REVIEW ARTICLE

Creatine supplementation as a potential therapeutic aid in peripheral arterial obstructive disease rehabilitation

Suplementação de creatina como potencial agente terapêutico na reabilitação da doença arterial obstrutiva periférica

Lucas Caseri Câmara[1], Erika Magalhães Suzigan[2], Marcelo Andrade Starling[1]

ABSTRACT

Creatine (Cr) Supplementation has been efficient and safely used as a therapeutic aid in many health and sickness conditions including muscle weakness, atrophy and metabolic disturbances. In Peripheral arterial obstructive disease (PAOD), chronic ischemia leads to muscle fiber atrophy and denervation, negative muscle metabolism alterations, thus reducing strength and endurance, impairing general physical fitness. Adding the studied benefits of Cr supplementation and the clinical frame of PAOD, it presents Cr Supplementation as a potential therapeutic aid to be considered. **Objective:** To make a systematic review in scientific literature, searching for studies involving Cr supplementation in PAOD individuals. **Method:** A search for Portuguese and English written articles, published over the last ten years, including terms related to PAOD and Cr supplementation, was conducted on PubMed SciELO, and LILACS. **Results:** Only one study evaluated the influence of Cr supplementation in the desired sample (PAOD), describing positive effects in walking distance and blood properties. Due to lack of scientific data, the use Cr supplementation in PAOD population, including metabolic, functional and structural considerations was discussed. **Conclusion:** Despite the presented discussion for using Cr supplementation in PAOD as a potential therapeutic aid, only one previous study could verify its benefits. Therefore, it still has a *gap* in scientific literature, leaving several possibilities for future studies researching for possible benefits to counteract the loss of functional fitness and impairments in musculoskeletal structure and metabolism of diseased individuals.

Keywords: Creatine, Peripheral Arterial Disease/rehabilitation, Intermittent Claudication

RESUMO

Suplementação de Creatina (Cr) têm sido utilizada de forma segura e eficaz em diversas condições de saúde e doença, incluindo fraqueza, atrofia e distúrbios metabólicos musculares. Na Doença arterial obstrutiva periférica (DAOP), a isquemia crônica promove atrofia, denervação e prejuízos metabólicos musculares, reduzindo a força e resistência, prejudicando a aptidão física geral. Tomando em conjunto, os benefícios conhecidos da suplementação de Cr e a apresentação clínica da DAOP, apresentam a suplementação de Cr como potencial agente terapêutico a ser considerado. **Objetivo:** Realizar uma revisão sistemática da literatura científica procurando por estudos envolvendo a suplementação de Cr em portadores de DAOP, publicados nos últimos dez anos. **Método:** Uma pesquisa por artigos escritos em português e inglês no período descrito, incluindo o cruzamento de termos relacionados a DAOP e a suplementação de Cr foi realizada no PubMed, SciELO, e LILACS. **Resultados:** Um único estudo avaliou a influência da suplementação de Cr na amostra desejada (DAOP), descrevendo efeitos positivos na distância de caminhada e em propriedades sanguíneas. Devido à escassez de dados sobre o tema, o potencial uso da Cr na DAOP incluindo considerações metabólicas, funcionais e estruturais foi discutido. **Conclusão:** Apesar das apresentadas considerações para a utilização da Cr como potencial agente terapêutico na DAOP, apenas um estudo prévio verificou benefícios. Assim ainda há uma grande lacuna na literatura científica, deixando campo aberto para futuros estudos na procura de possíveis benefícios no combate a perda funcional, prejuízo da estrutura e metabolismo muscular de indivíduos doentes.

Palavras-chave: Creatina, Doença Arterial Obstrutiva Periférica/reabilitação, Claudicação Intermitente

[1] Médico Residente em Medicina Física e Reabilitação, Universidade Federal de São Paulo - (UNIFESP-EPM).
[2] Médica Fisiatra, Assistente do Serviço de Reabilitação da Santa Casa de Misericórdia de São Paulo.

Mailing address:
Lucas Caseri Câmara
Rua Pascal, 1622, Campo Belo
São Paulo - SP
CEP 04616-005
E-mail: lucasccmed@hotmail.com

Received on November 16, 2012.
Accepted on July 26, 2013.

DOI: 10.5935/0104-7795.20130025

INTRODUCTION

Over the last two decades an increasing of evidences identified the nutritional supplement creatine (Cr) as the most effective ergogenic aid to improve exercise tolerance, muscle strength and lean body mass.[1,2]

The undeniable documented benefits associated with an excellent safety profile of its use, lead researches to explore Cr as a therapeutic aid in many health and sickness conditions,[3] as recent reviewed by Gualano et al.[4,5]

In this context, Cr supplementation can possibly counteract the final result of many degenerative diseases, like muscle weakness, atrophy and metabolic disturbances.[4,5]

In peripheral arterial obstructive disease (PAOD), the chronic obstruction in blood flow to distal territories due to atherosclerotic process, and its consequence and constant mismatch between oxygen delivery and demand, lead to a progressive disability cycle involving muscle fiber atrophy and denervation, negative muscle metabolism alterations, reduced strength and endurance, impairing general physical fitness capacity, specially walking capacity, in diseased individuals.[6-9]

Cost-effectiveness strategies[10] to counteract muscle, nerve and metabolism impairments, and to reduce the loss of physical fitness capacity, like exercise training have been previously proposed[11,12] and studied.[13-17]

Therefore, adding up the cost-effectiveness and the safety profile of studied benefits of Cr supplementation[18,19] and the clinical frame of PAOD, the use of Cr rises as a potential therapeutic aid to be considered.

OBJECTIVE

So, the goal of this study was to make a systematic review in scientific literature, searching for studies involving Cr supplementation in PAOD individuals, published in the last ten years.

METHOD

A search in the last ten years for Portuguese and English written articles including and incluiding terms related to PAOD and Cr supplementation was conducted on PubMed, SciELO, and LILACS.

Included terms: 1) PAOD: a) English - Peripheral Arterial Disease and Intermittent Claudication; b) Portuguese - Doença Arterial Periférica, Obstrução Arterial Periférica e Claudicação Intermittente. 2) Cr Supplementation: a) English - Creatine, Creatine Monohydrate and Creatine Supplementation; b) Portuguese - Creatina, Creatina Monohidratada, Suplementação de Creatina.

All included terms found in the articles were individually selected by the title and abstract to be included in this review. After the selection, the articles were taken from two open access libraries (University of São Paulo and Federal University of São Paulo).

RESULTS

After our research, only on Pubmed, articles related to the subject were found. Relevant studies (3 studies) were selected after matching "Intermittent Claudication x Creatine" (29 searched, 3 selected), and from "Peripheral Arterial Disease x Creatine" (85 searched, 13 selected).

Studies were excluded if they were not about investigations concerning the subject (ie. Creatine supplementation, or peripheral arterial disease). Articles that scope peripheral arterial disease metabolism, including ATP-PCr, were selected, even if they were not specific, and they were mentioned along this study.

One important detail to point out is that the previous period planned (last ten years) was extended to 15 years due to limited data.

Only one study[20] from Cardiology Center of Moscow (Russia), in fact, evaluated the influence of Cr supplementation in the desired sample (PAOD), describing positive influence not only in maximal walking distance, but as well as on platelet aggregation, blood rheology, coagulation and fibrinolytic system.

DISCUSSION

Despite the presented discussion of Cr supplementation as a potential therapeutic aid in PAOD population, we could only find one study published in 1994 from Russian researchers. Panchenko et al.[20] studied the influence of daily 10g supplementation of Cr in 37 PAOD patients, versus non-diseased paired sample men, with symptoms of intermittent claudication, with diagnosis confirmed by angiography or ultrasound technique. Comparing patients with control group (before and after this intervention), the diseased supplemented group significantly increased maximal walking distance. The authors attributed this improvement on walking due to positive influences on platelet aggregation, blood rheology, coagulation and fibrinolytic system.[20]

Surprisingly, the described method in the present research, no other studies were conducted until now (confirming or refuting the results), despite the clinical benefits observed and documented in the PAOD population of Panchenko et al.[20] study.

Due the lack of scientific data evaluating this subject, we believe it will be interesting to better discuss the potential use of Cr supplementation in PAOD population, including metabolic, functional and structural considerations:

Metabolic

In PAOD, due to chronic atherosclerotic process, the reduced blood flow leads to impaired oxygen delivery in peripheral territories distal to obstruction[6]. Therefore, every time the peripheral demand to oxygen increases, for example during repeated muscular contractions (eg. Walking), there is a mismatch between delivery and demand of oxygen, increasing the dependence of anaerobic energy supply, leading to increase in local acidosis and consequent fatigue.[21-24]

The peripheral metabolic fatigue can be observed clinically by ischemia symptoms (intermittent claudication), commonly described as pain while walking, that prevented the patient to continue.[6] Moreover, not only in the acute increase of demand of oxygen by active muscles (eg walking),[23,24] evidence suggests that this chronic ischemic process leads to more permanent decreases in energy storages (ATP-PCr, glycogen, lipids), reduced glycolitic and oxidative enzymes, and decreased mitochondrial function.[21-24] Adding up, the cited alterations impairs ATP synthesis and regeneration. In fact, previous studies using Phosphorus-31 magnetic resonance spectroscopy found a perturbation in oxidative ATP synthesis rate and a delayed PCr recovery time in PAOD patients.[21-23] PCr recovery time was the strongest inversely correlated factor together with walking capacity,[22] and predictor of late follow up requirements for surgical limb interventions and mortality.[23] One can argue that once blood flow can be restored (eg angioplasty, revascularization surgery), the metabolic impairments could reverse, but Pipinos et al.[25] could not find improvement of clinical performance after surgical procedure, suggesting that blood flow restriction is not the only factor implying in walking impairment in PAOD patients.

Wolosker et al.[26] found a very low predictive value of the ankle-brachial index in the evaluation of walking capacity in patients with intermittent claudication. According to

it, many exercise intervention studies could document significant gain in many spheres of physical fitness without a significant improvement in blood flow, confirming the data about an important metabolic contribution leading to function.[15-17]

Even in non diseased (normal blood flow) persons (eg athletes), an increase on metabolic function is capable to improve performance, as seen in studies with Cr supplementation, corroborating the data.[27,28] The ingestion of 20g/day of Cr for 5 days can lead to increase more than 20% of muscle Cr content, of which approximately 20% can be attributable to PCr form.[1] As reviewed previously by Rawson and Persky[27] (2007), in the context of exercise performance, Cr supplementation can act as an ergogenic aid through some mechanisms, mainly: a) increased storages of glycogen and PCr pre-exercise; b) reduced time to PCr resynthesys; c) reduced post exercise muscle damage and inflammation; d) increased training intensity, volume, and sensitivity of contractile muscle fibers to Ca++; e) acts in oxidative stress prevention via direct and indirect antioxidant action; f) maintains the ATP/ADP ratio and maintains cellular pH via H+ buffering; and g) provide activation of glycolysis and glycogenolysis through Pi release thereby integrating the carbohydrate and Cr degradation to provide energy at the early stage of exercises.

Finally, due to metabolic alteration seen in PAOD and the Cr supplementation benefits mapped until now, there is a large and extensive field of possibilities for original researches, until this moment only one study was done.[20] With a plausible application of this nutritional supplement (based on clinical reasoning), Creatine can act as a therapeutic aid aiming to restore the metabolic impairments of PAOD.

Functional

Performance in daily living regarding general physical efforts, with special consideration to walking capacity, is impaired in PAOD individuals.[6] The worsening of arterial obstruction and consequent disease evolutional stage was previously correlated with these impairments.[14,15,29] In fact, studies made with ambulatory measurements and subjective questionnaires to analyze physical function, observed decreasing levels of physical activity in more severe diseased patients.[14,15,29,30]

This scenario of reduced physical capacity due to PAOD, increases the levels of a more sedentary lifestyle, which provokes in end a "progressive disability cycle" of physical function.[31] In this field, scientific literature has been previously documented reduced values of strength, power and endurance in patients when compared with non diseased controls.[7-9,16,17,30,32-34]

Once muscular strength could be strongly correlated with walking capacity (most accessed measure of fitness capacity) in PAOD patients by Regensteiner et al.[34] and Gerdle et al.[32] interventions (resistance training) to counteract this condition has been proposed[11,12] and studied with documented positive benefits.[13-17]

Additional to resistance training, as a beneficial exercise type prescription in non diseased population,[35] association of Cr supplementation has been studied and proposed as a more effective intervention to improvements muscular strength.[36] In fact two recent meta-analysis[37,38] documented that Cr supplementation can significantly increase muscular capacity to generate strength.

In this context, despite of documented positive benefits, there is still a *gap* in actual knowledge about if Cr supplementation can increase strength *per se* or due to consequent positive adaptations in training capacity, but this discussion is beyond of scope of our present considerations and has been fashionably reviewed before by Lemon et al.[39] and Gualano et al.[40]

To our knowledge, no previous studies including strength training in combination with Cr supplementation was conducted yet in PAOD patients, leaving a large, open and a potential attractive field to original investigations.

Structural

Significant morphological changes in skeletal muscle are presented by PAOD patients, including atrophy (sarcopenia), modification in the patterns of fiber type distribution, disturbance in neural function, and these changes have been associated with impaired walking capacity.[34,41-43]

Askew et al.[42] and Regensteiner et al.[34] using muscular biopsy, found a reduction in skeletal muscle cross sectional area, and a reduction in size of fibers type I and IIa, comparing PAOD patients with their paired healthy controls.

Mc Guigan et al.[41] documented a significant increase in muscular capillary density due the chronic ischemic process, and also an increase in expression of myosin heavy chain (MHC) IIx, besides a reduction in MHC I. As mentioned before,[34,42] this study also verified a reduction in cross sectional area of fibers type I and IIa.

Mc Dermott et al.[43] showed a reduction in neural function, due to impairments in motoneuron, as measured by a reduction in nerve conduction velocity presented in electroneuromyography of 109 older Italian community-dwelling PAOD patients.

Gualano et al.[44] conducted a recent review about positive influence of Cr supplementation in enhancement of muscular hypertrophy and strength in healthy persons. The author's conclusion was a suggestion that the gains obtained was not due water retention, but gene expression and protein translation efficiency related to hypertrophy, and proliferation and activation of satellite cels.

Again, a beneficial combination of resistance training and Cr supplementation is capable to benefit patients with neuropathies[45] and several other nervous system conditions.[46-48]

In conclusion Cr supplementation can act as a main potential counter-actor of degenerative muscle and nervous impairments consequent to chronic PAOD, but unfortunately no studies were conducted before to corroborate or refute our present hypothesis.

Other Considerations

Taking into account, that the prevalence of PAOD increases with age,[49-51] is important to consider that the impairments exclusively due to disease occurs, most of the time, associated with the loss of physical function of normal sedentary aging process.[52-56] It is reasonable to conclude that the morphological and metabolic changes in skeletal muscle, as well as reduction in physical fitness derived from normal aging, can be empowered in PAOD patients.[41-43] Dalbo et al.[57] recently published a detailed manuscript about the benefits of Cr supplementation in promoting beneficial effects on many aspects of physical fitness loss due to aging.

Comorbidities as dyslipidemia, *diabetes mellitus*, chronic kidney disease, hypertension, pro-inflammatory status, cardiac dysfunctions (e.g. hearth failure), chronic obstructive pulmonary disease (due to high smoke prevalence) are frequently presented in the diseased pacients.[6]

As presented by Gualano et al.[4,5] Cr supplementation have already been studied showing benefits undoing some of the unfavorable changes for the majority of those

comorbidities. In the end, Cr monohydrate has been the most studied supplement applied on sports performance enhancement and several health conditions.[4,5,58]

CONCLUSION

Despite the presented discussion of Cr supplementation in PAOD patients as a potential therapeutic aid, to our knowledge, only one previous study could verify its benefits. There is a large and extensive field of possibilities for future studies, which are encouraged by the authors. These surveys should focus on the possible benefits to counteract the loss of functional fitness and impairments in musculoskeletal structure and metabolism of aging diseased individuals.

REFERENCES

1. Buford TW, Kreider RB, Stout JR, Greenwood M, Campbell B, Spano M, et al. International Society of Sports Nutrition position stand: creatine supplementation and exercise. J Int Soc Sports Nutr. 2007;4:6. DOI: http://dx.doi.org/10.1186/1550-2783-4-6
2. Terjung RL, Clarkson P, Eichner ER, Greenhaff PL, Hespel PJ, Israel RG, et al. American College of Sports Medicine roundtable. The physiological and health effects of oral creatine supplementation. Med Sci Sports Exerc. 2000;32(3):706-17. DOI: http://dx.doi.org/10.1097/00005768-200003000-00024
3. Câmara LC, Ritti-Dias RMR. Suplementação de creatina: efeitos ergogênicos e terapêuticos. Rev Med (São Paulo).2009;88(2):94-102.
4. Gualano B, Artioli GG, Poortmans JR, Lancha Junior AH. Exploring the therapeutic role of creatine supplementation. Amino Acids. 2010;38(1):31-44. DOI: http://dx.doi.org/10.1007/s00726-009-0263-6
5. Gualano B, Roschel H, Lancha-Jr AH, Brightbill CE, Rawson ES. In sickness and in health: the widespread application of creatine supplementation. Amino Acids. 2012;43(2):519-29. DOI: http://dx.doi.org/10.1007/s00726-011-1132-7
6. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45 Suppl S:S5-67. DOI: http://dx.doi.org/10.1016/j.jvs.2006.12.037
7. Basyches M, Wolosker N, Ritti-Dias RM, Câmara LC, Puech-Leão P, Battistella LR. Eccentric strength and endurance in patients with unilateral intermittent claudication. Clinics (São Paulo). 2009;64(4):319-22. DOI: http://dx.doi.org/10.1590/S1807-59322009000400009
8. Nakano L, Wolosker N, Rosoki RA, Netto BM, Puech-Leão P. Objective evaluation of upper limb claudication: use of isokinetic dynamometry. Clinics (São Paulo). 2006;61(3):189-96. DOI: http://dx.doi.org/10.1590/S1807-59322006000300002
9. Scott-Okafor HR, Silver KK, Parker J, Almy-Albert T, Gardner AW. Lower extremity strength deficits in peripheral arterial occlusive disease patients with intermittent claudication. Angiology. 2001;52(1):7-14.
10. Treesak C, Kasemsup V, Treat-Jacobson D, Nyman JA, Hirsch AT. Cost-effectiveness of exercise training to improve claudication symptoms in patients with peripheral arterial disease. Vasc Med. 2004;9(4):279-85. DOI: http://dx.doi.org/10.1191/1358863x04vm570oa
11. Dias RMR, Salvador EP, Wolosker N, Marucci MFN. Novas tendências no tratamento de indivíduos com claudicação intermitente por meio do exercício físico. Rev Bras Cienc Mov. 2006;14(2):111-6.
12. Câmara LC, Santarém JM, Wolosker N, Dias RMR. Exercícios resistidos terapêuticos para indivíduos com doença arterial obstrutiva periférica: evidências para a prescrição. J Vasc Bras. 2007;6(3):246-56. DOI: http://dx.doi.org/10.1590/S1677-54492007000300008
13. McGuigan MR, Bronks R, Newton RU, Sharman MJ, Graham JC, Cody DV, et al. Resistance training in patients with peripheral arterial disease: effects on myosin isoforms, fiber type distribution, and capillary supply to skeletal muscle. J Gerontol A Biol Sci Med Sci. 2001;56(7):B302-10. DOI: http://dx.doi.org/10.1093/gerona/56.7.B302
14. Wolosker N, Nakano L, Rosoky RA, Puech-Leao P. Evaluation of walking capacity over time in 500 patients with intermittent claudication who underwent clinical treatment. Arch Intern Med. 2003;163(19):2296-300. DOI: http://dx.doi.org/10.1001/archinte.163.19.2296
15. Rosoky RM, Wolosker N, Puech-Leão P. Performance of patients with intermittent claudication undergoing physical training, with or without an aggravation of arterial disease: retrospective cohort study. Clinics (São Paulo). 2006;61(6):535-8. DOI: http://dx.doi.org/10.1590/S1807-59322006000600008
16. Menêses AL, de Lima GH, Forjaz CL, Lima AH, Silva GQ, Cucato GG, et al. Impact of a supervised strength training or walking training over a subsequent unsupervised therapy period on walking capacity in patients with claudication. J Vasc Nurs. 2011;29(2):81-6. DOI: http://dx.doi.org/10.1016/j.jvn.2011.01.002
17. Ritti-Dias RM, Wolosker N, Moraes Forjaz CL, Carvalho CR, Cucato GG, Leão PP, et al. Strength training increases walking tolerance in intermittent claudication patients: randomized trial. J Vasc Surg. 2010;51(1):89-95. DOI: http://dx.doi.org/10.1016/j.jvs.2009.07.118
18. Persky AM, Rawson ES. Safety of creatine supplementation. Subcell Biochem. 2007;46:275-89.
19. Terjung RL, Clarkson P, Eichner ER, Greenhaff PL, Hespel PJ, Israel RG, et al. American College of Sports Medicine roundtable. The physiological and health effects of oral creatine supplementation. Med Sci Sports Exerc. 2000;32(3):706-17. DOI: http://dx.doi.org/10.1097/00005768-200003000-00024
20. Panchenko E, Dobrovolsky A, Rogoza A, Sorokin E, Ageeva N, Markova L, et al. The effect of exogenous phosphocreatine on maximal walking distance, blood rheology, platelet aggregation, and fibrinolysis in patients with intermittent claudication. Int Angiol. 1994;13(1):59-64.
21. Isbell DC, Berr SS, Toledano AY, Epstein FH, Meyer CH, Rogers WJ, et al. Delayed calf muscle phosphocreatine recovery after exercise identifies peripheral arterial disease. J Am Coll Cardiol. 2006;47(11):2289-95. DOI: http://dx.doi.org/10.1016/j.jacc.2005.12.069
22. Anderson JD, Epstein FH, Meyer CH, Hagspiel KD, Wang H, Berr SS, et al. Multifactorial determinants of functional capacity in peripheral arterial disease: uncoupling of calf muscle perfusion and metabolism. J Am Coll Cardiol. 2009;54(7):628-35. DOI: http://dx.doi.org/10.1016/j.jacc.2009.01.080
23. Greiner A, Esterhammer R, Messner H, Biebl M, Mühlthaler H, Fraedrich G, et al. High-energy phosphate metabolism during incremental calf exercise in patients with unilaterally symptomatic peripheral arterial disease measured by phosphor 31 magnetic resonance spectroscopy. J Vasc Surg. 2006;43(5):978-86. DOI: http://dx.doi.org/10.1016/j.jvs.2006.01.020
24. Esterhammer R, Schocke M, Gorny O, Posch L, Messner H, Jaschke W, et al. Phosphocreatine kinetics in the calf muscle of patients with bilateral symptomatic peripheral arterial disease during exhaustive incremental exercise. Mol Imaging Biol. 2008;10(1):30-9. DOI: http://dx.doi.org/10.1007/s11307-007-0118-z
25. Pipinos II, Shepard AD, Anagnostopoulos PV, Katsamouris A, Boska MD. Phosphorus 31 nuclear magnetic resonance spectroscopy suggests a mitochondrial defect in claudicating skeletal muscle. J Vasc Surg. 2000;31(5):944-52. DOI: http://dx.doi.org/10.1067/mva.2000.106421
26. Wolosker N, Rosoky RA, Nakano L, Basyches M, Puech-Leão P. Predictive value of the ankle-brachial index in the evaluation of intermittent claudication. Rev Hosp Clin Fac Med São Paulo. 2000;55(2):61-4. DOI: http://dx.doi.org/10.1590/S0041-87812000000200005
27. Rawson E, Persky A. Mechanisms of muscular adaptations to creatine. Int Sport Med J. 2007;8:43-53.
28. Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. J Strength Cond Res. 2003;17(4):822-31.
29. McDermott MM, Criqui MH, Greenland P, Guralnik JM, Liu K, Pearce WH, et al. Leg strength in peripheral arterial disease: associations with disease severity and lower-extremity performance. J Vasc Surg. 2004;39(3):523-30. DOI: http://dx.doi.org/10.1016/j.jvs.2003.08.038
30. Menêses AL, Lima AHRA, Farah BQ, Silva GQM, Lima GHC, Lins Filho OL, et al. Relação entre aptidão física e os indicadores de qualidade de vida de indivíduos com claudicação intermitente. Rev Bras Med Esporte.2011;17(3):175-8. DOI: http://dx.doi.org/10.1590/S1517-86922011000300005
31. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. N Engl J Med. 2002;347(24):1941-51. DOI: http://dx.doi.org/10.1056/NEJMra021135
32. Gerdle B, Hedberg B, Angquist KA, Fugl-Meyer AR. Isokinetic strength and endurance in peripheral arterial insufficiency with intermittent claudication. Scand J Rehabil Med. 1986;18(1):9-15.
33. McDermott MM, Tian L, Ferrucci L, Liu K, Guralnik JM, Liao Y, et al. Associations between lower extremity ischemia, upper and lower extremity strength, and functional impairment with peripheral arterial disease. J Am Geriatr Soc. 2008;56(4):724-9. DOI: http://dx.doi.org/10.1111/j.1532-5415.2008.01633.x
34. Regensteiner JG, Wolfel EE, Brass EP, Carry MR, Ringel SP, Hargarten ME, et al. Chronic changes in skeletal muscle histology and function in peripheral arterial disease. Circulation. 1993;87(2):413-21. DOI: http://dx.doi.org/10.1161/01.CIR.87.2.413
35. Kraemer WJ, Adams K, Cafarelli E, Dudley GA, Dooly C, Feigenbaum MS, et al. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2002;34(2):364-80. DOI: http://dx.doi.org/10.1097/00005768-200202000-00027

36. Volek JS, Duncan ND, Mazzetti SA, Staron RS, Putukian M, Gómez AL, et al. Performance and muscle fiber adaptations to creatine supplementation and heavy resistance training. Med Sci Sports Exerc. 1999;31(8):1147-56. DOI: http://dx.doi.org/10.1097/00005768-199908000-00011
37. Branch JD. Effect of creatine supplementation on body composition and performance: a meta-analysis. Int J Sport Nutr Exerc Metab. 2003;13(2):198-226.
38. Nissen SL, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. J Appl Physiol. 2003;94(2):651-9.
39. Lemon PW. Dietary creatine supplementation and exercise performance: why inconsistent results? Can J Appl Physiol. 2002;27(6):663-81. DOI: http://dx.doi.org/10.1139/h02-039
40. Gualano B, Benatti FB, Ferreira JCB, Franchini E, Brum PC, Lancha Junior AH. Efeitos da suplementação de creatina no exercício intermitente de alta intensidade: divergências e recomendações metodológicas. Rev Bras Cineantropom Desemp Hum. 2008;10(2):189-96.
41. McGuigan MR, Bronks R, Newton RU, Sharman MJ, Graham JC, Cody DV, et al. Muscle fiber characteristics in patients with peripheral arterial disease. Med Sci Sports Exerc. 2001;33(12):2016-21. DOI: http://dx.doi.org/10.1097/00005768-200112000-00007
42. Askew CD, Green S, Walker PJ, Kerr GK, Green AA, Williams AD, et al. Skeletal muscle phenotype is associated with exercise tolerance in patients with peripheral arterial disease. J Vasc Surg. 2005;41(5):802-7. DOI: http://dx.doi.org/10.1016/j.jvs.2005.01.037
43. McDermott MM, Guralnik JM, Albay M, Bandinelli S, Miniati B, Ferrucci L. Impairments of muscles and nerves associated with peripheral arterial disease and their relationship with lower extremity functioning: the InCHIANTI Study. J Am Geriatr Soc. 2004;52(3):405-10. DOI: http://dx.doi.org/10.1111/j.1532-5415.2004.52113.x
44. Gualano B, Acquesta FM, Ugrinowitsch C, Tricoli V, Serrão JC, Lancha Junior AH. Efeitos da suplementação de creatina sobre força e hipertrofia muscular: atualizações. Rev Bras Med Esporte.2010;16(3):219-23. DOI: http://dx.doi.org/10.1590/S1517-86922010000300013
45. Smith CA, Chetlin RD, Gutmann L, Yeater RA, Alway SE. Effects of exercise and creatine on myosin heavy chain isoform composition in patients with Charcot-Marie-Tooth disease. Muscle Nerve. 2006;34(5):586-94. DOI: http://dx.doi.org/10.1002/mus.20621
46. Andres RH, Ducray AD, Schlattner U, Wallimann T, Widmer HR. Functions and effects of creatine in the central nervous system. Brain Res Bull. 2008;76(4):329-43. DOI: http://dx.doi.org/10.1016/j.brainresbull.2008.02.035
47. Tarnopolsky MA. Clinical use of creatine in neuromuscular and neurometabolic disorders. Subcell Biochem. 2007;46:183-204.
48. Beal F. Neuroprotective effects of creatine. Amino Acids. 2001; 40(5):1305-13.
49. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral ar-terial disease in the elderly: The Rotterdam Study. Arterioscler Thromb Vasc Biol. 1998;18(2):185-92. DOI: http://dx.doi.org/10.1161/01.ATV.18.2.185
50. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J. 2002;143(6):961-5. DOI: http://dx.doi.org/10.1067/mhj.2002.122871
51. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004;110(6):738-43. DOI: http://dx.doi.org/10.1161/01.CIR.0000137913.26087.F0
52. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. J Apll Physiol. 2000;88(4):1321-6.
53. Brown DA, Miler WC. Normative data for strength and flexibility throughout life. Eur J Apll Physiol Occup Physiol. 1998;78(1):77-82. DOI: http://dx.doi.org/10.1007/s004210050390
54. Hobeika CP. Equilíbrium and balance in the elderly. Ear Nose Throat. 1999; 78(8):558-62.
55. Câmara LC, Santarem Sobrinho JM, Jacob Filho W, Kuwakino MH. Exercícios resistidos em idosos portadores de insuficiência arterial periférica. Acta fisiatr. 2006;13(2):96-102.
56. Câmara LC, Santarém JM, Wolosker N, Greve JMDA, Jacob Filho W. Avaliação da função muscular em doença arterial obstrutiva periférica: a utilização da dinamometria isocinética. Acta Fisiátr. 2007;14(3):176-80.
57. Dalbo VJ, Roberts MD, Lockwood CM, Tucker PS, Kreider RB, Kerksick CM. The effects of age on skeletal muscle and the phosphocreatine energy system: can creatine supplementation help older adults. Dyn Med. 2009;8:6. DOI: http://dx.doi.org/10.1186/1476-5918-8-6
58. Gualano B, Ugrinowitsch C, Seguro AC, Lancha Junior AH. A suplementação de creatina prejudica a função renal? Rev Bras Med Esporte. 2008;14(1):68-73. DOI: http://dx.doi.org/10.1590/S1517-86922008000100013