Research Trends on Exercise-Induced Muscle Damage

Subjects: Rehabilitation
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Exercise-induced muscle damage (EIMD) is a phenomenon that occurs following novel or unaccustomed exercise, particularly if the exercise includes a high number of eccentric contractions. The damage process is normally accompanied by a temporary decrease in muscle function (both muscle force and range of motion), increased swelling of the involved muscle group, increased circulation of muscle-specific proteins, and delayed-onset muscle soreness (DOMS). Most of the symptoms and signs of EIMD are present immediately after the initial exercise bout and persist for up to 14 days.

Keywords: delayed-onset muscle soreness ; nutritional strategy ; protein intake

1. Introduction

Exercise-induced muscle damage (EIMD) is a phenomenon that occurs following novel or unaccustomed exercise, particularly if the exercise includes a high number of eccentric contractions [1]. The damage process is normally accompanied by a temporary decrease in muscle function (both muscle force and range of motion) [2][3], increased swelling of the involved muscle group [2], increased circulation of muscle-specific proteins [4], and delayed-onset muscle soreness (DOMS) [5]. Most of the symptoms and signs of EIMD are present immediately after the initial exercise bout and persist for up to 14 days [6]. These variables are also widely used to assess the extent of muscle damage, with DOMS being the most commonly assessed marker, despite the fact that the underlying mechanisms of its occurrence remain inconclusive [7][8].

Although the exact mechanisms causing EIMD remain unclear, the damage model can be simplified into the initial phase or primary damage that occurs during the exercise bout and the secondary damage phase that occurs after exercise and is associated with an inflammatory response [9]. Various preventive and therapeutic methods are used to attenuate EIMD [10]. Nutritional intervention, in particular, is essential for modulating oxidative stress and inflammation, both of which are thought to be contributing factors to EIMD but also important for the adaptive response to an exercise stimulus [11]. Given that the nutritional strategy focuses on maximizing exercise recovery, nutrients and functional foods with the potential to alleviate EIMD are investigated [6]. As a consequence, to balance recovery and adaptation, nutritional strategies for alleviating EIMD symptoms need to be modified depending on the main purpose of the session [6][12].

Despite numerous research contributions to EIMD, the exact mechanisms causing muscle damage, soreness, repair, and adaptation from eccentric exercise remain speculative. Furthermore, there is much to be revealed about nutrition, such as the underlying mechanisms of the effects of functional foods and their derivatives, as well as the long-term effectiveness of various nutritional interventions [6][12]. Numerous studies have been conducted on a wide range of topics, including nutritional strategies and recovery techniques and complex mechanisms involving the investigation of various immunological [1][6][10][13] and endocrine signaling molecules [13][14][15].

Uncertainty arises from the fact that EIMD is a complex area of study involving a variety of factors, such as fitness level, nutrition, genetics, sex, age, and familiarity with the exercise mode [13], raising the question of whether using supplements and functional foods to treat EIMD is the best practice. A variety of recovery and treatment strategies have been introduced to help alleviate the severity of EIMD and restore muscle function as quickly as possible. These include stretching, massage, cryotherapy, ultrasound, and electrical stimulation [1][5][10][13][16][17]. None of them, however, are fully recognized. Surprisingly, few attempts have adequately addressed the broad range of studies and thoroughly investigated the scientific output.

2. Research Sources

From 1998 to 2022, the total number of publications on protein intake and EIMD steadily increased, albeit with some fluctuations, and reached 351 publications. The top ten authors dominated in the number of contributions, making up

90.88% of publications (319/351) on this topic, despite having authors from 60 different countries. The United States led in the number of publications (92, 26.21%), centrality (0.44), and international collaboration with peers, followed by England (51, 14.53%) and China (41, 11.68%). This area was supported by 590 authors from 359 institutions in various countries, but only 4 from two countries (Howatson, UK; Jamurtas, Fatouros, and Nikolaidis, Greece) had published more than ten research. Moreover, after Northumbria University (UK), which had the most publications, Greek institutions ranked second and third. Therefore, the United States' national-level advantage does not appear to be supported by researchers and institutions.

It is also discovered that many eminent scholars hold key positions in co-authorship networks. Outstanding scholars such as Saltin [18][19] and Bangsbo [20][21][22] in Denmark, Fridén [23] and Malm [24][25] in Sweden, Vihko and Salminen [26][27] in Finland, and Armstrong's research group (including Warren and Schwane et al.) [28][29][30] in the United States have made significant contributions to the field of muscle injuries and muscle damage. The significant contributions of these outstanding professors have served as the foundation for ongoing breakthroughs in this field. Carl Foster sincerely praised Professor Saltin as "*A Role Model for More Than a Generation of Scientists,*" and those illustrious scholars deserve to be admired.

According to the findings, the most important research categories for protein-related EIMD research were Sport Science, Physiology, Nutrition, and Biochemistry & Molecular Biology. Eur J Appl Physiol (20 publications), Appl Physiol Nutr Metab (16), and Med Sci Sports Exerc (13) had the most publications, while J Appl Physiol (240), Med Sci Sports Exerc (238), and Eur J Appl Physiol (142) had the highest H-index. Furthermore, the top ten co-citation frequency journals are all established journals in the Sport Science and Physiology discipline category (all print journals, IF ranging from 2.997 to 11.928, average 5.110), and the majority of high-centrality journals have relatively high impact factors (ranging from 3.322 to 69.504, average 13.845). Despite the fact that the top ten journals by frequency and centrality were completely different, it is difficult to pinpoint which journal or journals are more important in this field. The findings are useful for researcher communication and manuscript submission to appropriate potential journals. However, getting published in these high-quality journals is challenging.

3. Research Topics

The network of co-cited journals and co-citations is typically used to analyze a specific intellectual link and provide the following important information, which is commonly regarded as the foundation of a specific research field, thereby facilitating knowledge-domain exploration [31][32]. Researchers focused on the co-citation clustering results and combined the most cited and co-cited references to suggest the following research topics:

- Exercise modes. Exercise modes that can result in EIMD and/or DOMS include long-distance running [33], resistance exercise [34], high-intensity intermittent exercise [35], and downhill running [36]. Eccentric contractions cause more severe symptoms than isolated or concentric contractions [1]. Muscle-damaging exercise modes are also classified as aerobic exercise and strength training [13]. Interestingly, both clustering results (#10 one-off soccer match, #3 match-related fatigue, #11 athletic performance injury, and #17 progressive resistance exercise) and recent studies revealed that the effect of specific sports (e.g., soccer [37] and basketball [38]) on muscle damage is a research focus. This implies that specific sports with greater ecological validity are receiving increased attention. Improving the ecological validity of studies for better application can provide useful insights into how to avoid cumulative fatigue and overtraining, as well as lower the risk of injury. While the preceding studies [37][38] examined muscle damage, their primary purpose was to review or investigate the effects of a one-off match (combined with supplementation) on athletic performance. From this perspective, the reduced risk of injury and improved human performance in real-world settings [37][38][39] broaden the application scenarios of "exercise modes". Another application is performing an unusual eccentric exercise that triggers the so-called "repetitive bout effect (RBE)", which has been shown to be a protective adaptive response that significantly reduces EIMD [40]. Therefore, as an important research topic, "exercise mode" has evolved from human- and animal-tested exercise protocols to the current training and intervention model.

- Nutritional strategies and recovery techniques. Co-citation clustering (#0, #2, #9, #13, and #20), as well as several high-cited and high-co-cited references [41][42][43][44], and keyword clustering all pointed to "nutritional strategies" as one of the most dominant research topics in the field of EIMD and protein intake. Not only is "diet strategies" (#0) the top-ranked co-citation cluster, but it is also widely accepted that optimal nutritional supplementation is essential for muscle repair and regeneration [45].

- Specifically, branched-chain amino acids (BCAA) are effective supplements for reducing muscle damage and accelerating recovery after exercise [46][47]. β-Hydroxy-β-methylbutyrate (HMB), a BCAA metabolite, has gained popularity as a human nutritional supplement, particularly among strength athletes [48], by preventing muscle protein degradation and muscle damage during intense training [10]. Another promising strategy for reducing muscle damage is the combination of carbohydrates and protein (e.g., carbohydrate–protein beverages) [41][42]. Furthermore, in the context of nutritional strategies, the parallel to nutritional supplements is diet and food. The importance of diet and food is supported by the top ten co-cited references (three studies using milk or Montmorency cherry) and co-citation clusters [41][42][43][44]. Diet and food containing various ingredients (clusters #9 nitrate-rich beetroot juice and #20 grandiflorum-derived saponin) have also been studied to alleviate EIMD [49][50]. Overall, diet and food are a more practical and secure alternative to supplements for athletes to prevent unintentional doping [51]. It is also worth noting that when conducting a clinical trial (e.g., nutritional changes or massage), it has become standard practice to use a randomized, double-blind, and placebo study design whenever possible to avoid expectations (bias) of main and subject/participant effects. Therefore, double-blind placebo was identified as a significant cluster (#13) for this topic. Finally, skeletal muscle inflammation and soreness are frequently treated with non-nutritive recovery techniques, such as massage and cold-water immersion [16][17]. Although physical recovery techniques were not included in the clustering of co-cited references and keywords, two highly cited studies [16][17] were among the top ten cited references. Combining the evidence presented above and considering the practical applications of physical recovery techniques in the field of sports and fitness (likely accompanied by EIMD or DOMS), it is reasonable to conclude that non-nutrition treatments are a promising research topic. Intriguingly, the potential mechanisms by which physical recovery techniques affect EIMD or DOMS, as well as whether they interact with nutritional supplements, need to be investigated further. To summarize, gaining a comprehensive understanding of nutritional strategies to alleviate EIMD symptoms and accelerate recovery [6][10] is the predominant research objective.

- Beneficial outcomes. As previously stated, the EIMD- and DOMS-related “exercise mode” and “nutritional strategies” are becoming more application-oriented. This implies that “beneficial outcomes” will inevitably receive more attention, as evidenced by cluster #5 (practical application), which is provided by Peake et al.’s review [52]. Cluster #1 (skeletal muscle hypertrophy) demonstrates that muscle inflammation and increased protein turnover during EIMD recovery are required for long-term hypertrophic adaptations [14]. Peake et al.’s review concluded that EIMD and the subsequent inflammatory responses are unavoidable because both are thought to be essential components of muscle repair [52]. Furthermore, as evidenced by the top-cited and top co-cited references, numerous application-based studies on training interventions and nutritional supplements have highlighted their beneficial outcomes. Measures of exercise performance (muscle strength, vertical jump, and speed), muscle function and muscle cell morphology (muscle cell and subcellular disruptions, muscle swelling, and cytoskeletal muscle fiber components), the inflammatory response (leukocyte count, C-reactive protein, cytokines, and interleukin-6), enzymes (creatine kinase and lactate dehydrogenase), and hormones/metabolites are the main components included (cortisol, testosterone, thiobarbituric acid-reactive substances, protein carbonyls, and uric acid). Given the previous findings, the role of EIMD in muscle function and hypertrophy is an especially intriguing research hotspot.

- Taking all of the above outcomes into account, the role of EIMD in muscle function and hypertrophy is an intriguing research hotspot. Muscle hypertrophy, for example, can benefit the elderly’s health by preventing the onset of sarcopenia and (or) muscle atrophy [53]. Therefore, this topic is supported by a large number of beneficial outcomes. However, transferring the beneficial effects from the laboratory to the clinic remains a challenge.

- Proposed mechanisms. Exploring the underlying mechanisms of EIMD or DOMS has always been regarded as an important research topic. It is widely accepted that the complex damage model can be divided into two phases: the initial phase, or primary damage, that results from the mechanical and metabolic stress caused by an exercise bout, and secondary damage that propagates tissue damage via processes associated with the inflammatory response [9]. Numerous studies, as evidenced by the clusters of co-citations and keywords, concentrated on oxidative stress and inflammation, which are thought to be EIMD contributing factors but are also required for recovery and adaptation processes [6][11]. It is also important to recognize muscle protein functions (co-citation cluster #16 obscurin) and pro-inflammatory cytokine gene expression (cluster #7 messenger RNA and keyword cluster #7 nociceptor interleukin). Finally, assessing the efficacy of the proposed EIMD-associated-protein mechanisms assists researchers in determining the precise effect of various nutritional and therapeutic strategies on EIMD reduction and recovery [4][13].

4. Frontiers and Future Directions

In general, research frontiers are inferred by analyzing the evolution of keyword bursts and end years [54]. However, it has been revealed that using only high-frequency keyword data is insufficient, potentially ignoring some high-quality research [31][32]. As a result, researchers combined burst keywords and keyword clusters with a co-cited reference timeline map. The frontiers can be categorized as follows.

- The foundation of muscle hypertrophy and protein supplements. In recent years, investigating whether or not EIMD is related to muscle hypertrophy appears to be cutting-edge, as the frontier keywords “protein synthesis” and “eccentric exercise” have an association with muscle hypertrophy. Although muscle hypertrophy can occur in the absence of muscle damage [55][56], increased exercise-induced reactive oxygen species (ROS) and inflammatory responses are more commonly associated with muscle hypertrophy and are attracting researchers’ attention. Muscle adaptation necessitates low-to-moderate-exercise-induced ROS production; if it exceeds a certain threshold, not only do the physiological benefits diminish, but muscle damage worsens [57]. Although post-exercise oxidative stress and inflammation are important for both recovery and adaptation [11], long-term nutritional interventions that rely too heavily on these two factors have not resulted in the expected improvement in muscle adaptation [6]. Moreover, the trade-off between recovery and adaptation varies depending on the primary goal of the session. To optimize the “beneficial outcomes”, for example, a periodized approach to nutrition should be fully considered to adequately support exercise/training in order to achieve a balance between the potential for recovery and adaptation [6][12]. This might be partially supported by the concept of exercise-induced hormesis theory, which purports that biological systems respond with a bell-shaped curve [57][58]. Furthermore, the first half of the “stratification” of burst references (2014–2019) reflects and corroborates this. Therefore, it is likely to become a research frontier that applies the concept of hormesis of nutritional supplementation to various training purposes, training phases, fitness levels, genders, and ages and then applies these findings in real-world scenarios.

- In practice, however, a single theory and/or hypothesis has limited explanatory power when the cause–effect relationship is not proven. More research is needed to confirm that there is a link between muscle damage and hypertrophy [14] and to investigate the potential dose–response relationship. The optimal level for determining muscle damage caused by hypertrophy can be determined in this direction. Thus, researchers believe that “exercise modes” and “nutritional strategies” are important in activating antioxidants, DNA repair, and protein-degrading enzymes. It is more than just muscle recovery and adaptation and includes, perhaps more subtly, oxidative stress-related diseases and, more broadly, aging.

- Potential mechanisms of muscle fiber and muscle membrane damage. Applied research is frequently supported by basic science. Aside from the aforementioned applied research, the evidence presented below has a common but easily overlooked theme: the “stratification” of citation burst references, which have been continuously followed and cited until now. Influential basic studies can be found in high-impact journals (Nature, FASEB J, Free Radic Biol Med, and Am J Physiol) [59][60][61][62]. Furthermore, studies published in high-impact journals and the bursts of keywords (expression, metabolism, and protein synthesis) all focused on the morphological hallmarks of eccentric-contraction-induced injury and/or the protective effect of nutritional supplements, such as the myofibrillar Z-disc, α-actin, and the cytoskeleton (desmin, titin, nebulin, dystrophin, dysferlin, and so on) [8][63][64][65]. Since studies published in high-centrality journals such as Nature [61][62] revealed that the most common human muscular myopathy (Duchenne muscular dystrophy) is caused by a lack of dystrophin on the cytoplasmic surface of the skeletal muscle membrane, cytoskeleton proteins have been the focus. Furthermore, cytoskeleton degradation is an important potential mechanism of muscle damage/EIMD [8][63][64][65]. Accordingly, despite significant research contributions to EIMD, the precise mechanisms causing muscle damage, soreness, repair, and adaptation remain speculative, calling for further research.

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