

INPLASY PROTOCOL

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Review Stage at time of this submission: Preliminary searches.

Conflicts of interest:
None declared.

Myokines secretion and their role in critically ill patients. A scoping review protocol

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Review question / Objective: 1-How and by which means stimulated muscle from critically ill patients can liberate myokines?, 2-Which are the main characteristics of the critically ill population studied and if some of these influenced myokine's secretion?, 5-Can myokines exert local or distant effects in critically ill patients?, 5-Which are the potential effects of myokines in critically ill patients?

Eligibility criteria: Participants and context: We will include primary studies (randomized or non-randomized trials, observational studies, case series or case report) that consider hospitalized critically ill adult patients (18 years or older) in risk for developing some degree of neuromuscular disorders such as ICU-AW, diaphragmatic dysfunction, or muscle weakness, therefore the specific setting will be critical care. Concept: This review will be focused on studies regarding the secretion or measure of myokines or similar (exerkines, cytokines or interleukin) by any mean of muscle activation or muscle contraction such as physical activity, exercise or NMES, among others. The latter strategies must be understood as any mean by which muscle, and there for myocytes, are stimulated as result of muscle contraction, regardless of the frequency, intensity, time of application and muscle to be stimulated (upper limb, lower limb, thoracic or abdominal muscles). We also will consider myokine's effects, local or systemic, over different tissues in terms of their structure or function, such as myocytes function, skeletal muscle mass and strength, degree of muscle wasting or myopathies, among others.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 September 2021 and was last updated on 16 September 2021 (registration number INPLASY202190048).

INTRODUCTION

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critically ill patients can liberate myokines?, 2-Which are the main characteristics of the critically ill population studied and if some of these influenced myokine's secretion?,

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Background: Critically ill patients hospitalized at ICU are characterized by an accelerated skeletal muscle wasting, partially attributed to sepsis, multiple organ failure, as well as immobilization. This muscle insult is gravitating at several levels since skeletal muscle is a highly organized tissue which provides structural support, locomotion, breathing, shape, facial expression, and metabolic support to the body. Muscle weakness affecting both the respiratory muscles and peripheral muscles of the axial skeleton is thought to be the key mediator for disability after critical illness. The development of ICU-acquired weakness (ICU-AW), a neuromuscular disorder characterized by profound peripheral muscle weakness and loss of physical functions even after discharge, is associated with delayed weaning from MV, prolonged ICU and hospital stay, and increased mortality. Particularly, respiratory muscle weakness will occur in up to 60% of mechanically ventilated patients, being an independent risk factor for prolonged weaning from MV and increased mortality.

Rationale: For ICU patients, sepsis and muscle inactivity derived from sedation and MV use, are key driver mechanisms to an accelerated muscle wasting, which leads to general muscle weakness and loss of physical functions even after discharge. Particularly, muscle respiratory wasting will occur early (18 to 69 hours) in up to 60% of patients with mechanical ventilation (MV), leading rapidly to diaphragmatic weakness which can be avoided through early physical activation. However, vigorous exercise is limited at early stages of care in great proportion of these population, where sedation and MV are needed, delaying muscle activation, and favoring a vicious circle. Passive limb mobilization, mild degrees of muscle activation and even external muscle contraction induced through neuromuscular electrical stimulation (NMES) represents an alternative to

traditionally exercise conception, being able to prevent local muscle wasting and, according to some ICU reports, has the potential to induce a systemic effect through myokines, a diverse range of cytokines and chemokines secreted by myocytes during muscle stimulation. These factors can modulate the function and metabolism of distant organs and can promote a protective profile for the development of several ICU complications, being not only useful for the local prevention of muscle wasting. Although it is true that the potential role of myokines in the critical patient is new, the isolated secretion of some of them has been previously reported in this context, however there is no research focused on this specific topic, being necessary to explore and resume the evidence regarding to myokine's secretion and its local or systemic effects in the critical ill patient, especially in early stages of disease as a novel approach.

METHODS

Search strategy: To identify original studies suitable for answering the research questions, MEDLINE, CINAHL, Embase, Scopus and WoS database will be searched since establishment of the database. The search strategy will consist of controlled terms (MeSH, Emtree, among others) and natural language keywords, which will be adjusted according to the database and platform consulted. The syntax for the Pubmed platform is shown below: (((((((((((((((((((((((((((((((((((("Cytokines"[Mesh]) OR ("Chemokines"[Mesh]) OR ("Interleukins"[Mesh]) OR (exerkin*) OR (Interleukin*) OR (myokin*)) OR ("Angiopietin-like 4") OR (ANGPTL4) OR (Apelin) OR ("aminoisobutyric acid") OR (BAIBA) OR ("Brain-derived neurotrophic factor") OR (BDNF) OR ("Chemokine ligand") OR ("C-X-C motif") OR (Decorin) OR ("Fibroblast growth factor 21") OR (FGF21) OR (IL-6)) OR (IL-8)) OR (IL-10)) OR (IL-13)) OR (IL-15)) OR (IL-18)) OR (Irisin) OR (FNDC5) OR (Musclin) OR (Myonectin) OR (C1QTNF5) OR (Myostatin) OR ("Leukemia inhibitory factor") OR (LIF) OR ("Secreted protein acidic rich in cysteine"))

OR (SPARC)) OR ("Tumor necrosis factor-alpha") OR (TNF-a)) AND (((("Critical Illness"[Mesh]) OR ("Critical Care"[Mesh])) OR ("Intensive Care Units"[Mesh])) OR (((intensive) OR (critical)) OR (critical)) AND (care))) OR ((critical*) AND ((ill) OR (illness*)))) AND (((((((("Electric Stimulation Therapy"[Mesh]) OR ("Transcutaneous Electric Nerve Stimulation"[Mesh])) OR ("Electric Stimulation"[Mesh])) OR ((neuromuscular OR functional) AND electric*)) OR (electrotherap* OR electromyostimulation OR electrostimulation OR (electric* AND stimulation))) OR (NMES OR FES OR TENS)) OR (((((((("Exercise"[Mesh]) OR ("Exercise Therapy"[Mesh])) OR ("Physical Therapy Modalities"[Mesh])) OR ("Occupational Therapy"[Mesh])) OR ("Recovery of Function"[Mesh])) OR ("Muscle Contraction"[Mesh])) OR (physiotherap* OR "physical therap*" OR kinesiotherap*)) OR ("Resistance Training"[Mesh])) OR ("strength training")) OR ("physical rehabilitation")) OR (((muscle) OR (muscular)) AND (((exercis*) OR (training)) OR (contraction)) OR (activation))))). In addition, other search resources will be explored: (1) relevant references will be selected from reviews identified in the biomedical databases described above, (2) Contact with specialists in the field to obtain key references for this scoping review, and (3) clinical practice guidelines, protocols and/or recommendations published on web pages of scientific societies affiliated to the "World Federation of Intensive and Critical Care (WFICC)" available at [https:// http://www.wficc.com/societies](https://http://www.wficc.com/societies), will be selected.

Eligibility criteria: Participants and context: We will include primary studies (randomized or non-randomized trials, observational studies, case series or case report) that consider hospitalized critically ill adult patients (18 years or older) in risk for developing some degree of neuromuscular disorders such as ICU-AW, diaphragmatic dysfunction, or muscle weakness, therefore the specific setting will be critical care. Concept: This review will be focused on studies regarding the secretion or measure of myokines or

similar (exerkines, cytokines or interleukin) by any mean of muscle activation or muscle contraction such as physical activity, exercise or NMES, among others. The latter strategies must be understood as any mean by which muscle, and there for myocytes, are stimulated as result of muscle contraction, regardless of the frequency, intensity, time of application and muscle to be stimulated (upper limb, lower limb, thoracic or abdominal muscles). We also will consider myokine's effects, local or systemic, over different tissues in terms of their structure or function, such as myocytes function, skeletal muscle mass and strength, degree of muscle wasting or myopathies, among others.

Source of evidence screening and selection: Hand search for documents will be developed in three formats: (1) relevant references will be selected from reviews identified in the biomedical databases described above, (2) search for documents in personal archives, and (3) clinical practice guidelines, protocols and/or recommendations published on web pages of scientific societies affiliated to the "World Federation of Intensive and Critical Care (WFICC)" available at [https:// http://www.wficc.com/societies](https://http://www.wficc.com/societies), will be selected. Two researchers will independently carry out the selection of scientific documents through two stages: 1) screening of titles and abstracts of identified studies through our search strategy to determine whether they meet our eligibility criteria and rate them as "included", "excluded" or "maybe" and 2) selection of studies categorized as "included" or "maybe" will be reviewed in full text to ultimately determine whether they are included in our review or not. For this stage of our study, we will use the Rayyan® application. For disagreements during documents selection, a third investigator will decide.

Data management: Data extraction stages will be conducted independently and blinded. Disagreements will be resolved by consensus or, ultimately, by the decision of a third reviewer. Once documents to be included has been defined, the extraction of information from them will be done by

two reviewers using a standardized form. Information such as study design, population (age, sex, comorbidities, medical diagnosis), intervention (muscle contraction and dose, frequency, stimulation time and muscle group involved), myokine secreted and assessment method, as well as details of study design and outcome data regarding any effect of myokine secretion (local or systemic).

Reporting results / Analysis of the evidence: PRISMA-ScR will be used as a reference for this scoping review. Quantitative data from original studies will be organized and presented into a tabular format, with further explanations where further interpretation is required to explain the research results in depth. In this study, the quality assessment and bias evaluation won't be carried out for the included studies, because the scoping review did not involve this process. However, we will include the general characteristics of the studies, types of studies (randomized controlled and observational studies among others), reported bias, and statistics data and principal findings of included studies.

Presentation of the results: PRISMA-ScR will be used as a reference for this scoping review. Flow diagram for the for the evidence screening and selection will be provided, and quantitative data will be organized and presented into a tabular format, highlighting myokine's role and secretion mean in critical care setting, with further explanations where further interpretation is required to explain the research results in depth. If is needed, the data extracted from the study will be presented visually or graphically so that it can be summarized or conceptualized.

Language: Our search will not be limited by the language in which the studies are published.

Country(ies) involved: The ScR will be carried out in Chile.

Other relevant information: None.

Keywords: Myokines; cytokines; interleukin; Intensive care unit; critically ill patients; muscle wasting; exercise; Neuromuscular electrical stimulation.

Dissemination plans: The protocol of this review and its results will be presented at conferences and published in journals related to critical care, rehabilitation and physical therapy.

Contributions of each author:

Author 1 - Yorschua Jalil - The author drafted the manuscript, Conceived and designed the search strategy and contributed to proposed analysis tools and preliminary searches. The author 1 drafted the manuscript.

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Author 2 - Ruvistay Gutierrez - The author reviewed and corrected the manuscript, designed collection data form and perform preliminary searches of the review.

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