

· 临床研究 ·

循证初步构建老年肌少症营养功能性食品临床试验指标池

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【摘要】 **目的** 构建老年肌少症营养功能性食品临床试验指标池, 为后续确定核心指标集提供依据。**方法** 检索中国知网、维普、万方、Ovid-Embase、Cochrane Library 和 PubMed 数据库中老年肌少症营养功能性食品干预相关随机对照研究, 提取其结局指标集合(A); 检索中、美临床试验注册平台相关试验方案, 提取其结局指标集合(B); 采用便利抽样法, 以半开放式问卷对全国 17 家该领域影响力较大的三甲医院的临床医师及患者进行调查, 收集医师所关注的结局指标集合(C)和患者所关注的结局指标集合(D)。综合 A、B、C、D 共 4 个指标集合, 初步构建 5 个维度、共 64 个末级指标的指标池。**结果** 共纳入 16 篇随机对照研究和 15 个临床试验方案, 经过结局指标提取, 获得 A 集合结局指标 95 个, B 集合结局指标 86 个; 共调研 86 名医师和 85 例患者意见, 收集到 C 集合结局指标 38 个、D 集合结局指标 35 个。按照既定的指标纳入排除方法, 经过工作组讨论, 确定含有末级指标 64 个的指标池。**结论** 本研究建立了老年肌少症营养功能性食品临床试验指标池, 并发现该领域临床试验结局指标存在异质性及不一致等问题, 对后续构建老年肌少症营养功能性食品临床试验核心指标集具有重要意义。

【关键词】 临床试验; 肌少症; 结局指标; 系统评价

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Initiative evidence-based establishment of an indicator pool for clinical evaluation of nutritional and functional food for the elderly with sarcopenia

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【Abstract】 **Objective** To establish an indicator pool for clinical trials on nutritional and functional food interventions for the elderly with sarcopenia as the basis of subsequent core outcome set. **Methods** CNKI, VIP, WANFANG DATA, Ovid-Embase, Cochrane Library and PubMed databases were electronically searched to collect randomized control trials on nutritional and functional food interventions for the elderly with sarcopenia. The outcome indicators were extracted as set A. Chi-CTR and the Clinical Trials were then searched to collect the related registration schemes, and the outcome indicators were extracted to form set B. Using the convenience sampling, a semi-open questionnaire survey was conducted among the clinicians and patients in 17 first-class tertiary hospitals with great influence in this field to collect the set (C) of outcome indicators concerned by the doctors and the set (D) of outcome indicators concerned by the patient. A 5-dimension indicators pool of 64 end-class indicators was initially constructed by integrating the sets A, B, C and D. **Results** A total of 16 randomized control studies and 15 clinical trial protocols were included, yielding 95 outcomes in set A and 86 in set B. A total of 86 doctors and 85 patients' opinions were investigated, and 38 and 35 outcome indicators were collected in set C and set D. According to inclusion and exclusion standard of indicators, a final pool of 64 terminal indicators was established. **Conclusion** This study established an indicator pool for the elderly patients with sarcopenia and found heterogeneity and inconsistencies in the outcome indicators of clinical trials in this field. It is of great significance to continue constructing the core outcome set on nutritional and functional food interventions for those patients.

【Key words】 clinical trials; sarcopenia; outcome; systematic review

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肌少症是一类进行性的广泛性的骨骼肌量和肌力减少, 以及骨骼肌功能减退导致机体功能和生活

质量下降甚至死亡的综合征, 已成为危害我国老年人群健康的重要疾病。系统评价结果显示, 我国社

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区老年人肌少症患病率为12%^[1]。营养干预结合运动训练是改善肌少症的有效手段之一^[2]。目前仍无肌肉衰减综合征特定全营养配方食品注册成功,现阶段营养干预多为蛋白粉和固体饮料等形式,这些以有效活性成分为基础研制的营养功能性食品在肌肉衰减综合征的营养治疗上具有较高的应用价值。目前,不同国家和组织对营养功能性食品的定义尚未达成一致,但总体而言,是指一类含有有益活性成分或者通过特殊工艺优化,可以令人信服地证明对于人体健康有某种或多种益处、有足够营养效果改善健康状况或能减少患病的食品,有望应用于多种慢性非传染性疾病的营养干预治疗^[3]。传统认为食品除了提供营养素外,不具有或不能宣传任何生理功能,但随着科技的发展,越来越多真正具有生理功能的食品被开发出来,却无法获得认可,极大地阻碍了食品产业营养功能升级。为了突破产业发展瓶颈,实现食品产业转型,必须建立一套科学、合理及可行的评价营养功能性食品的评价标准。本研究旨在通过临床试验核心指标集(core outcome set, COS)构建方法^[4],建立老年肌少症营养功能性食品临床试验指标池,为后续核心指标集的确定提供科学依据。

1 对象与方法

1.1 系统评价

1.1.1 纳入与排除标准 纳入标准:已发表的随机对照研究及发表或注册的随机对照研究的研究方案,研究对象为增龄相关肌少症老年患者(诊断明确,符合国际认可的任一诊断标准或课题组自拟标准,年龄 ≥ 65 岁),以营养功能性食品干预为试验组和对照组的唯一区别。排除标准:研究主要包括年龄 < 65 岁的患者或疾病相关性肌少症患者;其他研究类型文献;未报告结局指标的文献;无法获取全文的研究。本研究已获四川大学华西医院伦理委员会批准,并于COMET数据库注册,可于<https://www.comet-initiative.org/Studies/Details/1693>获取。

1.1.2 文献检索策略 中文检索词以肌肉、骨骼肌、衰减、减少、少肌症、肌少症、成人、患者、病患、居民、病人、老年、肠内、肠道、膳食、食品、食物、饮食、肌酸、制剂、饮料、HMB、肽、氨基酸、蛋白质、营养、维生素、脂肪酸及矿物质在中国知网、维普和万方数据库进行检索。英文检索词以 diet, food and nutrition, enteral nutrition, diet therapy, amino acids, peptide(s), proteins, nutrition, nutrient, food, feed, drink, HMB, beta-hydroxy-beta-methylbutyrate, vitamin, creatine, keratin, enteral,

fatty acid, PUFA, mineral, muscular atrophy 及 sarcopenia 在 Ovid-Embase, Cochrane Library 和 PubMed 数据库中进行检索。检索日期均从建库至2019年3月11日。以 sarcopenia, sarcopenic obesity, 肌肉衰减, 肌少症和少肌症为关键词,检索中、美临床试验注册平台,检索时限截至2019年7月29日。文献均导入 Endnote X8 软件进行查重。

1.1.3 文献筛选及信息提取 文献筛选由2名研究人员独立同步进行,如若出现意见不统一,则由第3名研究者对分歧进行评判并最终确定是否纳入。如遇引文信息提供不全及文献全文无法获得而不能确定的文献,与作者邮件联系获得有关信息后再决定取舍。对数据来源于同一研究的若干文献进行合并。提取符合纳排标准的随机对照试验(randomized controlled trial, RCT)结局指标,形成指标集合A。

对于注册方案,筛选已注册或已发表研究方案但截止检索日期仍未发表研究结果的随机对照研究,在线提取其结局指标,形成指标集合B。

1.1.4 纳入研究的偏倚风险评价 使用 RevMan 5.3 软件,由2名研究人员独立同步采用 Cochrane 偏倚风险评估工具^[5]对纳入的已发表 RCT 研究进行文献质量评价。

1.2 医患意见调查

采用便利抽样法,以半开放式问卷调查全国17家该领域影响力较大的三甲医院的临床医师及患者。对患者采取问卷访谈形式,由医师根据访谈结果代填问卷,若患者所述指标无法简单归纳为某一临床常见指标,要求医师填写时详细描述其原始表述。所调查医师需曾经或正在参与老年肌少症患者的诊治工作,其职称、学历、工作年限及所在科室不限,诊治经验丰富者优先考虑。优先选择受教育程度、配合度高,且于该院接受营养干预治疗的老年肌少症患者作为调查对象。收集医师和患者所关注的结局指标(每人限填 ≤ 5 个指标),分别形成指标集合C和指标集合D,以补充指标池。

17家受调查单位包括:四川大学华西医院、江苏省人民医院、河北医科大学第一医院、天津市第三中心医院、青海省人民医院、空军军医大学西京医院、陆军军医大学新桥医院、郑州大学第一附属医院、中南大学湘雅二医院、西南医科大学附属医院、云南省第一人民医院、成都市第五人民医院、绵阳市中心医院、解放军联勤保障部队第940医院、乐山市人民医院、成都市老年康疗院及内蒙古自治区人民医院。

1.3 指标池初建

指标池指标来源于已发表的 RCT(A)、已注册的试验方案(B)、医师意见(C)和患者意见(D)4个指标集,排除其中90%的工作组成员认为不重要的指标,按照树形结构初建指标体系。

2 结果

2.1 文献筛选结果

共获取题录 22 185 条,经过初筛与复筛,最终纳入 16 项 RCT 研究^[6-21]。从中、美临床试验注册平台分别检索到 22 和 328 条注册方案,纳入其中 15 条注册方案。从已发表的 RCT 研究中提取结局指标 95 个(指标集合 A),注册试验方案中提取结局指标 86 个(指标集合 B)。

2.2 文献偏倚风险评估结果

纳入的 16 篇 RCT 风险偏倚评估结果,详见表 1。由表可见,纳入研究的方法学质量普遍不高。多数文献未对其分配隐藏和盲法的实施过程进行详细描述,未查见研究方案,尚无法判断其是否存在发表偏倚。

2.3 医患调查结果

本研究共调查 17 家单位 86 名临床医师、85 例肌少症患者所关注的结局指标,问卷回收率 100%。86 名医师,年龄(34.09±6.28)岁,其中 57 名(66.33%)为硕士研究生及以上学历,58 名(67.50%)为中级及以上职称。85 例患者,年龄(71.56±15.05)岁;男性

47 例(55.29%),女性 38 例(44.71%);19 例(22.35%)来自老年病科,16 例(18.82%)来自干部保健科,8 例(9.41%)来自肿瘤科,6 例(7.06%)来自呼吸内科,4 例(4.71%)来自内分泌科,4 例(4.71%)来自全科医学科,其余 28 例(32.9%)分散来自其他内科或外科科室。经校正,共收集到医师关注的结局指标 38 个(指标集合 C)、患者关注的结局指标 35 个(指标集合 D)。

2.4 指标池构建结果

本研究从已发表的随机对照研究中提取到结局指标 95 个,形成指标集合 A;从注册或发表的试验方案中,提取到结局指标 86 个,形成指标集合 B;从医师关注的结局指标中,提取到结局指标 38 个,形成指标集合 C;从患者关注的结局指标中,提取到结局指标 35 个,形成指标集合 D。已发表的 16 篇 RCT 中,出现频率≥3 次的指标 25 个;15 个在研的临床试验方案中,出现频率≥3 次的指标 21 个。仅 11 个指标在已发表文献和在研试验中出现频率均≥3 次。

经过上述结局指标收集过程,共获取到 158 个指标,其中 88 个指标在 4 个指标集合中出现总频次仅为 1。综合指标集合 A、B、C、D,将符合纳入标准的结局指标按照从属关系扩展为三级目录结果,初步形成老年肌少症营养功能性食品临床评价指标池,分为临床有效性、安全性、营养充足性、经济性及其他,共 5 个指标域,含有末级指标 64 个,以便后续

表 1 纳入文献的偏倚风险评价结果

Table 1 Results of bias risk assessment for included literature

Study	Radom sequence generation	Blinding	Allocation concealment	Incomplete outcome data	Selective reporting	Other bias
Takeuchi <i>et al</i> ^[6] , 2019	Random number table	Single blind	No	Yes,ITT analyses	Unclear	Unclear
Bo <i>et al</i> ^[7] , 2019	Computer randomization	Double blind	Envelope concealment	No	Unclear	Unclear
Zhu <i>et al</i> ^[8] , 2019	Computer randomization	Triple blind	Envelope concealment	Yes,without ITT analyses	Unclear	Unclear
Bauer <i>et al</i> ^[9] , 2015	Computer randomization	Triple blind	Unclear	Yes,ITT analyses	Yes	Unclear
Miao <i>et al</i> ^[10] , 2017	Draw lots	Unclear	Unclear	No	Unclear	Unclear
Wang <i>et al</i> ^[11] , 2016	Random number table	Unclear	Unclear	No	Unclear	Unclear
Ren <i>et al</i> ^[12] , 2016	Unclear	Unclear	Unclear	No	Yes	Unclear
Rondanelli <i>et al</i> ^[13] , 2016	Random table	Double blind	Envelope concealment	No	Unclear	Unclear
Maltais <i>et al</i> ^[14] , 2016	Unclear	Unclear	Package concealment	Unclear	Unclear	Unclear
Kim <i>et al</i> ^[15] , 2016	Computer randomization	Unclear	Unclear	Yes,without ITT analyses	Unclear	Unclear
Cramer <i>et al</i> ^[16] , 2016	Unclear	Double blind	Unclear	Yes,without ITT analyses	Unclear	Unclear
Zdzieblik <i>et al</i> ^[17] , 2015	Computer randomization	Double blind	Unclear	Unclear	Unclear	Unclear
Kim <i>et al</i> ^[18] , 2013	Computer randomization	Triple blind	Unclear	Unclear	Unclear	Unclear
Kim <i>et al</i> ^[19] , 2012	Computer randomization	Single blind	Unclear	Unclear	Unclear	Unclear
Alemán-Mateo <i>et al</i> ^[20] , 2012	Unclear	Unclear	No	Yes,ITT analyses	Unclear	Unclear
Solerte <i>et al</i> ^[21] , 2008	Unclear	Unclear	Unclear	No	Unclear	Unclear

ITT:intention-to-treat.

进行专家咨询遴选核心指标集,详见表2。分为5个指标域,共有一级目录指标20个,二级目录指标41个,三级目录指标24个。其中临床有效性指标域含一级目录指标4个,二级目录指标9个和三级目录指标20个;安全性指标域含一级目录指标

7个和二级目录指标15个;营养充足性指标域含一级目录指标4个,二级目录指标10个和三级目录指标4个;经济性指标域含一级目录指标1个和二级目录指标3个;其他指标域含一级目录指标4个和二级目录指标4个。

表2 老年肌少症营养功能性食品临床评价指标池三级目录结果

Table 2 An index pool of clinical evaluation on nutritional and functional food for elderly patients with sarcopenia

Domain	Level 1	Level 2	Level 3	Source				
				A	B	C	D	
Clinical effectiveness	Muscle mass	Muscle mass	Total muscle mass	√	√	√	√	
			Upper limb muscle mass	√				
			Leg muscle mass	√	√			
			Appendicular skeletal muscle mass	√	√	√	√	
			Circumference	Arm circumference	√		√	√
				Calf circumference	√		√	√
				Muscle mass ratio	Total muscle mass ratio	√		√
			Trunk muscle ratio		√			
			Appendicular skeletal muscle mass ratio		√			
			Appendicular skeletal muscle mass index		√	√	√	√
	Muscle strength	Hand grip strength	Hand grip strength	√	√	√	√	
			Strength of lower limb muscles	√	√	√	√	
		Leg extension	Leg extension	√	√	√	√	
			Muscle strength of knee-flexor	√	√			
			Isokinetic quadriceps strength of right leg	√				
	Muscle function	Gait speed	Fast gait speed	√				
			Usual gait speed	√	√	√	√	
		Short physical performance battery	Chair stand test	√	√			
			Balance test	√	√			
			Time up and go test	√	√			
		Physical activity ability	Self-reported physical activity	√	√			
			Physical activity scale for the elderly	√	√			
			Activity of daily living scale	√	√			
					√			
					√			
Security	Muscle protein synthesis					√		
	Incidence of adverse events					√		
						√		
	Lipid metabolism	Low density lipoprotein cholesterol					√	
		High density lipoprotein cholesterol					√	
		Triglyceride					√	
		Total cholesterol					√	
	Renal function	Creatinine					√	
		Urea					√	
		Glomerular filtration rate					√	
	Liver function	Alanine aminotransferase					√	
		Aspartate aminotransferase					√	
		Transglutaminase					√	
		Alkaline phosphatase					√	
	Glucose metabolic	Fasting glucose					√	
		Glycosylated hemoglobin					√	
	Blood pressure	Systolic pressure					√	
		Diastolic pressure					√	
Serum phosphorus						√		

(续表)

Domain	Level 1	Level 2	Level 3	Source					
				A	B	C	D		
Nutritive	Anthropometric measuring	Body mass index		√	√	√	√		
		Body mass		√	√	√	√		
		Waist circumference			√				
		Body composition	Total fat mass		√	√			
			Body fat rate		√	√			
			Visceral fat area				√		
			Body cell mass					√	
	Dietary survey	Total dietary protein intake			√	√	√	√	
		Total dietary energy intake			√	√	√	√	
	Laboratory examination	Albumin			√	√	√	√	
		Total protein			√	√	√	√	
		Vitamin D			√	√	√		
		Hemoglobin			√	√			
	Mini-nutritional assessment-short form				√	√	√	√	
Economic	Cost-effectiveness ratio	Price of nutritional and functional food used by each 0.1 m/s gait speed increases					√	√	
		Price of nutritional and functional food used by each 0.1 kg hand grip strength increases					√	√	
		Price of nutritional and functional food used by each 0.1kg appendicular skeletal muscle mass increases						√	√
Others	Inflammatory Indicators	Serum C-reactive protein		√	√	√	√		
		Interleukin-6		√	√				
		Tumor necrosis factor alpha		√	√				
		Insulin-like growth factor-1		√	√				
	Compliance			√	√				
	Life quality			√	√	√	√		
	Gastrointestinal intolerance			√					

3 讨论

随着疾病谱向慢性非传染性疾病转变和健康型消费模式的出现,我国营养功能性食品需求日益增强,产业规模年均增幅达10%~15%,已成为未来食品行业的重要发展方向^[3]。研究提示,高蛋白、HMB、乳清蛋白、维生素D和抗氧化营养素等功效成分对肌少症患者存在有益作用^[22,23]。肌少症国际临床实践指南和中国肌少症营养与运动干预中国专家共识均明确了营养治疗在肌少症治疗中的有效性^[2,24]。以上述有效活性成分为基础研制的营养功能性食品在老年肌少症的营养治疗上具有较高的应用价值。其介于普通食品与药品之间,涵盖范围广,参考我国对特殊医学用途配方食品的管理办法,为规范其市场监管和提高其接受度,上市前宜通过临床试验验证其功效。

已发表的16篇RCT中,仅26.32%(25/95)的指标出现频率≥3次;15个在研的临床试验方案中,仅24.42%(21/95)的指标出现频率≥3次。当前老年肌少症营养功能性食品临床试验结局指标存在异质性及不统一等问题,不利于后续该领域的二次研究及决策者的政策制定,而构建核心指标集目的正是寻找该研究领域临床试验报告的最小结局指标集合,减少报告偏倚^[25],生产出可用于指导老年肌少症营养治疗的高质量证据,对推动营养功能性食品产业发展意义重大。

通过调研医师和患者所关注的结局指标,补充了已发表文献和试验方案中未提及的部分血液生化指标和经济性指标和精神神经状况指标。按照既定的指标纳入排除标准,结合工作组内部讨论,最终纳入了3个成本效果比指标(步速每增加0.1m/s使用的营养功能性食品价格、握力每增加0.1kg使用的

营养功能性食品价格、四肢骨骼肌质量每增加0.1 kg使用的营养功能性食品价格)进入经济性指标域,补充了原指标体系经济性指标的缺失,以便后续在该研究领域进行卫生经济学研究。

本研究的局限性:(1)本研究未纳入非随机干预性研究或其他观察性研究的结局指标,可能对研究结果造成一定影响;(2)本研究未对营养功能性食品进行进一步分类,指标池里指标数量较多,尚需进一步遴选出通用于各类食品的核心指标集,故研究者在指标池中选用指标应用于不同分类的食品临床试验时应谨慎;(3)由于不同国家、组织对肌少症的诊断标准不一致,纳入研究对象间存在异质性,研究结果可能存在一定偏倚;(4)本研究指标纳入排除标准较为宽松,任何1个指标集合出现的指标进入工作组讨论以纳入或排除,通过此方法尽可能纳入更多的各利益相关群体关心的结局指标,由后续指标遴选的共识过程完成指标补充及精选。后续研究将从指标的重要性、可操作性和独立性3个维度广泛征求各利益相关群体意见,基于本研究构建的肌少症营养功能性食品临床试验指标池,精选指标,完成其核心指标集构建。

综上,本研究基于当前已发表的随机对照研究、临床试验方案和医师患者意见等资料结局指标的异质性构建了肌少症营养功能性食品临床试验指标池,分为临床有效性、营养充足性、安全性、经济性和其他5个指标域共64个末级指标,为后续遴选核心指标集提供依据。

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