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SAO PAULO STATE UNIVERSITY
"JÚLIO DE MESQUITA FILHO"
SCHOOL OF MEDICINE

Julí Thomaz de Souza

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Thesis presented to the School of Medicine,
Sao Paulo State University "Júlio de Mesquita Filho",
Campus Botucatu, to obtain the title of Ph.D. in
Pathophysiology in Internal Medicine

Advisor: Professor Paula Schmidt Azevedo Gaiolla
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Palavras-chave: Creatine; Skeletal Muscle; Stroke.

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Câmpus de Botucatu

ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE JULÍ THOMAZ DE SOUZA, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM FISIOPATOLOGIA EM CLÍNICA MÉDICA, DA FACULDADE DE MEDICINA - CÂMPUS DE BOTUCATU.

Aos 05 dias do mês de maio do ano de 2023, às 10:00 horas, no(a) Sala da Congregação - FM/Botucatu - Unesp, realizou-se a defesa de TESE DE DOUTORADO de JULÍ THOMAZ DE SOUZA, intitulada **Influence of Protein and Creatine Supplementation on Functional Capacity, Quality of Life and Muscle Function After Stroke**. A Comissão Examinadora foi constituida pelos seguintes membros: Profa. Dra. PAULA SCHMIDT AZEVEDO GAIOLLA (Orientador(a) - Participação Presencial) do(a) Depto. de Clínica Médica / FM/Botucatu - Unesp, Prof. Dr. MARCOS FERREIRA MINICUCCI (Participação Presencial) do(a) Depto. de Clínica Médica / FM/Botucatu - Unesp, Prof. Dr. ADAM LEE GORDON (Participação Virtual) do(a) Medical School / University of Nottingham, Prof. Dr. GUSTAVO JOSÉ LUVIZUTTO (Participação Virtual) do(a) Depto. de Fisioterapia Aplicada / Universidade Federal do Triângulo Mineiro (UFTM), Prof. Dr. IVAN APRAHAMIAN (Participação Virtual) do(a) Faculdade de Medicina de Jundiaí (FMJ). Após a exposição pela doutoranda e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, a discente recebeu o conceito final: APROVADA . Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Profa. Dra. PAULA SCHMIDT AZEVEDO GAIOLLA

Dedication

To my parents, Luiz and Fernanda, who always encouraged me and gave me all the support I needed to have the opportunity to follow my dreams.

To my sister Camila, who, in addition to being a sister, is my friend and has always been by my side in all important moments. To my nieces Serena and Videl, who are everything to me.

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Epigraph

“O real não está na saída nem na chegada: ele se dispõe
para a gente é no meio da travessia”

Grande sertão: Veredas - João Guimarães Rosa

“The truth is not in the setting out nor in the arriving: it comes to us
in the middle of the journey”

The Devil to Pay in the Backlands - João Guimarães Rosa

RESUMO

Introdução: O AVC é uma das principais causas de mortalidade e incapacidade. A fase aguda do AVC é marcada por inflamação, inapetência, disfagia, repouso no leito e alterações da mobilidade que podem comprometer o estado nutricional. Este estudo teve como objetivo avaliar o efeito da suplementação de creatina na massa muscular, força e capacidade funcional de idosos com AVC. Além disso, foram avaliados marcadores bioquímicos de inflamação, degradação muscular e síntese.

Metodologia: Ensaio clínico randomizado, duplo-cego, com idosos na fase aguda do AVC. Os participantes foram divididos em dois grupos: Tratamento (recebeu 10g de creatina 2x/dia) e Controle (recebeu 10g de placebo 2x/dia). Ambos os grupos receberam suplementação com proteína isolada do soro do leite em pó para atingir a meta de 1,5g de proteína/kg de peso corporal/dia e atendimento de fisioterapia diário. A intervenção ocorreu em 7 dias de internação. Verificou-se a influência da creatina na massa muscular (bioimpedância e ultrassonografia muscular), força (preensão manual e National Institutes of Health Stroke Scale), capacidade funcional (Escala de Rankin modificada), marcadores bioquímicos (3-Metil-histidina, Interleucina-6, Fator de crescimento semelhante à insulina tipo 1, fator de crescimento/diferenciação-15, procolágeno tipo III, insulina e progranulina). Acompanhamento para verificar capacidade funcional, força muscular, mortalidade e qualidade de vida 90 dias após o AVC.

Resultados: Trinta idosos foram incluídos em 2 grupos homogêneos, a maioria do sexo masculino com AVC isquêmico moderado. A suplementação de creatina não influenciou o peso corporal, força muscular, capacidade funcional e massa muscular avaliada por ultrassom e bioimpedância. No entanto, houve um aumento no índice de massa muscular apendicular em homens, mas não em mulheres. Não houve diferença estatisticamente significativa em relação ao uso de creatina e níveis séricos de IL-6 e IGF-1, bem como procolágeno Tipo III, insulina, GDF-15 e 3-Metil-histidina. A creatina influenciou na diminuição da progranulina. A oferta calórica de 21-25 kcal/kg com 1,5g de proteína/kg por dia mostrou-se adequada para a manutenção do peso independentemente da administração de creatina. A creatina não influenciou a mortalidade e a percepção de qualidade de vida 90 dias após o AVC.

Discussão: A suplementação foi segura com poucos eventos adversos relacionados e boa tolerância e aceitação. Houve um aumento no índice de massa muscular apendicular em

homens, mas não em mulheres. Esse aumento agudo da massa muscular pode ser devido ao edema muscular, uma vez que o transporte de creatina para dentro da célula depende do sódio. De fato, a resposta muscular à creatina é diferente em homens e mulheres. Observa-se que há potencial para a creatina modular alguns aspectos relacionados a biomarcadores inflamatórios no AVC agudo. A literatura mostra a associação entre aumento da progranulina e mortalidade e pior prognóstico funcional após o AVC. Em nossos achados, no grupo tratamento, observou-se redução da progranulina, mas não no grupo controle. Este resultado representa o papel anti-inflamatório da creatina. Assim, a novidade deste estudo é mostrar o potencial da creatina em modular a progranulina na fase aguda do AVC. O trabalho trouxe dados essenciais relacionados à ingestão calórico-proteica durante a internação, mostrando a importância da adequação nutricional para evitar a perda de peso nesse período.

Conclusão: A suplementação de creatina provou ser segura. Tem o potencial de modular alguns marcadores inflamatórios após o AVC e influenciou na redução dos valores de progranulina, refletindo seu papel anti-inflamatório. A creatina não afetou a capacidade funcional e a força, mas aumentou a massa muscular apendicular em homens. Estudos com maior número de participantes e maior tempo de intervenção devem ser realizados para melhor compreender a influência da suplementação de creatina na fase aguda do AVC.

Palavras-chave: Acidente vascular cerebral; Creatina; Músculo esquelético.

ABSTRACT

Background: Stroke is a leading cause of mortality and disability. The acute phase of stroke is marked by inflammation, loss of appetite, dysphagia, bed rest, and mobility changes that can compromise the nutritional status. This study aimed to evaluate the effect of creatine supplementation on muscle mass, strength, and functional capacity of older people with stroke. In addition, biochemical markers of inflammation, muscle degradation, and synthesis were assessed.

Methodology: Randomized, double-blind, clinical trial with older people in the acute phase of stroke. The participants were divided into two groups: Treatment (received 10g of creatine 2x/day) and Control (received 10g of placebo 2x/day). Both groups received supplementation with powdered milk protein serum isolate to achieve the goal of 1.5g of protein/kg of body weight/day and daily early mobility training. The intervention occurred in 7-days hospitalization. Were verified the influence of creatine on muscle mass (bioimpedance and muscle ultrasound), strength (handgrip and National Institutes of Health Stroke Scale), functional capacity (Modified Rankin Scale), biochemical markers (3-Methylhistidine, Interleukin-6, Insulin-like growth factor 1, Growth/Differentiation Factor-15, type III procollagen, insulin, and progranulin). Follow-up to verify functional capacity, muscle strength, mortality, and quality of life 90 days after stroke.

Results: Thirty older people were included in 2 homogeneous groups, mostly male with moderate ischemic stroke. Creatine supplementation did not influence body weight, muscle strength, functional capacity, and muscle mass evaluated by ultrasound and bioimpedance. However, there was an increase in appendicular muscle mass index in men but not in women. There was no statistically significant difference regarding the use of creatine and serum levels of IL-6 and IGF-1, as also Type III procollagen, insulin, GDF-15, and 3-Methylhistidine. Creatine influenced the decrease of progranulin. The caloric supply of 21-25 kcal/kg with 1.5g of protein/kg per day proved adequate for weight maintenance regardless of creatine administration. Creatine did not influence mortality and perception of quality of life 90 days after stroke.

Discussion: Supplementation was safe with few related adverse events and good tolerance and acceptance. There was an increase in appendicular muscle mass index in men but not in women. This acute increase in muscle mass may be due to muscle edema since creatine

transport into the cell depends on sodium. Indeed, the muscular response to creatine is different in men and women. It is observed that there is potential for creatine to modulate some aspects related to inflammatory biomarkers in acute stroke. Literature shows the association between increased progranulin and mortality and worse functional prognosis after stroke. In our findings, in the treatment group, the reduction in progranulin was observed, but not in the control group. This result represents the anti-inflammatory role of creatine. Thus, the novelty of this study is to show the potential of creatine to modulate progranulin in the acute phase of the stroke. The work brought essential data related to caloric-protein intake during hospitalization, showing the importance of nutritional adjustment to avoid weight loss during this period.

Conclusion: Creatine supplementation proved to be safe. It has the potential to modulate some inflammatory markers after stroke and influenced the reduction of progranulin values, reflecting its anti-inflammatory role. Creatine did not impact functional capacity, and strength but increased appendicular muscle mass in men. Studies with a larger number of participants and longer intervention time should be carried out to better understand the influence of creatine supplementation in the acute phase of stroke.

Keywords: Stroke; Creatine; Skeletal Muscle.

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LIST OF ABBREVIATIONS AND ACRONYMS

AC: Arm circumference

AMA: Arm muscle area

AMMI: Appendicular muscle mass index

APMT: Adductor pollicis muscle thickness

ASPECTS: Alberta Stroke Program Early CT Score

BBM: Biceps brachii muscle

BMI: Body mass index

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

cm: Centimeter

ECW: Extracellular water

ELISA: Enzyme-Linked Immunosorbent Assay

ET: End of treatment

EuroQol-5D: The European Quality of life Scale Five Dimension

FAS: Full Analysis Set

FFMI: Fat free mass index

FFQ: Food Frequency Questionnaire

FOIS: Functional Oral Intake Scale

g: Grams

GDF-15: Growth/Differentiation Factor-15

h: Hour

HADS: Hospital Anxiety and Depression Scale

HbA1C: Hemoglobin A1C

HDL: High-density lipoprotein

HOMA-IR: Homeostasis assessment model of insulin resistance

ICaRUS: Influence of protein and **C**reatine supplementation on functional capacity, quality of life and m**US**cle function after **S**troke

IGF-1: Insulin-like growth factor 1

IL-6: Interleukin-6

kg: Kilograms

kgf: Kilogram-force

kHz: Kilohertz

l: Liters

LACS: Lacunar syndrome

LDL: Low-density lipoprotein

m: Meter

3MH: 3-Methylhistidine

MHz: Megahertz

min: Minute

ml: Milliliter

mm: millimeter

MPB: Muscle protein breakdown

MPS: Muscle protein synthesis

mRs: Modified Rankin Scale

N: Number

NIHSS: National Institutes of Health Stroke Scale

NRS: Nutritional risk screening

P3NP: Type III procollagen N-terminal peptide

PACS: Partial anterior circulation syndrome

PL: Placebo

POCS: Posterior circulation syndrome

PP: Per-Protocol

RFM: Rectus femoris muscle

rpm: Revolutions per minute

SMM: Skeletal muscle mass

ST: Start of treatment

TACS: Total anterior circulation syndrome

TBW: Total body water

TNF- α: Tumour necrosis factor α

TOAST: Trial of Org 10172 in Acute Stroke Treatment

TR: Treatment

TST: Triceps skinfold thickness

US: Ultrasound

SUMMARY

in the acute phase of stroke and its reduction with the use of creatine need to be explored in future studies, as this is a site of therapeutic potential.

7 CONCLUSION

Creatine supplementation proved to be safe, with good tolerance and easy acceptance. Creatine did not impact functional capacity, and strength but increased appendicular muscle mass in men. It has the potential to modulate some inflammatory markers after stroke and had an influence on the reduction of progranulin values, reflecting its anti-inflammatory role. Supplementation had no impact on mortality and quality of life after the event. This study helped to understand the potencial role and safe of creatine in the acute phase of the stroke, which supports the development of other trials. In fact, studies with larger number of participants and longer intervention time should be carried out to better understand the influence of creatine supplementation in the acute phase of stroke.

REFERENCES

1. Ministério da Saúde (BR). Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Diretrizes de atenção à reabilitação da pessoa com acidente vascular cerebral. 2013. Available in: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/s/saude-da-pessoa-com-deficiencia/publicacoes/diretrizes-de-atencao-a-reabilitacao-da-pessoa-com-acidente-vascular-cerebral.pdf/view. Accessed 06 Mar 2023.

2. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study2015. Lancet 2016; 388(10053): 1459-1544. doi: 10.1016/S0140-6736(16)31012-1.

3. Katan M, Luft A. Global Burden of stroke. Semin Neurol. 2018 Apr; 38(2):208-211. doi: 10.1055/s-0038-1649503. Epub 2018 May 23.

4. Silva ASD, Lima AP, Cardoso FB. A relação benéfica entre o exercício físico e a fisiopatologia do acidente vascular cerebral. Revista Brasileira de Prescrição e Fisiologia do Exercício. 2014; 8: 88-99.

5. Pires SL, Gagliardi RJ, Gorzoni MLStudy of the main risk factors frequencies for ischemic cerebrovascular disease in elderly patients ArqNeuropsiquiatr 2004; 62(3-B):844-851. https://doi.org/10.1590/S0004-282X2004000500020

6. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997 May 3;349(9061):1269-76. doi: 10.1016/S0140-6736(96)07493-4.

7. Wolfe CDA. The impact of stroke. *British Medical Bulletin*, Volume 56, Issue 2, 2000, Pages 275–286, https://doi.org/10.1258/0007142001903120

8. Herpich F, Rincon F. Management of Acute Ischemic Stroke. Crit Care Med. 2020 Nov; 48(11):1654-1663. doi: 10.1097/CCM.0000000000004597.

9. NINDS Group. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995 Dec; 333(24):1581-7. doi: 10.1056/NEJM199512143332401.

10. FOOD Trial Collaboration. Poor nutritional status on admission predicts poor outcomes after stroke: Observational data from the FOOD trial. Stroke. 2003 Jun; 34 (6); 1450-6. doi: 10.1161/01.STR.0000074037.49197.8C

11. Scherbakov N, von Haehling S, Anker SD, Dirnagl U, Doehner W. Stroke induced Sarcopenia: muscle wasting and disability after stroke. Int J Cardiol. 2013 Dec 10;170(2):89-94. doi: 10.1016/j.ijcard.2013.10.031.

12. Scherbakov N, Sandek A, Doehner W. Stroke-related sarcopenia: specific characteristics. J Am Med Dir Assoc. 2015 Apr;16(4):272-6. doi: 10.1016/j.jamda.2014.12.007. Epub 2015 Feb 10. PMID: 25676847.

13. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, Compher C, Correia I, Higashiguchi T, Holst M, Jensen GL, Malone A, Muscaritoli M, Nyulasi I, Pirlich M, Rothenberg E, Schindler K, Schneider SM, de van der Schueren MA, Sieber C, Valentini L, Yu JC, Van Gossum A, Singer P. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017 Feb;36(1):49-64. doi: 10.1016/j.clnu.2016.09.004.

14. Jeejeebhoy NK. Malnutrition, fatigue, frailty, vulnerability, sarcopenia, and cachexia: overlap of clinical features. Curr Opin Clin Nutr Metab Care 2012. May;15(3):213-9. doi: 10.1097/MCO.0b013e328352694f.

15. Scherbakov N, Pietrock C, Sandek A, Ebner N, Valentova M, Springer J et al. Body weight changes and incidence of cachexia after stroke. J Cachexia Sarcopenia Muscle. 2019 Jun;10(3):611-620. doi: 10.1002/jcsm.12400.

16. Cruz-Jentoft AJ, Gonzalez MC, Prado CM. Sarcopenia ≠ low muscle mass. Eur Geriatr Med. 2023 Apr;14(2):225-228. doi: 10.1007/s41999-023-00760-7.

17. De Deyne PG, Hafer-Macko CE, Ivey FM, Ryan AS, Macko RF. Muscle molecular phenotype after stroke is associated with gait speed. Muscle Nerve. 2004 Aug;30(2):209-15. doi: 10.1002/mus.20085.

18. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options - a mini-review. Gerontology. 2014;60(4):294-305. doi: 10.1159/000356760.

19. Carin-Levy G, Greig C, Young A, Lewis S, Hannan J, Mead G. Longitudinal changes in muscle strength and mass after acute stroke. Cerebrovasc Dis. 2006;21(3):201-7. doi: 10.1159/000090792.

20. Jorgensen L, Jacobsen BK. Changes in muscle mass, fat mass, and bone mineral content in the legs after stroke: A 1-year prospective study. Bone 2001; 28:655e659. doi: 10.1016/s8756-3282(01)00434-3.

21. Ryan AS, Buscemi A, Forrester L, Hafer-Macko CE, Ivey FM. Atrophy and intramuscular fat in specific muscles of the thigh: associated weakness and hyperinsulinemia in stroke survivors. Neurorehabil Neural Repair. 2011 Nov-Dec;25(9):865-72. doi: 10.1177/1545968311408920.

22. Ryan AS, Dobrovolny CL, Smith GV, Silver KH, Macko RF. Hemiparetic muscle atrophy and increased intramuscular fat in stroke patients. Arch Phys Med Rehabil. 2002 Dec;83(12):1703-7. doi: 10.1053/apmr.2002.36399. PMID: 12474173.

23. Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. ClinNutr. 2014 Oct;33(5):737-48. doi: 10.1016/j.clnu.2014.03.007. Epub 2014 Mar 29.

24. Csete ME. Basic Science of Frailty-Biological Mechanisms of Age-Related Sarcopenia. Anesth Analg. 2021 Feb; 132(2):293-304. doi: 10.1213/ANE.0000000000005096.

25. Cardoso AL, Fernandes A, Aguilar-Pimentel JA, de Angelis MH, Guedes JR, Brito MA, Ortolano S, Pani G, Athanasopoulou S, Gonos ES, Schosserer M, Grillari J, Peterson P, Tuna BG, Dogan S, Meyer A, van Os R, Trendelenburg AU. Towards frailty biomarkers:

Candidates from genes and pathways regulated in aging and age-related diseases. Ageing Res Rev. 2018 Nov;47:214-277. doi: 10.1016/j.arr.2018.07.004.

26. Sarvas JL, Khaper N, Lees SJ. The IL-6 Paradox: Context Dependent Interplay of SOCS3 and AMPK. J Diabetes Metab. 2013 May 24;Suppl 13:10.4172/2155-6156.S13-003. doi: 10.4172/2155-6156.S13-003.

27. Chen F, Lam R, Shaywitz D, Hendrickson RC, Opiteck GJ, Wishengrad D, Liaw A, Song Q, Stewart AJ, Cummings CE, Beals C, Yarasheski KE, Reicin A, Ruddy M, Hu X, Yates NA, Menetski J, Herman GA. Evaluation of early biomarkers of muscle anabolic response to testosterone. J Cachexia Sarcopenia Muscle. 2011 Mar;2(1):45-56. doi: 10.1007/s13539-011-0021-y.

28. Lasek-Bal A, Jedrzejowska-Szypulka H, Student S, Warsz-Wianecka A, Zareba K, Puz P, Bal W, Pawletko K, Lewin-Kowalik J. The importance of selected markers of inflammation and blood-brain barrier damage for short-term ischemic stroke prognosis. J Physiol Pharmacol. 2019 Apr;70(2). doi: 10.26402/jpp.2019.2.04.

29. Xie S, Lu L, Liu L, Bi G, Zheng L. Progranulin and short-term outcome in patients with acute ischaemic stroke. Eur J Neurol. 2016 Mar;23(3):648-55. doi: 10.1111/ene.12920.

30. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc. 2013; 14(8):542–59. Updated recommendations for optimal dietary protein intake in older adults. [PubMed: 23867520]

31. Churchward-Venne TA, Breen L, Phillips SM. Alterations in human muscle protein metabolism with aging: Protein and exercise as countermeasures to offset sarcopenia. Biofactors. 2014; 40(2): 199–205. [PubMed: 24105883]

32. Gualano B, Rawson ES, Candow DG, Chilibeck PD. Creatine supplementation in the aging population: effects on skeletal muscle, bone, and brain. Amino Acids. 2016 Aug; 48(8):1793-805. doi: 10.1007/s00726-016-2239-7.

33. Kazak L, Cohen P. Creatine metabolism: energy homeostasis, immunity and cancer biology. Nat Rev Endocrinol. 2020 Aug; 16(8):421-436. doi:10.1038/s41574-020-0365-5.

34. Dolan E, Artioli GG, Pereira RMR, Gualano B. Muscular Atrophy and Sarcopenia in the Elderly: Is There a Role for Creatine Supplementation? Biomolecules. 2019 Oct; 9(11):642. doi: 10.3390/biom9110642.

35. Bell KE, Snijders T, Zulyniak M, Kumbhare D, Parise G, Chabowski A, Phillips SM. A whey protein-based multi-ingredient nutritional supplement stimulates gains in lean body mass and strength in healthy older men: A randomized controlled trial. PLoS One. 2017 Jul 18;12(7):e0181387. doi: 10.1371/journal.pone.0181387.

36. Collins J, Longhurst G, Roschel H, Gualano B.Resistance Training and Co-supplementation with Creatine and Protein in Older Subjects with Frailty. J Frailty Aging. 2016;5(2):126-34. doi: 10.14283/jfa.2016.85.

37. Pinto CL, Botelho PB, Carneiro JA, Mota JF. Impact of creatine supplementation in combination with resistance training on lean mass in the elderly. Journal of Cachexia, Sarcopenia and Muscle 2016; 7: 413–421. doi: 10.1002/jcsm.12094.

38. Bernhardt J, Godecke E, Johnson L, Langhorne P. Early rehabilitation after stroke. CurrOpin Neurol. 2017 Feb; 30(1):48-54. doi: 10.1097/WCO.0000000000000404.

39. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, Cederholm T, Cruz-Jentoft A, Krznariç Z, Nair KS, Singer P, Teta D, Tipton K, Calder PC. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group.ClinNutr. 2014 Dec;33(6):929-36. doi: 10.1016/j.clnu.2014.04.007.

40. Gotshalk LA, Volek JS, Staron RS, Denegar CR, Hagerman FC, Kraemer WJ. Creatine supplementation improves muscular performance in older men. Med Sci Sports Exerc 2002 Mar; 34(3):537-43. doi: 10.1097/00005768-200203000-00023.

41. Lanhers C, Pereira B, Naughton G, Trousselard M, Lesage FX, Dutheil F. Creatine Supplementation and Lower Limb Strength Performance: A Systematic Review and Meta-Analyses. Sports Med. 2015 Sep;45(9):1285-1294. doi: 10.1007/s40279-015-0337-4.

42. Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, et al. AVERT Collaboration Group. Prespecified dose-response analysis for a Very Early Rehabilitation Trial (AVERT). Neurology. 2016 Jun; 86(23):2138-45. doi: 10.1212/WNL.0000000000002459.

43. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC et al. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016 Jun; 47(6): e98-e169. doi: 10.1161/STR.0000000000000098

44. BRASIL. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de atenção básica. Guia alimentar para a população brasileira. 2014;158. Available in: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://bvsms.saude.gov.br/bvs/publicacoes/guia_alimentar_populacao_brasileira_2ed.pdf. Accessed 06 Mar 2023.

45. Cincura C, Pontes-Neto OM, Neville IS, Mendes HF, Menezes DF, Mariano DC, Pereira IF, Teixeira LA, Jesus PA, de Queiroz DC, Pereira DF, Pinto E, Leite JP, Lopes AA, Oliveira-Filho J. Validation of the National Institutes of Health Stroke Scale, modified Rankin Scale and Barthel Index in Brazil: the role of cultural adaptation and structured interviewing. Cerebrovasc Dis. 2009;27(2):119–22. doi: 10.1159/000177918.

46. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet. 2000 May 13;355(9216):1670-4. doi: 10.1016/s0140-6736(00)02237-6.

47. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 Jan;24(1):35-41. doi: 10.1161/01.str.24.1.35.

48. Crary MA, Mann GD, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch Phys Med Rehabil. 2005 Aug;86(8):1516-20. doi: 10.1016/j.apmr.2004.11.049.

49. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. Int J Obes. 1985; 9(2):147-53.

50. Smith-Ryan AE, Fultz SN, Melvin MN, Wingfield HL, Woessner MN. Reproducibility and validity of A-mode ultrasound for body composition measurement and classification in overweight and obese men and women. PLoS One. 2014 Mar 11;9(3):e91750. doi: 10.1371/journal.pone.0091750. doi: 10.1371/journal.pone.0091750

51. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z; Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003 Jun;22(3):321-36. doi: 10.1016/s0261-5614(02)00214-5.

52. Eickemberg M, Oliveira CC, RORIZ AKC, Sampaio LR. Bioelectric impedance analysis and its use for nutritional assessments. Rev. Nutr., 2011 Nov; 24(6):883-893.

53. Bosy-Westphal A, Jensen B, Braun W, Pourhassan M, Gallagher D, Müller MJ. Quantification of whole-body and segmental skeletal muscle mass using phase-sensitive 8-electrode medical bioelectrical impedance devices. Eur J Clin Nutr. 2017 Sep;71(9):1061-1067. doi: 10.1038/ejcn.2017.27.

54. Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, Der G, Gale CR, Inskip HM, Jagger C, Kirkwood TB, Lawlor DA, Robinson SM, Starr JM, Steptoe A, Tilling K, Kuh D, Cooper C, Sayer AA. Grip strength across the life course: normative data from twelve British studies. PLoS One. 2014;9(12):e113637. doi: 10.1371/journal.pone.0113637.

55. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019 Jul 1;48(4):601. doi: 10.1093/ageing/afz046.

56. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Research Quarterly for Exercise & Sport. 2013; 70(2):113-9. doi: 10.1080/02701367.1999.10608028.

57. Brott T, Adams Jr HP, Olinger CP, Marler JR, Barsan WG, Biller J et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke, 1989 Jul;20(7):864-70. DOI: 10.1161/01.str.20.7.864.

58. Barry E, Galvin R, Keogh C, Horgan F, Fahey T. Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis. BMC Geriatr. 2014 Feb; 14:14. DOI: 10.1186/1471-2318-14-14.

59. Mayer JP, Zhang F, DiMarchi RD. Insulin structure and function. Biopolymers. 2007;88(5):687-713. doi: 10.1002/bip.20734.

60. Hayes CA, Valcarcel-Ares MN, Ashpole NM. Preclinical and clinical evidence of IGF-1 as a prognostic marker and acute intervention with ischemic stroke. J Cereb Blood Flow Metab. 2021 Oct;41(10):2475-2491. doi: 10.1177/0271678X211000894.

61. McMaster WG, Kirabo A, Madhur MS, Harrison DG. Inflammation, immunity, and hypertensive end-organ damage. Circ Res.2015 Mar 13;116(6):1022-33. doi: 10.1161/CIRCRESAHA.116.303697.

62. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev. 2008 Oct;88(4):1379-406. doi: 10.1152/physrev.90100.2007.

63. Peppler WT, Townsend LK, Wright DC. Recent advances in the role of interleukin-6 in health and disease. Curr Opin Pharmacol. 2020 Jun;52:47-51. doi: 10.1016/j.coph.2020.04.010.

64. Berry SD, Ramachandran VS, Cawthon PM, Gona P, McLean RR, Cupples LA, Kiel DP. Procollagen type III N-terminal peptide (P3NP) and lean mass: a cross-sectional study. J Frailty Aging. 2013;2(3):129-34. PMID: 24244927; PMCID: PMC3828748.

65. Nielsen MJ, Nedergaard AF, Sun S, Veidal SS, Larsen L, Zheng Q, Suetta C, Henriksen K, Christiansen C, Karsdal MA, Leeming DJ. The neo-epitope specific PRO-C3 ELISA measures

true formation of type III collagen associated with liver and muscle parameters. Am J Transl Res. 2013 Apr 19;5(3):303-15. PMID: 23634241; PMCID: PMC3633973.

66. Cegielski J, Brook MS, Quinlan JI, Wilkinson DJ, Smith K, Atherton PJ, Phillips BE. 4-week, lifestyle-integrated, home-based exercise training programme elicits improvements in physical function and lean mass in older men and women: a pilot study. F1000Res. 2017 Jul 26;6:1235. doi: 10.12688/f1000research.11894.2. eCollection 2017.

67. Crossland H, Smith K, Atherton PJ, Wilkinson DJ. A novel stable isotope tracer method to simultaneously quantify skeletal muscle protein synthesis and breakdown. Metabol Open 2020 Mar;5:100022. doi: 10.1016/j.metop.2020.100022.

68. Sheffield-Moore M, Dillon EL, Randolph KM, Casperson SL, White GR, Jennings K et al. Isotopic decay of urinary or plasma 3-methylhistidine as potencial biomarker of skeletal muscle loss. J Cachexia Sarcopenia Muscle. 2014 Mar;5(1):19-25. doi: 10.1007/s13539-013-0117-7.

69. Vasques AC, Rosado LE, Cássia GAlfenas Rd, Geloneze B. Análise crítica do uso dos índices do Homeostasis Model Assessment (HOMA) na avaliação da resistência à insulina e capacidade funcional das células-beta pancreáticas [Critical analysis on the use of the homeostasis model assessment (HOMA) indexes in the evaluation of the insulin resistance and the pancreatic beta cells functional capacity]. Arq Bras Endocrinol Metabol. 2008 Feb;52(1):32-9. Portuguese. doi: 10.1590/s0004-27302008000100006.

70. Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the hospital anxiety and depression scale. Psychol Health Med. 2007;12(2):225–35. doi: 10.1080/13548500500524088.

71. Pinto EB, Maso I, Vilela RN, Santos LC, Oliveira-Filho J. Validation of the EuroQol quality of life questionnaire on stroke victims. Arq Neuropsiquiatr. 2011; 69(2B):320-3. doi: 10.1590/s0004-282x2011000300010.

72. Costa AGV, Priore SE, Sabarense CM, Franceschini SCC. Food frequency questionnaire and 24-hour recall: methodological aspects in the assessment of lipid intake. Rev. Nutr. 2016; 19(5): 631-641.

73. Candow DG, Forbes SC, Kirk B, Duque G. Current Evidence and Possible Future Applications of Creatine Supplementation for Older Adults. Nutrients. 2021 Feb 26;13(3):745. doi: 10.3390/nu13030745.

74. Zhao J, Yuan F, Song C, Yin R, Chang M, Zhang W, Zhang B, Yu L, Jia Y, Ma Y, Song Y, Wang C, Song C, Wang X, Shang L, Yang F, Jiang W; OPENS Trial Investigators. Safety and efficacy of three enteral feeding strategies in patients with severe stroke in China (OPENS): a multicentre, prospective, randomised, open-label, blinded-endpoint trial. Lancet Neurol. 2022 Apr;21(4):319-328. doi: 10.1016/S1474-4422(22)00010-2.

75. Perasso L, Spallarossa P, Gandolfo C, Ruggeri P, Balestrino M. Therapeutic use of creatine in brain or heart ischemia: available data and future perspectives. Med Res Rev. 2013 Mar;33(2):336-63. doi: 10.1002/med.20255.

76. Izquierdo M, Ibañez J, González-Badillo JJ, Gorostiaga EM. Effects of creatine supplementation on muscle power, endurance, and sprint performance. Med Sci Sports Exerc. 2002 Feb;34(2):332-43. doi: 10.1097/00005768-200202000-00023.

77. Johansmeyer S, Candow DG, Brahms CM, Michel D, Zello GA. Effect of creatine supplementation and drop-set resistance training in untrained aging adults. Exp Gerontol. 2016 Oct;83:112-9. doi: 10.1016/j.exger.2016.08.005.

78. Cordingley DM, Cornish SM, Candow DG. Anti-Inflammatory and Anti-Catabolic Effects of Creatine Supplementation: A Brief Review. Nutrients. 2022 Jan 27;14(3):544. doi: 10.3390/nu14030544.

79. Farshidfar F, Pinder MA, Myrie SB. Creatine Supplementation and Skeletal Muscle Metabolism for Building Muscle Mass- Review of the Potential Mechanisms of Action. Curr Protein Pept Sci. 2017;18(12):1273-1287. doi: 10.2174/1389203718666170606105108.

80. McCarthy MS, Martindale RG. Immunonutrition in Critical Illness: What Is the Role? Nutr Clin Pract. 2018 Jun;33(3):348-358. doi: 10.1002/ncp.10102. PMID: 29878555.

81. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. JPEN J Parenter Enteral Nutr. 2013 Sep;37(5 Suppl):21S-9S. doi: 10.1177/0148607113496117.

82. Inoue T, Ueshima J, Kawase F, Kobayashi H, Nagano A, Murotani K, Saino Y, Maeda K. Trajectories of the Prevalence of Sarcopenia in the Pre- and Post-Stroke Periods: A Systematic Review. Nutrients. 2022 Dec 26;15(1):113. doi: 10.3390/nu15010113.

83. Whiteley W, Jackson C, Lewis S, Lowe G, Rumley A, Sandercock P, Wardlaw J, Dennis M, Sudlow C. Inflammatory markers and poor outcome after stroke: a prospective cohort study and systematic review of interleukin-6. PLoS Med. 2009 Sep;6(9):e1000145. doi: 10.1371/journal.pmed.1000145.

84. Chitramuthu BP, Bennett HPJ, Bateman A. Progranulin: a new avenue towards the understanding and treatment of neurodegenerative disease. Brain. 2017 Dec 1;140(12):3081-3104. doi: 10.1093/brain/awx198.

85. Liu CJ, Bosch X. Progranulin: a growth factor, a novel TNFR ligand and a drug target. Pharmacol Ther. 2012 Jan;133(1):124-32. doi: 10.1016/j.pharmthera.2011.10.003.

86. Li X, Cheng S, Hu H, Zhang X, Xu J, Wang R, Zhang P. Progranulin protects against cerebral ischemia-reperfusion (I/R) injury by inhibiting necroptosis and oxidative stress. Biochem Biophys Res Commun. 2020 Jan 15;521(3):569-576. doi: 10.1016/j.bbrc.2019.09.111.

87. Horinokita I, Hayashi H, Oteki R, Mizumura R, Yamaguchi T, Usui A, Yuan B, Takagi N. Involvement of Progranulin and Granulin Expression in Inflammatory Responses after Cerebral Ischemia. Int J Mol Sci. 2019 Oct 21;20(20):5210. doi: 10.3390/ijms20205210.

88. Corre J, Hébraud B, Bourin P. Concise review: growth differentiation factor 15 in pathology: a clinical role? Stem Cells Transl Med. 2013 Dec;2(12):946-52. doi: 10.5966/sctm.2013-0055.

89. Rasmussen RS, Østergaard A, Kjær P, Skerris A, Skou C, Christoffersen J, Seest LS, Poulsen MB, Rønholt F, Overgaard K. Stroke rehabilitation at home before and after discharge

reduced disability and improved quality of life: a randomised controlled trial. Clin Rehabil. 2016 Mar;30(3):225-36. doi: 10.1177/0269215515575165.

90. Ramos-Lima MJM, Brasileiro IC, Lima TL, Braga-Neto P. Quality of life after stroke: impact of clinical and sociodemographic factors. Clinics (Sao Paulo). 2018 Oct 8;73:e418. doi: 10.6061/clinics/2017/e418.

91. Seidel G, Röttinger A, Lorenzen J, Kücken D, Majewski A, Klose K, Terborg C, Klass I, Wohlmuth P, Zukunft E, Debacher U. Lebensqualität und Behinderung nach schwerem Schlaganfall und neurologischer Frührehabilitation [Quality of life and disability after severe stroke and early neurological rehabilitation]. Nervenarzt. 2019 Oct;90(10):1031-1036. German. doi: 10.1007/s00115-019-0740-4.