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# Validity of the indirect biomarkers used in exercise-induced muscle damage: A systematic review with meta-analysis

Emeric Chalchat <sup>\* 1,2</sup>, Anne-Fleur Gaston <sup>3</sup>, Keyne Charlot <sup>2,4</sup>,  
Luis Peñailillo <sup>5</sup>, Omar Valdés <sup>5</sup>, Pierre-Emmanuel Tardo-Dino <sup>2,4</sup>,  
Kazunori Nosaka <sup>6</sup>, Vincent Martin <sup>1,7</sup>, Sebastian Garcia-Vicencio <sup>2,4</sup>,  
Julien Siracusa <sup>2,4</sup>

<sup>1</sup> Laboratoire AME2P (EA 3533) – Université Clermont Auvergne – France

<sup>2</sup> Institut de Recherche Biomédicale des Armées – Service de Santé des Armées – France

<sup>3</sup> Laboratoire Européen Performance Santé Altitude – Université de Perpignan Via Domitia : EA4604 – France

<sup>4</sup> Laboratoire de Biologie de l'exercice pour la Performance et la Santé – Université d'Évry-Val-d'Essonne, Université Paris-Saclay, Institut de recherche biomédicale des armées – France

<sup>5</sup> Exercise Science Laboratory, School of Kinesiology, Faculty of Medicine, Universidad Finis Terrae – Santiago – Chile

<sup>6</sup> Centre for Exercise and Sports Science Research, School of Medical and Health Sciences, Edith Cowan University – Joondalup, WA – Australia

<sup>7</sup> Institut Universitaire de France – France

## Introduction

It has extensively been reported that performing unaccustomed, prolonged and/or vigorous exercise may result in exercise-induced muscle damage (EIMD). Muscle function measured at 24-48h is considered a reliable, valid and indirect marker of the degree of EIMD. However, early measurements (< 2h) must be interpreted with caution because these measures may reflect a combination of muscle damage and muscle fatigue rather than muscle damage alone. In the clinical and sport context, it is important to identify valid and/or early markers to determine the extent of EIMD. The aim of the present work was to conduct a systematic review and meta-analysis to: 1) describe the time-course of the most commonly used EIMD markers for different levels of muscle damage; 2) test whether some of these markers were associated with the magnitude of strength loss.

## Methods

Databases were searched using the following terms: (*"muscle damage" OR "muscle injury" OR "EIMD"*) AND (*contraction OR exercise*) AND (*strength OR MVC OR torque OR force OR "muscle function" OR "neuromuscular function" OR "maximal voluntary contraction"*) NOT (*"mouse" OR "Mice" OR "rat" OR "animal"*). 2209 articles were then screened for eligibility using the following criteria: (1) they implemented a model to study EIMD of the lower limb muscles in healthy human's adults (2) the outcome included valid measures of strength at least two times (before and 24h or 48h after exercise) combined with the evaluation of at least one indirect marker of EIMD (3) they did not use recovery techniques or others interventions (4) they

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\*Speaker

reported all necessary data to calculate effect sizes. Standardized mean differences of the most commonly used EIMD markers were calculated for each experimental group at several timing of measurement ( $< 6, 24, 48, 72, > 96\text{h}$ ). Meta-regressions were performed to determine the association between the largest decrease in maximal voluntary contraction (MVC) force observed at 1-2 days after EIMD and muscle damage biomarkers kinetics. In order to compare EIMD markers changes across different levels of MVC force reduction (i.e., 24h – 48h), a k-medoids analysis was performed to identify clusters.

## Results and discussion

Experimental groups were classified into three clusters with low, moderate and high MVC reductions. Meta-Analyses were performed for jump height (JH), range of motion (ROM), limb circumference, delayed-onset muscle soreness (DOMS), pressure pain, creatine kinase (CK), myoglobin (Mb), lactate dehydrogenase, interleukin-6, rate of force development (RFD), evoked response, voluntary activation level (VAL), transverse relaxation time (T2). Meta-regressions showed significant correlations between peak changes in maximal voluntary contraction (MVC) and changes in JH ( $< 6, 24, 72\text{h}$ ), ROM ( $< 6, 48\text{h}$ ) CK (72h), Mb ( $< 6\text{h}$ ), DOMS ( $< 6, 48, 72, > 96\text{h}$ ), RFD (24h), VAL ( $< 6, 72\text{h}$ ), evoked response (24, 48, 72,  $> 96\text{h}$ ) and T2 (24, 48h).

## Conclusion

The time-course of the most commonly used EIMD markers could vary as a function of levels of muscle damage (low, moderate and high). Kinetics of biomarkers of EIMD must be interpreted cautiously between studies and take into account methodological factors which could determine the extent of the strength loss.

**Keywords:** meta, regression, eccentric exercise, EIMD, rhabdomyolysis, neuromuscular function, creatine kinase, myoglobin, DOMS.