The effect of protein and essential amino acid supplementation on muscle strength and performance in patients with chronic heart failure – A systematic review

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The effect of protein and amino acid supplementation on muscle mass and function in patients with chronic heart failure – A systematic review

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Online Resource 1 – PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7-8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7 and online resource 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-9

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10-11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	26
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19-25
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	4

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Online Resource 2 - Search Strategy

Embase:
1. "heart failure".ti,ab
2. HEART FAILURE/
3."left ventricular failure".ti,ab
4. "cardiac failure".ti,ab
5. 1 OR 2 OR 3 OR 4
6. "cachexia".ti,ab
7. CACHEXIA/
8. SARCOPENIA/
9. "sarcopenia".ti,ab
10. "skeletal muscle".ti,ab
11. "lean mass".ti,ab
12. "muscle mass".ti,ab
13. 6 OR 7 OR 8 OR 9 Or 10 OR 11 OR 12
14. "Amino acids".ti,ab
15. "AMINO ACIDS"/
16. ("Branch* Chain Amino Acid").ti,ab
17. "BRANCHED-CHAIN AMINO ACIDS"/ OR "AMINO ACID"/
18. ("Protein").ti,ab
19. 14 OR 15 OR 16 OR 17 OR 18
20. 5 AND 13 AND 19

PubMed:
1. "heart failure".ti,ab
2. "cardiac failure".ti,ab
3."left ventricular failure".ti,ab
4. 1 OR 2 OR 3
5. "cachexia".ti,ab
6. "sarcopenia".ti,ab

7. "skeletal muscle".ti,ab
8. "lean mass".ti,ab
9. "muscle mass".ti,ab
10. 5 OR 6 OR 7 OR 8 OR 19
11. "Amino acids".ti,ab
12. ("Branch* Chain Amino Acid").ti,ab
13. ("Protein").ti,ab
14. 11 OR 12 OR 13
15. 4 AND 10 AND 14

Medline
1. "heart failure".ti,ab
2. HEART FAILURE/
3."left ventricular failure".ti,ab
4. "cardiac failure".ti,ab
5. 1 OR 2 OR 3 OR 4
6. "cachexia".ti,ab
7. CACHEXIA/
8. SARCOPENIA/
9. "sarcopenia".ti,ab
10. "skeletal muscle".ti,ab
11. "lean mass".ti,ab
12. "muscle mass".ti,ab
13. 6 OR 7 OR 8 OR 9 Or 10 OR 11 OR 12
14. "Amino acids".ti,ab
15. "AMINO ACIDS"/
16. ("Branch* Chain Amino Acid").ti,ab
17. "AMINO ACIDS, BRANCHED-CHAIN"/
18. ("Protein").ti,ab
19. 14 OR 15 OR 16 OR 17 OR 18
20. 5 AND 13 AND 19

Online Resource 3 - Mixed Methods Appraisal for Lombardi et al [26]

Questions	**Responses**			
	Y	**N**	**?**	**Comment**
First author and year	Lombardi et al 2014			
Are there clear qualitative and quantitative research questions (or objectives*), or a clear mixed methods question (or objective*)?	Y			Effect of intervention (11 different AA's supplementation) on functional capacity in CHF (VO2 max and 6MWT).
Do the collected data allow address the research question (objective)? E.g., consider whether the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components).	Y			Although only 13 patients enrolled, open labelled, therefore prone to bias.
1.1				N/A
1.2				N/A
1.3				N/A
1.4				N/A
2.1				N/A
2.2				N/A
2.3				N/A
2.4				N/A
3.1 Are participants (organizations) recruited in a way that minimizes selection bias?		N		Although reports consecutive patients enrolled, there is no mention of the time period for recruitment and thus no way to evaluate if the number recruited really does represent all consecutive patients. The text suggests this is a convenience sample.

3.2 re measurements appropriate (clear origin, or validity known, or standard instrument; and absence of contamination between groups when appropriate) regarding the exposure/intervention and outcomes?	Y			Measurements are clear, quantitative and validated measures in patients with heart failure (VO2 max and 6MWT).
3.3 In the groups being compared (exposed vs. non-exposed; with intervention vs. without; cases vs. controls), are the participants comparable, or do researchers take into account (control for) the difference between these groups?			NA	Single arm study. Patients themselves act as controls in pre and post study.
3.4 Are there complete outcome data (80% or above), and, when applicable, an acceptable response rate (60% or above), or an acceptable follow-up rate for cohort studies (depending on the duration of follow-up)?	Y			100% complete outcome data at pre-specified time-point.
4.1				N/A
4.2				N/A
4.3				N/A
4.4				N/A
5.1				N/A
5.2				N/A
5.3				N/A

Online Resource 4 –Excluded studies

Study	Year	intervention	Intervention Duration	Reason for Exclusion
Machhi et al	2010	Amino Acid Supplementation only	3 Months	Did not measure strength or muscle performance
Aquilani et al	2008	Amino Acid Supplementation only or Standard Care +Placebo	30 Days	Did not measure strength or muscle performance

Scognamiglio et al	2008	Amino Acid Supplementation only or Standard Care +Placebo	6 Months	Did not measure strength or muscle performance
Mancini et al	1992	Amino Acid Supplementation only or Standard Care +Placebo	6 Months	Did not measure strength or muscle performance
Azuma et al	1985	Amino Acid Supplementation only or Standard Care +Placebo	4 weeks	Did not measure strength or muscle performance
Anand et al	1998	Amino Acid Supplementation only or Standard Care +Placebo	30 days	Did not measure strength or muscle performance
Caponnetto et al	1994	Amino Acid Supplementation only or Standard Care +Placebo	6 Months	Did not measure strength or muscle performance

Online Resource 5 - Intervention Attrition and Adherence

Study	**Participants Recruited (*n*=)**	**Attrition**	**Compliance**
Aquilani et al. (22)	I: 22	I: 1 (5%)	I: 100%
	C:22	C: 4 (18%)	C: 100%

Rozentryt et al. (23)	I: 23	I: 1 (4%)	Not Report
	C: 6	C: 0 (0%)	
Pineda-Juares et al. (24)	I:34	I: 3 (9%)	Not Report
	C:32	C: 4 (13%)"	
Wu et al. (25)	I:17	I: 3 (18%)	Not Report
	C:14	C: 2 (14%)"	
George et al. (26)	I:6	I: 3 (50%)	Not Report
	C:5	C:2 (40%)"	
Lombardi et al. (27)	I:6	I: 0 (0%)	Not Report
	C:N/A	C: N/A	

I = Intervention Group; C = Control Group;