Thieme

Advances in Delayed-Onset Muscle Soreness (DOMS): Part I: Pathogenesis and Diagnostics

Delayed Onset Muscle Soreness – Teil I: Pathogenese und Diagnostik

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ZUSAMMENFASSUNG

Die Delayed Onset Muscle Soreness (DOMS) oder auch „verzögert einsetzender Muskelkater" wird zu den ultrastrukturellen Muskelschädigungen gezählt. Ursächlich werden vorausgegangene exzentrische Kontraktionsformen oder ungewohnte Muskelbelastungen angesehen. Klinische Symptome imponieren in Form einer reduzierten Kraftentfaltung, schmerzhafter Bewegungseinschränkungen, einer Erhöhung des Muskeltonus, Schwellungen sowie Funktionseinschränkungen angrenzender Gelenke. Obwohl die DOMS den milden Schädigungsformen zugeordnet wird, hat sie aufgrund der leistungseinschränkenden Auswirkungen eine große Bedeutung – insbesondere für den Leistungssport. In den letzten Jahrzehnten sind viele Hypothesen zur Ursache und Pathophysiologie beschrieben worden. Auch, wenn der genaue pathophysiologische Signalweg bis heute nicht vollständig geklärt ist, gilt als primärer Schädigungsmechanismus eine mechanische, ultrastrukturelle Schädigung des Muskelparenchyms, die zu einer weiteren Proteindegradation, Autophagie und einer lokalen Entzündungsantwort führt. Klinische Symptome manifestieren sich typischerweise verzögert (Hauptmanifestation zwischen 24 und 72 h nach der Belastung), als Folge einer komplexen lokalen und systemischen Inflammationsphase. Die vorliegende Arbeit hat das Ziel, eine Übersicht über diese Schädigungsentität zu liefern und dabei Grundlagen der schädigenden Mechanismen, der Pathophysiologie und der Diagnostik aufzuzeigen.

ABSTRACT

Delayed-onset muscle soreness (DOMS) is a type of ultrastructural muscle injury. The manifestation of DOMS is caused by eccentric or unfamiliar forms of exercise. Clinical signs include reduced force capacities, increased painful restriction of movement, stiffness, swelling, and dysfunction of adjacent joints. Although DOMS is considered a mild type of injury, it is one of the most common reasons for compromised sportive performance. In the past few decades, many hypotheses have been developed to explain the aetiology of DOMS. Although the exact pathophysiological pathway remains unknown, the primary mechanism is currently considered to be the ultrastructural damage of muscle cells due to unfamiliar sporting activities or eccentric exercise, which leads to further protein degradation, apoptosis and local inflammatory response. The development of clinical symptoms is typically delayed (peak

soreness at 48 – 72 h post-exercise) as a result of complex sequences of local and systemic physiological responses. The following narrative review was conducted to present an overview of the current findings regarding the damaging mechanisms as well as the pathophysiology of DOMS and its diagnostic evaluation.

Introduction

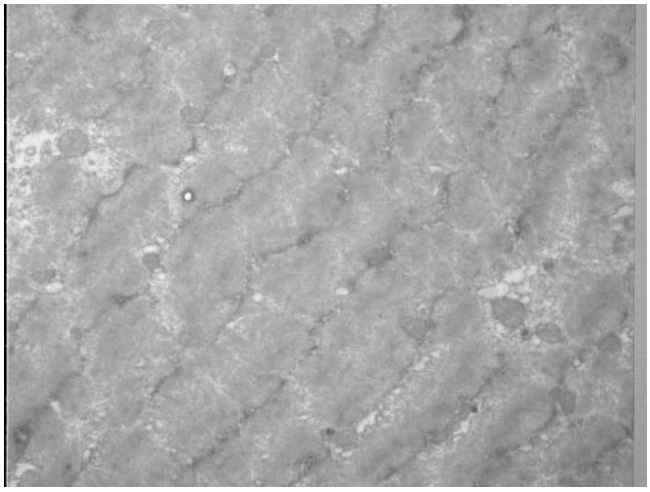
Injuries and overload to the skeletal muscle in sport are common sports injuries, presenting an overall incidence of 10 – 55 % of all sports injuries [1 – 4]. In competitive sports, muscle injuries and overload are responsible for a loss of training or competition days. Delayed onset muscle soreness (DOMS) describes an entity of ultrastructural muscle damage. According to the "Munich Consensus Statement", DOMS is classified as an overexertion-functional muscle disorder type Ib [5]. The progression of DOMS can be caused by eccentric muscle contractions or unfamiliar forms of exercise [6]. Biopsy analyses of muscles have revealed ultrastructural lesions, including Z-band streaming and broadening, which destroys the sarcomeres in the myofibrils [7], a leading cause of further apoptosis and inflammation [8, 9]. Although DOMS is considered as a mild type of muscle damage, it is one of the most common reasons for compromised sportive performances. Precise epidemiological data on DOMS are lacking due to a high number of unassessed cases. Furthermore, there is still no clear-cut definition for the diagnosis of DOMS; there are shifting overlaps between muscle overload, muscle damage, and muscle injury [5]. In recent years, DOMS has received increased scientific attention, particularly, concerning the pathophysiological process, imaging modalities or recovery interventions [10]. DOMS is associated with impaired muscular force capacities and increased soreness, pain, stiffness, and swelling, and also with some altered biomechanics to the adjacent joints [11 – 13]. Clinical signs are highly variable. They range from mild forms of muscle soreness, that subside with moderate activity, to pain and the inability to perform certain movements [13]. Thereby, in elite sports, recovery interventions may play a key role in professional sports. Prevention and treatment of DOMS, implying the recovery from exercise induced muscle damage (EIMD), is an integral part of regaining muscular force capacities and performance levels. Understanding the benefits of treatment requires knowledge of muscle damaging mechanisms, pathophysiological basics and diagnosis. Thus, the aim of this review is to provide an overview of the current findings on the pathophysiology and diagnostics of DOMS.

Mechanisms and pathogenesis

In the field of structural muscle injuries (according to grade 2a-3b [5]), signs and symptoms usually begin at the time point of the injury mechanism or develop during continued exercise. In DOMS, the earliest clinical manifestations begin at 6 – 12 h post exercise that is caused by the ultrastructural damage (i. e., exercise induced muscle damage (EIMD)) and increase progressively until reaching a peak pain level at 48 – 72 h after the EIMD. Then, the symptoms decrease until they disappear 5 – 7 days later [14]. The manifestation of DOMS based on a complex sequence of local and systemic physiological responses, as described by Böning or Hoppeler at al. [15, 16].

Injury mechanisms – the role of eccentric contraction forms

During the last decade, many hypotheses have been developed to explain the etiology of DOMS [17]. Although the exact causes of DOMS remain unknown [9], it is accepted that the main mechanisms is related to mechanical damage of skeletal muscle tissue due to eccentric exercise or/and not familiarized sporting activities [18, 19]. In fact, biopsy analysis of eccentric strained muscle tissue has proved a loss of myofibrillar integrity with Z-band streaming and a disruption of sarcomeres in the myofibrils [7, 8, 20] (▶ **Fig. 1**), which leads to further protein degradation, autophagy and a local inflammatory response [9]. To explain, during eccentric exercise, the external load is – under some conditions – greater than the force generated by the muscles fibres under concentric conditions; the muscles fibres are actively lengthened [21]. Thereby, and as shown by the force-velocity relationship, the muscles produce more force at the same angular velocity than during active shortening (i. e., concentric exercise) [22]. While the detailed reasons for this phenomenon are beyond the scope of this review, the higher muscular force is caused by "active-muscle" (i. e., more number of active cross-bridges) [23] and, in particular, by "passive-elastic" factors (i. e., Ca^{2+} triggered increased stiffness of titin and its winding on actin) [24], which cause elastic energy to be stored and released [21], as described in the three-filament model and winding filament hypothesis elsewhere [25]. However, during eccentric exercise, and mainly due to spinal inhibition [26], less [27] and predominantly fast twitch motor units are recruited [28], consisting of type II muscle fibres that are more damageable than type I fibres [29]. Overall, the potential injury mechanism inducted by eccentric exercise leading to DOMS is due to the higher muscular forces produced by less active and more damageable muscle fibers. However, during external valid conditions in sports, there are no isolated eccentric contractions that induce a "pure eccentric overload" as applied in numerous DOMS models. Instead, during sportive activities as running, change of directions, and jumps, eccentric contractions are shorter and part of the entire stretch-shortening cycle [30], also involving, and per time more, concentric contractions [31]. The previous points do not explain sufficiently the fact, that DOMS could also be develop under submaximal, moderate load conditions, particularly after not familiarized and not well coordinated sporting activities. Possibly there is no sufficient intra- and intermuscular coordination between the muscle fibres with an overstressing and damaging of single muscle fibers. Moreover, disorders of the lower spine should to be considered as contributing factors that may reinforce the development of EIMD and DOMS. Although there is a lack of scientific evidence, altered neu-



▶ **Fig. 1** Z-disk disintegration and myofilament disarrangement as sign of ultrastructural damage was evaluated by electron microscopy of biopsies of human vastus lateralis 24 h after strenuous resistance exercise for 70 s time under tension leading to DOMS.

romuscular innervation due to spine related disorders have been described as risk factors for the development of muscle injuries [32 – 34]. Thus, more research to understand the relationships between DOMS and sportive activities involving the entire stretch-shortening cycle are needed.

Inflammatory and healing responses

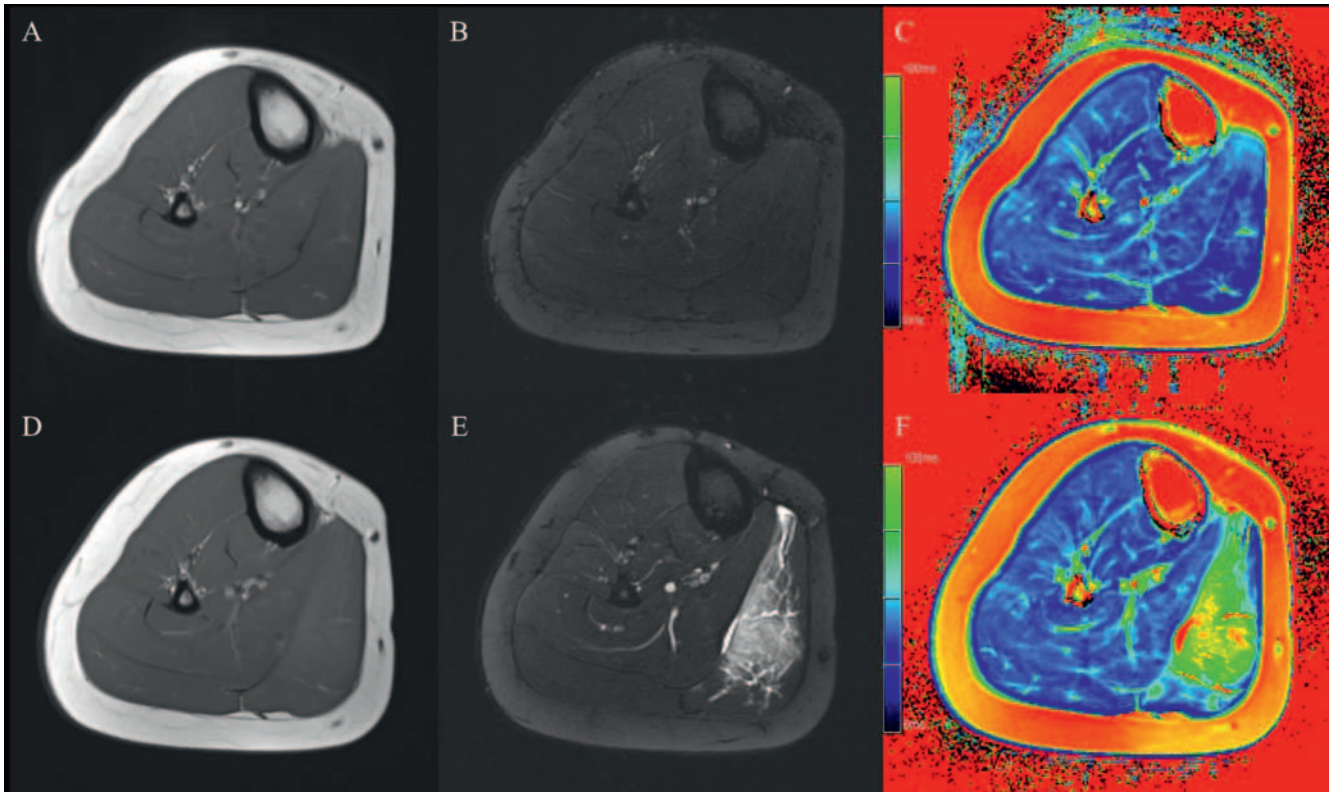
DOMS is associated with electrolyte imbalances, leukocyte accumulation and infiltration in the exercised muscle as well as an upregulation of circulating pro-inflammatory cytokines. However, the cellular sources of these cytokines remain unclear [9, 18]. Additionally, the released cytokines lead to a higher vascular permeability and microcirculation disturbances as they act as inflammatory mediators [35]. A recent study investigating intramuscular tissue perfusion by quantifiable contrast-enhanced ultrasound in DOMS demonstrated statistically significant increases in intramuscular perfusion 60 hours after exhausting eccentric exercise of the gastrocnemius muscle [36]. Affected muscle tissue is invaded by neutrophils several hours after eccentric exercise and replaced by macrophages [18, 37]. Another study reported that skeletal muscle damage is related to the production of reactive oxygen species (ROS), resulting in further inflammation and oxidative stress [17, 38 – 40]. Ultrastructural muscle damage has been estimated to be associated with increased cytosolic calcium concentrations, which are considered to activate proteolytic enzymes and increase cell membrane and vascular permeability, although its exact role remains unclear [18]. However, the accumulation of interstitial fluid accompanied by intramuscular edema and compartment swelling as well as the presence of diverse proinflammatory substances such as nerve growth factor (NGF), histamine, bradykinins and prostaglandins are described to be responsible for nociceptor activation and pain sensation [17, 41]. Satellite cells, which are located beneath the basal lamina in adult skeletal muscles fibres, act as muscle precursor cells and are considered to play a key role in the healing of particularly structurally damaged muscle tissue [1, 42 – 44]. However, their role in ultrastructural injuries such as EIMD is not fully understood. Intrinsic signals (sphingosine-1-phosphate) and extrinsic signals (mechanical pathway by nitrite oxide and activating promyogenic growth factors and cytokines) are thought to activate satellite cells after muscle damages through eccentric exercising and after muscle injuries [9, 44]. An upregulation of satellite cell populations has been found in the context of exhausting eccentric training by stimulated extracellular matrix. However, further maturation and differentiation of the satellite cells into myoblasts has not previously been ascertained [45].

Clinical Diagnostics

In general, a careful anamnesis and clinical examination with inspection, palpation, and functional testing of the affected muscle groups with and without resistance can provide important information about the extent and severity of a muscle injury, including in cases of DOMS [46]. DOMS is often accompanied by awareness of muscle contraction and with inhibition of contraction or reduced force capacities upon manual testing [11 – 13]. The clinician may be able to palpate a local or even global area of increased muscle tone [5, 47]. DOMS causes local muscle soreness and reduced range of motion of the adjacent joints [11 – 13, 48]. The signs and symptoms of DOMS begin 6 – 12 h after exercise, increase progressively until they reach peak pain at 48 – 72 h, and decrease until they disappear 5 – 7 days later [13, 14].

Laboratory-chemical examinations

DOMS is associated with increased creatine kinase (CK) activity levels, which can be seen as an indirect marker of muscle damage, as CK is almost expressed in muscle tissues and is released into the circulation according to a loss of sarcolemmal integrity (i. e., due to an increased damage or permeability of the plasmamembrane). These processes are due to the mechanical stress of eccentric exercise or metabolic causes like glycogen depletion [8, 11, 35, 49]. In addition to CK, a wide range of diverse biomarkers can be assessed. Interleukin 6 (IL-6) and C-reactive protein (CRP) are the most commonly assayed markers [50], which are upregulated during inflammation within damaged tissue. However, markers are thought to influence multiple physiological processes, even in the absence of inflammation [51]. Anti-inflammatory Pentraxin-3 (PTX-3) has been found to be upregulated after an acute bout of maximal aerobic and resistance exercise [52]. Lactate dehydrogenase (LDH) catalyzes the reversible process of pyruvate to lactate under anaerobic conditions. As an enzyme mainly occurring in the cytoplasm, LDH can be seen as a marker indicating cell damage. However, elevated levels of CK, CRP, IL-6, PTX-3 and LDH have be considered as non-specific. Thus, its clinical determination should be reserved in context of monitoring over a course of time or even in the context of scientific issues [53].



▶ **Fig. 2** T1-weighted (**A, D**), T2-weighted fat-suppressed (**B, E**) and T2-mapping images (**C, F**) of the lower leg before (**A–C**) and after eccentric exercise (**D–F**) in the same participant. The increased signal intensity (**E**) and T2 time value (**F**) reflect a rising fluid content in the gastrocnemius medialis muscle as equivalent of DOMS.

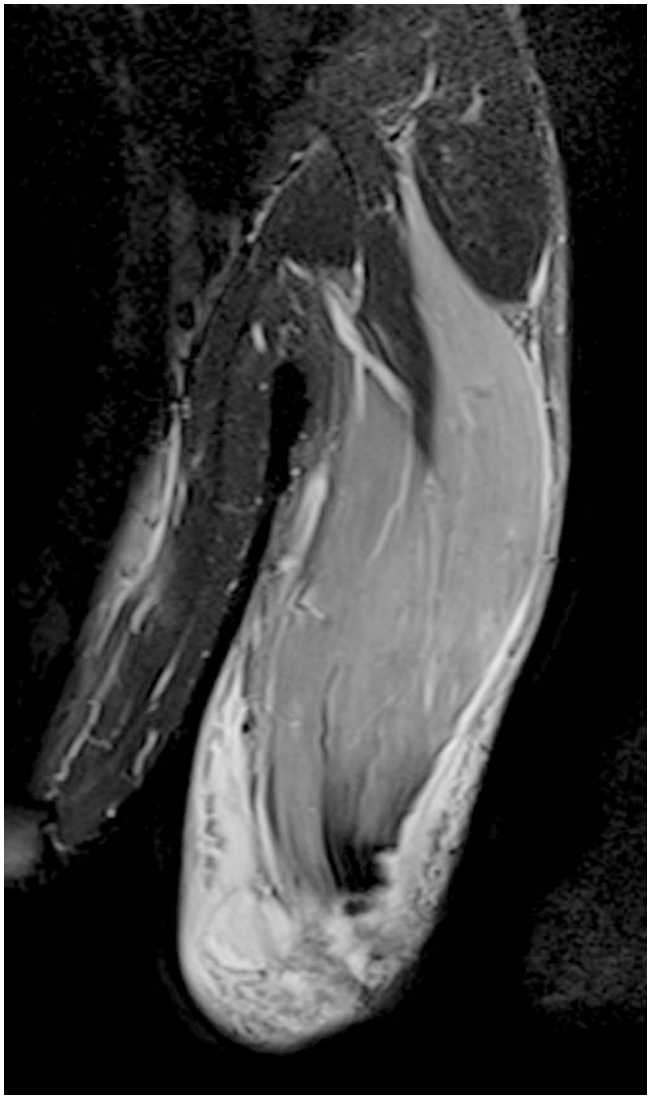
Imaging

Magnetic Resonance imaging (MRI)

Imaging of muscle tissue is essential for providing a correct assessment of the severity of muscle damage or muscle injury [54, 55]. In diagnostic imaging of DOMS, several imaging modalities are described in the literature, but so far, MRI has been reported as the preferred modality providing detailed image analysis and characterization of this kind of muscular lesion [55 – 58] (▶ **Fig. 2, 3**). MRI may be performed on either a 1.5 or 3 T system, ideally with skin markers at the site of the athlete's maximum pain prior to imaging [47]. The MRI study should include a combination of acquisitions in three orthogonal planes (i. e., axial, coronal, sagittal) [47, 59]. A typical protocol would include at least one plane of a T1-weighted sequence and at least two planes of short tau inversion recovery (STIR)/T2-weighted fat suppressed/proton density-weighted fat suppressed sequences [14, 35, 47, 60]. In clinical practice examination protocols often contain a large examination volume and an expanded slice thickness. This circumstance limits the spatial resolution and interpretation of MRI data in context of ultrastructural lesions. Hence, the slice thickness of MRI imaging should allow precise definition of small injuries, often necessitating a slice thickness of 4 mm or less [47]. The exact choice of sequences will depend on the location of the damaged tissue or muscle injury and, to some extent, on the individual radiologist's preference [47]. DOMS can be detected on MRI as intramuscular edema with generalized, patchy high signal changes affecting one or several muscles [35, 47]. Increased T2-weighted signal intensity does not only indicate intramuscular fluid accumulation; it also shows strong correlation to the degree of ultrastructural damage in the context of DOMS [35, 61]. For research purposes, MRI T2 mapping sequences can also be applied to quantify intramuscular edema [59, 62, 63]. However, in case of EIMD, MRI performed directly after exhausting exercises may reveal negative results as the signal intensity of edema commonly begin to increase during the inflammatory response. Otherwise, an examination performed at peak level may lead to an overestimation of this kind of lesion. Further, intra-individual differences in DOMS expression have to be respected and an ideal point of time cannot be generally given. However, we prefer MR imaging between 24 and 72 hours after exercise as previous studies have reported changes in T2-weighted signal intensity peak after approximately 3 days post–eccentric exercise [35, 56, 59] (▶ **Fig. 2**). Partial or complete tears to either the muscle or tendon are not detectable in DOMS. According to the British Athletics Classification system, it is rated as 0b muscle injury in MRI.

Ultrasound

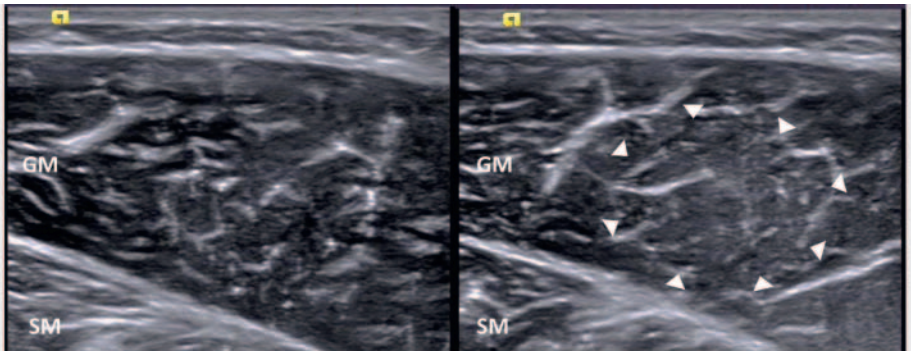
Conventional ultrasound has been utilized for approximately 3 decades to diagnose muscle damages and muscle injuries [54, 64 – 66]. In low-grade muscle damage such as DOMS, conventional ultrasound imaging of the concerned muscle tissue often



▶ **Fig. 3** MRI of DOMS in the triceps brachii muscle of a 41 years old recreational crossfit athlete four days after exhausting training. In addition to an intramuscular edema, an edema in the subcutaneous tissue is evident.

appears normal or shows small hyperechoic areas regarding its echogenicity [54, 63, 64]. Focusing on indirect signs, damaged muscles exhibit mechanical property changes, which are closely related to changes in their internal structure, including fascicle length, pennation angle, and muscle thickness [48]. The pennation angle and muscle thickness has been shown to be increased after DOMS induction [48]. A comparison to the contralateral leg or follow-up examinations may reveal relevant information concerning these indirect signs (▶ **Fig. 4**). But generally, the sensitivity of gray-scale ultrasound imaging in DOMS is severely limited [67, 68]. However, this lack of sensitivity can be improved with the use of contrast media. Contrast-enhanced ultrasound (CEUS) is a modality that has been successfully established and validated in the field of internal medicine to evaluate pathologies of the abdominal organs, such as tumors or inflammatory processes [69 – 72]. Changes in dynamic blood perfusion can be visualized through signal changes from the gas-filled microbubble contrast media, which will be eliminated as gas (sulfur hexafluoride) via the lungs. CEUS has been shown to be superior to conventional ultrasound in the diagnostic workup of low-grade muscle damage (lesions) and in identifying intramuscular edema as hypoenhancement [63, 73].

Another ultrasound-based technology for tissue characterization is Acoustic Radiation Force Impulse (ARFI) imaging, which has been widely validated and established in different medical disciplines, providing tissue characterization without the need for invasive biopsy [74, 75]. The tissue displacement and the resulting deformation response of the tissue depend on the tissue's viscoelastic properties. Commonly, it is observed and confirmed by histopathological findings that shear wave velocities (SWVs) are correlated with the stiffness of a tissue, and consequently, a stiffer tissue leads to increasing SWV [76 – 79]. Alterations in muscle tissue stiffness associated with DOMS have been reported in previous studies, which may be related to inflammatory responses following microtrauma [62, 80]. ARFI SWV could represent an additional functional imaging marker for the acquisition and monitoring of ultrastructural muscle damages and injuries.



▶ **Fig. 4** Transversal ultrasound scan of a dorsal calf (S 2000, linear probe 9L4, Siemens Healthineers, Erlangen, Germany). Physiological conditions (**A**), and DOMS conditions with indirect signs of ultrastructural muscle damage, 48 hours after exhausting exercises (**B**). Triangles: demonstrating a diffuse hyperechoic area, located at the center of pain; GM: gastrocnemius medialis muscle, SM: Soleus muscle.

Conclusions

The present work provides an overview of the damaging mechanisms, pathogenesis and diagnostics of DOMS. Currently, the exact trigger mechanism of the muscle damages and and related cellular mechanisms in DOMS are not fully understood, but many hypotheses exist to explain these phenomena. The primary mechanism of DOMS is currently thought to be a mechanical damage of skeletal muscle tissue due to eccentric exercise and not familiarized and not well coordinated sporting activities, which lead to further protein degradation, autophagy and a local inflammatory response. The predominant significance of preceding eccentric contraction may be explained by passive force generating factors including titin and an altered motor unit activation, which have both to be researched in future studies. To date, magnetic resonance imaging (MRI) has been reported as the preferred modality, providing detailed image analysis and characterization of DOMS and muscle lesions. However, newly emerging ultrasound modalities demonstrate promising results in a non-invasive functional approach.

Conflict of Interest

The authors declare that they have no conflict of interest.

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