INPLASY PROTOCOL

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Support: **None.**

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An umbrella review of systematic reviews of β-hydroxy-β-methyl butyrate (HMB) supplementation in promoting skeletal muscle mass and function in aging and clinical practice

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Review question / Objective: **An umbrella review of systematic reviews of the use of β-hydroxy-β-methyl butyrate (HMB) supplementation in promoting skeletal muscle mass and function in aging and clinical practice.**
Condition being studied: **Muscle mass (and various proxies thereof), strength, and physical function.**
Information sources: **Pubmed, Web of Science, Embase.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 October 2021 and was last updated on 19 October 2021 (registration number INPLASY2021100072).

INTRODUCTION

Review question / Objective: **An umbrella review of systematic reviews of the use of β-hydroxy-β-methyl butyrate (HMB) supplementation in promoting skeletal muscle mass and function in aging and clinical practice.**

Rationale: **There are abundant data from cells, pre-clinical models, and humans to indicate that HMB is also a potent stimulator of muscle protein synthesis and inhibits muscle protein breakdown. However, importantly there are now numerous systematic reviews of HMB and its effectiveness. The main aim of this review was to examine these systematic reviews in which HMB has been examined for its effects on older persons and clinical populations. Specifically, the aim was to look at HMB as a compound alone or**

combined with macronutrients (usually as part of an oral nutritional supplement) to stimulate gains in muscle mass. In most reports, it is not muscle mass that is measured but fat- and bone-free lean mass or lean soft-tissue mass (LSTM); hence, we accepted these proxies of muscle mass in this review. While it is often implied, particularly in narrative reviews of HMB, we also sought to determine the role of HMB in improving muscle function manifest either as an improvement in mobility, physical function, or strength. Improvements in these outcomes would be beneficial for mitigating sarcopenia and improving outcomes in clinical populations. Several early studies also showed a positive impact of HMB supplementation in mitigating age-related losses of LSTM in older persons and in older hospitalized patients and potentially in older patients receiving critical care. A review of systematic reviews was undertaken here to answer a critically important question: is HMB an effective supplement in promoting retention and/or mitigating the loss of muscle mass and enhancing physical function in older persons (with or without sarcopenia) and also in clinical populations?

Condition being studied: Muscle mass (and various proxies thereof), strength, and physical function.

METHODS

Search strategy: Web of Science core collection: ((((((TS=(HMB)) OR TS=(beta-hydroxy-beta-methylbutyrate)) OR TS=(*-hydroxy-*-methylbutyrate) OR TS=(beta-hydroxy-beta methylbutyrate)) OR TS=(b-hydroxy-b-methylbutyrate)) OR TS=(3-hydroxy-3-methylbutyrate))) AND (TS=systematic review) Pubmed: Search: (((((HMB) OR (beta-hydroxy-beta-methylbutyrate)) OR ((3-hydroxy-3-methylbutyrate))))) AND (systematic review) Sort by: Most Recent ("HMB"[All Fields] OR ("beta hydroxyisovaleric acid"[Supplementary Concept] OR "beta hydroxyisovaleric acid"[All Fields] OR "beta hydroxy beta methylbutyrate"[All Fields]) OR "3-hydroxy-3-methylbutyrate"[All Fields]) AND ("systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review"[All Fields]) Embase: Database: Embase Search Strategy: 1 ((HMB or beta-hydroxy-beta-methylbutyrate or 3-hydroxy-3-methylbutyrate or b-hydroxy-b-methylbutyrate or beta hydroxy beta methylbutyrate or beta-hydroxy beta-methylbutyrate or beta-hydroxy beta methylbutyrate or beta hydroxy beta-methylbutyrate) and (systematic review or systematic)).af. (159) 2 Heavy menstrual bleeding.af. (2014) 3 1 not 2 (90).

Participant or population: Adults aged 50 or older.

Intervention: Ingestion of HMB alone or as part of a multi-ingredient supplement.

Comparator: No HMB-containing placebo (various forms).

Study designs to be included: Systematic reviews of HMB.

Eligibility criteria: Systematic reivews.

Information sources: Pubmed, Web of Science, Embase.

Main outcome(s): Muscle mass (MRI or CT or biopsy) and its proxies from DXA (lean soft-tissue mass), strength, physical function (various tests).

Quality assessment / Risk of bias analysis: AMSTAR.

Strategy of data synthesis: AMSTAR, standardized effectiveness statements, GRADE-type analysis for systematic reviews.

Subgroup analysis: None.

Sensitivity analysis: None.

Language: English.

Country(ies) involved: Canada.

Keywords: muscle mass, HMB, sarcopenia, strength, physical function.

Dissemination plans: Publication in a scientific journal.

Contributions of each author:

Author 1 - Stuart Phillips - Conceived study design, aided in reviewing papers, aided and oversaw data synthesis, drafted the initial copy of the paper, drafted final copy of the paper, submitted paper.
Email: phillis@mcmaster.ca
Author 2 - Kyle Lau - Aided in reviewing papers, aided in data synthesis, reviewed and edited the initial copy of the paper, agreed on the final copy of the paper.
Email: lauk19@mcmaster.ca
Author 3 - Alysha D'Souza - Aided in reviewing papers, aided in data synthesis, reviewed and edited the initial copy of the paper, agreed on the final copy of the paper.
Email: dsouza14@mcmaster.ca
Author 4 - Everson Nunes - Conceived study design, drafted and ran search strategy, edited and provided feedback on the initial copy of the paper, agreed on the final copy of the paper.
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Conflicts of interest: Dr. Phillips reports grants from US National Dairy Council, during the conduct of the study; personal fees from the US National Dairy Council, non-financial support from Enhanced Recovery, outside the submitted work; In addition, Dr. Phillips has a patent Canadian 3052324 issued to Exerkine, and a patent US 20200230197 pending to Exerkine but reports no financial gains.