT-10 [120], the Sydney Swallow Questionnaire [121], or the SwalQol [122] can help to identify OD 	<ul style="list-style-type: none"> ● OD symptoms vary per individual – SLTs should tailor interventions based on comprehensive assessment ● The <u>Best Practise Recommendations for SLT in paediatric NMD</u> [123] provide a useful framework for children with DM ● The <u>Care Guidelines for Speech and Language Pathologists Treating Adults and Children with Myotonic Dystrophy</u> [124] provide recommendations applicable to both children and adults with DM ● Clear explanation and education on OD symptoms and advice are essential ● Strategies must be individualised, never applied generically. Example strategies: <ul style="list-style-type: none"> - For weak oral muscles and prolonged mealtimes: soft, smooth textures and small bite-sized portions to reduce fatigue and improve safety - If food remains in the mouth or throat: drink water during/after meals to clear residues - Ensure upright, well-supported posture during meals ● If oral intake is too tiring or time-consuming, consider oral nutritional supplements in collaboration with a dietitian ● If swallowing is unsafe or if oral intake remains insufficient despite supplements, a percutaneous endoscopic gastrostomy (PEG) may be considered as an alternative for long-term partial (i.e., still allowing the enjoyment of smaller meals or food tastings) or exclusive enteral feeding ● For patients who struggle with swallowing tablets, it may be appropriate – following consultation with a pharmacist – to consider alternative formulations, such as liquid medication ● Anterior and/or posterior drooling may be diminished by optimising factors that influence or perpetuate drooling, as well several behavioural, pharmacological, or surgical treatment options [125,126]
Oesophagus Oesophageal dysphagia and motility disorders	<p>Diagnostic approaches include [127]:</p> <ul style="list-style-type: none"> ● Upper endoscopy with biopsies (to rule out strictures or eosinophilic oesophagitis) ● Upper GI X-ray (i.e., barium swallow study) to evaluate motility disorders ● Oropharyngeal oesophageal scintigraphy (OPES) allowing qualitative and quantitative analysis of swallowing disorders ● Oesophageal manometry to assess contractions and pressure ● Functional lumen imaging probe (FLIP) to assess the contractions and pressure within the oesophagus in select cases 	<ul style="list-style-type: none"> ● Referral to gastroenterologist ● Avoiding large meals, dry or stringy foods, and preferring soft and moist food, semi-liquid or liquid food, depending on the severity of symptoms ● Consider prucalopride [127] (N.B.: This is ineffective if oesophageal motility is present) ● Consider smooth muscle relaxants [127] (e.g., calcium channel blockers, nitrates, peppermint oil) if spastic disorders of the oesophagus are present ● Consider endoscopic botulinum toxin injections, endoscopic dilation, peroral endoscopic myotomy (or surgical myotomy in select cases) for achalasia [127] ● Feeding tube may be considered ● Lifestyle advice: diet, weight loss, raise pillow or the head of the bed [128] ● Antisecretory therapy (i.e., proton pump inhibitors, histamine 2 receptor antagonists, antacids) [128] ● Referral to gastroenterologist in case of refractory reflux [128]
Gastro-oesophageal reflux	<p>Diagnostic approaches include [128]:</p> <ul style="list-style-type: none"> ● Upper endoscopy ● 24-hour pH-impedance testing ● Oesophageal manometry ● Upper GI X-ray (i.e., barium swallow study) 	<ul style="list-style-type: none"> ● Lifestyle advice: diet, weight loss, raise pillow or the head of the bed [128] ● Antisecretory therapy (i.e., proton pump inhibitors, histamine 2 receptor antagonists, antacids) [128] ● Referral to gastroenterologist in case of refractory reflux [128]
Liver Lipid accumulation (MASLD/MASH)	<ul style="list-style-type: none"> ● Current guidelines emphasise non-invasive screening for patients with MASLD, including liver enzyme panels and transient elastography to detect subclinical fibrosis [129] ● Ultrasound at diagnosis, regardless of age, is recommended 	<ul style="list-style-type: none"> ● Lifestyle modifications – especially adherence to a Mediterranean diet – can reduce ACC1-driven lipogenesis ● Weight loss targets of 7–10 %, as recommended for MASLD [129] must be adjusted for the mobility limitations commonly seen in DM1 ● Pharmacotherapies such as GLP1R agonists show promise in reducing steatohepatitis, though data specific to the DM1 population remain limited
Impaired liver function	<ul style="list-style-type: none"> ● Imaging every 2 to 3 years to screen for liver fibrosis in case of low risk of fibrosis with non-invasive tests ● Regular liver function test (incl. GGT levels) 	Hepatological consultation
Gallbladder Cholecystitis; gallstones	<p>Diagnostic approaches include [130]:</p> <ul style="list-style-type: none"> ● Ultrasound (i.e. gold standard for gallstones) ● CT scan / Magnetic resonance cholangiopancreatography (MRCP) 	Surgical treatment in symptomatic patients and/or complicated cholelithiasis [130]
Stomach Functional dyspepsia or gastroparesis	<p>Diagnostic approaches include [131,132]:</p> <ul style="list-style-type: none"> ● <i>Helicobacter pylori</i> infection testing ● Octanoic acid breath test ● Upper GI X-ray (i.e., barium swallow study) ● Gastric scintigraphy ● Upper endoscopy (if alarm signs or symptoms) ● Patient-generated subjective global assessment (PG-SGA) to screen for malnutrition 	<ul style="list-style-type: none"> ● Nutritional advice: dietary changes including small meals, bite-sized pieces, low fat, low fibre, enough liquids ● Efforts to reduce swallowing of air; referral to SLT ● Medication including prokinetics and antiemetics ● Deflating the stomach by nasogastric tube or gastrostomy has shown good effects in several cases discussed during the workshop
Small and large intestines		

(continued on next page)

Table 1 (continued)

GI manifestation	Screening/assessment	Treatment approaches
Abdominal pain		Referral to a gastroenterologist is recommended in case of persistent abdominal pain
(Chronic) intestinal pseudo-obstruction	Diagnostic approaches include [133]: <ul style="list-style-type: none"> ● X-ray ● CT-scan ● Barium study (upper GI series) in select cases ● Scintigraphy in select cases 	<ul style="list-style-type: none"> ● Avoid unnecessary surgery! [133] ● Dietary changes (same as for gastroparesis) [133] ● Nutritional support (e.g., IV hydration, total parenteral nutrition (TPN)) [133] ● Pharmacological treatment [133]: <ul style="list-style-type: none"> - Same recommendations as for gastroparesis (i.e., prokinetics, antiemetics) - Treatment of small intestine bacterial overgrowth with antibiotics (e.g., ciprofloxacin/rifaximin) - Hyoscyamine has had success in four cases discussed at the workshop [55] - Pyridostigmin/neostigmin has successfully been used in one published case study [134] - Pantothenic acid may be useful (personal experience of one of the neurologists participating in the workshop)
Chronic diarrhoea	Diagnostic approaches include [52,135]: <ul style="list-style-type: none"> ● Bristol Stool Scale ● X-ray (considering that diarrhoea is sometimes an overflow diarrhoea, resulting from severe constipation) ● Coeliac disease serology, C-reactive protein, thyroid function tests ● Stool testing for calprotectin, parasites and pathogenic bacteria ● Lactose breath test ● Breath test for bacterial overgrowth 	<ul style="list-style-type: none"> ● Always try to better define and quantify the issue (bowel movement per day, Bristol Stool Scale, volume of each bowel movement and total faecal volume, presence of tenesmus, presence of anal incontinence, presence of macroscopic blood) [135] ● Rule out bowel infections, coeliac disease, thyroid dysfunctions and lactose intolerance [135] ● In clinical practice, a stepwise approach is often used to manage diarrhoea: <ul style="list-style-type: none"> - Step 1: normalise nutritional intake by ensuring adequate fibre and fluid consumption, along with promoting a healthy lifestyle - Step 2: introduce probiotics to support gut microbiota balance - Step 3: if symptoms persist and Small Intestinal Bacterial Overgrowth (SIBO) is suspected, consider treatment with antibiotics ● When total intake is high, it may be necessary to reduce consumption of sorbitol and fructose. Increasing fat intake while reducing caffeine, alcohol and nicotine can be beneficial. Structuring meals into six smaller portions throughout the day is recommended
Constipation	Diagnostic approaches include [136]: <ul style="list-style-type: none"> ● Bristol Stool Scale ● X-ray ● Bowel transit time X-ray ● Anorectal manometry ● Defecography (X-ray or MRI) 	<p>Normal colonic transit time (< 72 hours):</p> <ul style="list-style-type: none"> ● Increase dietary fibre – through food and/or supplements – and ensure adequate fluid intake ● Larger meals with sufficient caloric content may stimulate gastrocolic reflex ● Physical activity and proper posture play supportive roles <p>Slow colonic transit time:</p> <ul style="list-style-type: none"> ● Reduce fibre intake, particularly fermentable fibre (to reduce bloating) ● Introduce laxatives/stool softeners to support bowel function ● Peppermint oil may be effective due to its antispasmodic properties ● Enemas/bowel irrigation/intestinal flushing <p>Evaluate for obstructed defecation (pelvic floor muscles incoordination, pelvic anatomical issues, improper defecation technique). Referral to a gastroenterologist is recommended in case of refractory constipation</p>
Pelvic floor muscles		
Anal in-continance; anal urgency; urinary symptoms		Pelvic floor muscle rehabilitation was shown to be effective in a pilot study of five women presented at the workshop

Note: Referenced guidelines are based on data from the general public and not necessarily individuals with DM; healthcare providers should determine their appropriateness on a case-by-case basis when used in patients with DM. Abbreviations: DM, myotonic dystrophy; GI, gastrointestinal; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; OD, oropharyngeal dysphagia; SLT, Speech and Language Therapist

studies, at a minimum as secondary endpoints. Patient-reported outcome measures (PROMs) were identified as a key component of this effort, both to understand symptom burden better and to evaluate intervention effectiveness from the patient's perspective. Selecting or adapting appropriate PROMs for DM populations remains an area for further development.

Looking ahead, participants proposed several research questions to help advance the understanding and treatment of GI manifestations. Longitudinal studies are needed to characterise the natural history of GI symptoms across age groups and DM subtypes. Other areas of interest include the potential overlap in genetic pathways linking ASD and GI symptoms in DM, differences in chloride channel function between congenital or childhood and adult-onset forms of the disease, and the role of age in shaping GI symptomatology. Identifying predictors of liver dysfunction and better characterising metabolic risk are also key. Finally, participants discussed the importance of monitoring the effects

of emerging therapies, such as cannabidiol (CBD), while also recognising that some patients may use these treatments independently, without consulting their healthcare providers, which has implications for both clinical care and research.

3.3. Recommendations for animal research

In generating animal models to investigate the pathogenic mechanisms of GI dysfunction in DM, additional recommendations can be made to improve the likelihood of identifying disease drivers and ensure the reproducibility of findings.

While smooth muscle dysfunction appears to be a key driver of GI symptoms, evaluation of other GI cell types should be included. A multitude of cell types contribute to GI function, including the nerves of the enteric nervous system, neuroendocrine cells, interstitial cells of Cajal, and immune factors, and may be affected by toxic repeat

expression in DM. Small animal models would be ideal for investigating potential cell-type-specific effects in a high-throughput manner that can then be further evaluated in larger animal models. The use of such tissue-specific models allows for the decoupling of tissue interactions within multisystemic diseases, such as DM. It increases the likelihood of identifying cell-type-specific disease mechanisms contributing to symptoms. Of course, developing a model that expresses expanded repeats from the endogenous *DMPK* or *CNBP* locus would be of great benefit to the DM field, allowing for a more holistic approach in therapeutic development. Given the somatic instability and anticipation observed in DM, both early and late onset models would be ideal to investigate differences between childhood and adult onset of disease.

Genetic tools that allow for temporal control of gene knockout or repeat expression are often induced by drug administration, such as tamoxifen or doxycycline. However, tamoxifen administration has been shown to affect GI transit [114], while doxycycline, as an antibiotic, has been shown to adversely affect the oesophagus in human patients or alter the microbiome [115,116]. To control for these potential outcomes, both experimental and control animals should receive the drug and/or undergo a washout period, during which normal GI function is restored in control animals, prior to phenotyping.

In phenotyping animal models, it is essential to consider that extrinsic factors can impact GI function. The environment in which animals are housed and tested should be free of stressors (e.g., sudden noise, changes in smell). The time of day, the animals' fed or fasted state, age, and biological sex will influence experimental outcomes and must be kept consistent between cohorts to maintain rigor and reproducibility of results [117]. It is also imperative to maintain the same diet formulation and housing environment (e.g., bedding type) between cohorts as changes can alter microbiome makeup and affect GI function [118]. Keeping records of all aspects of the experimental set-up will help control for each variable and identify the environment needed to capture GI phenotypes.

4. Conclusion

Given the high prevalence and burden of GI symptoms in children and adults with DM1 and DM2, systematic screening, diagnostic evaluation, and tailored management are warranted. This workshop highlighted the broad spectrum of GI manifestations and the need for increased clinical awareness. Expert consensus formed the basis for preliminary recommendations to optimise current care, enhance the design of clinical trials, and guide future directions in animal research. In collaboration with patient representatives, a practical one-page questionnaire was developed to facilitate symptom recognition in routine care. While this meeting represents an important initial step, ongoing efforts are needed to build consensus and ultimately create clinical guidelines for the management of GI symptoms in individuals with DM, as well as develop animal models to identify key drivers of GI symptoms. Improved understanding and management of GI symptoms in DM have the potential to significantly enhance patient well-being and quality of life; it is time this domain receives the clinical and research attention it deserves.

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Declaration of competing interest

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