International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

INPLASY202520089

doi: 10.37766/inplasy2025.2.0089

Received: 19 February 2025

Published: 19 February 2025

Biomarkers of Skeletal Muscle Atrophy Based on Atrogenes Evaluation: A Systematic Review and Meta-Analysis Study

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ADMINISTRATIVE INFORMATION

Support - CAPES, FAPERJ, CNPq.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

INPLASY registration number: INPLASY202520089

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 February 2025 and was last updated on 19 February 2025.

INTRODUCTION

Review question / Objective The objective is to evaluate the association between E3 ligases MAFbx/Atrogin-1 (Fbxo32) and MuRF-1 (TRIM63) mRNA levels, the reduction in skeletal muscle CSA measures, and the atrophy statement.

Rationale Our study is meticulously designed to establish a sensitive, repro-ducible, and quantitative molecular marker for skeletal muscle atrophy.

Condition being studied Skeletal muscle atrophy, characterized by a reduction in muscle mass and a decrease in its contractile capacity is commonly identified through a reduction in the cross-sectional area (CSA) of muscle fibers. The atrophy occurrence is a converging feature of several muscle skeletal disorders, in addition to being an important determinant of the functional performance of patients with other diseases such as cancer, sepsis, car-diomyopathies and methylmercury poisoning. With the increase in average life ex-pectancy, it is reasonable to estimate that more individuals will be committed with muscle disorders during their lifetime. Taking into account the importance of skeletal muscle for autonomy and quality of life, researches on morphological, functional and metabolic changes in skeletal muscle tissue have gained prominence in the scientific community. According to the PubMed® database, from 1856 to date there are 47,627 results of articles in which the key words “muscle atrophy” are searched. However, the mechanisms that trigger muscle atrophy continue to be under constant debate in specialized literature.

METHODS

Search strategy The studies were selected without a publishing date limitation. The following

key-words were used in a combined way: “E3 ligases and muscle atrophy” and “E3 ligases and muscle hypertrophy”.

Participant or population The animals included in the studies were adult male mice, aged between 4 to 77 weeks submitted to muscle atrophy induction protocols.

Intervention The current meta-analysis only included studies that had analyzed mice skeletal muscles CSA by histology and among staining methods were: H&E; laminin-stained immunohistochemistry; dye-ATPase. Fbxo32 (Atrogin/MAFbx gene) and Trim63 (MuRF1 gene) mRNA amounts by polymerase chain reaction in real time (qPCR) or Northern Blot-ting.

Comparator The animals included in the studies were adult male mice, aged between 4 to 77 weeks submitted to muscle atrophy induction protocols or control conditions.

Study designs to be included Randomized, non-randomized and controlled studies, published in the English language, available in the PubMed®, Scopus and Web of Science databases were selected for inclusion.

Eligibility criteria Not applicable.

Information sources The mean and standard deviation values were extracted from the studies by a di-mensional tool for graphical analysis (CorelDRAW®, Graphics Suite, version 12.0 for Windows). When it was not possible to obtain data from the graphs of a certain result, it was not included in the analysis.

Main outcome(s) The search generated a total of 584 studies which were completely revised by three researchers who were responsible for randomly selecting the studies for subsequent anal-ysis. A fourth experienced researcher was responsible for settling any disagreement be-tween the three reviewers, when necessary.

Additional outcome(s) Figure 1 presents the identification process of the number of studies included in the analysis flow chart. By means of the selection strategy used, 584 studies were retrieved. After removing duplicates, 360 studies were screened. 330 studies were excluded after application of inclusion criteria such as E3 ligases untested, not been performed on mouse skeletal muscle and had not analyzed CSA. Another 44 studies were excluded for reasons, such as retractation by fails, female mice or CSA and qPCR obtained from different muscles. Finally, twenty-nine out of the 584 were selected for analysis based on the eligibility and inclusion criteria.

Data management The mean and standard deviation values were extracted from the studies by a di-mensional tool for graphical analysis (CorelDRAW®, Graphics Suite, version 12.0 for Windows). When it was not possible to obtain data from the graphs of a certain result, it was not included in the analysis.

Quality assessment / Risk of bias analysis The funnel plot was used to visualize the data symmetry and Egger’s test to deter-mine the bias risk [13]. Two researchers analyzed the quality level of the studies utilizing a NIH-Study Quality Assessment Tool for controlled intervention studies [14].

Strategy of data synthesis The pooled effect size (ES) (also mentioned as standardized mean difference (SMD) and standard deviation (SD) data were calculated from the average, SD and sample size (n) of control and treatment groups. A pooled analysis of the estimated ranges was devel-oped with a fixed effects model performed using the software STATA 10.0 (StataCorp LP, College Station, USA).

Subgroup analysis After establishing the ES of the studies which was ordered ascendingly, a quartile division was employed considering the magnitude of the ES of CSA change across each study. A set of subgroup studies were scrutinized for each quartile.

Sensitivity analysis The heterogeneity among the selected studies was analyzed by Cochran Q test [15] and by the I2 statistics: I2 = 100% x(Q – df)/Q (1) Where Q is the Cochran Q test and df the degrees of freedom.

Language restriction Only studies published in the English language.

Country(ies) involved Brazil.

Other relevant information Not applicable

Keywords musculoskeletal; atrophy; E3 ligases; molecular research; animal models; tissue alterations.

Contributions of each author

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