Creatine 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
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,3,4 as recent reviewed by Gualano et al.5,6

In this context, Cr supplementation can possibly counteract the final result of many degenerative diseases, like muscle weakness, atrophy and metabolic disturbances.6,7

In peripheral arterial obstructive disease (PAOD), the chronic obstruction in blood flow to distant 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.6,8

Cost-effectiveness strategies9 to counteract muscle, nerve and metabolism impairments, and to reduce the loss of physical fitness capacity, like exercise training have been previously proposed10,11 and studied.12,13

Therefore, adding up the cost-effectiveness and the safety profile of studied benefits of Cr supplementation14,15 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 including 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 study16 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.17 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.18

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.17 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 obstruction19. 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.20,21

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.22 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.21,22 PCr recovery time was the strongest inversely correlated factor together with walking capacity,12 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 angio-plasty, 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 metabolitic contribution leading to function.5-17

Even in non diseased (normal blood flow) persons (eg athletes), an increase on metabolitic function is capable to improve performance, as seen in studies with Cr supplementation, corroborating the data.17,18 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 Persky17 (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 resynthesis; 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 evolutiona stage was previously correlated with these impairments.14,15,19 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.14,15,19,30

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 proposed11-12 and studied with documented positive benefits.19,27

Additional to resistance training, as a beneficial exercise type prescription in non diseased population,33 association of Cr supplementation has been studied and proposed as a more effective intervention to improvements muscular strength.34 In fact two recent meta-analysis35,36 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 neuronal function, and these changes have been associated with impaired walking capacity.34,41-43

Askev 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,34,43 this study also verified a reduction in cross sectional area of fibers type I and Ila.

Mc Dermott et al.44 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.45 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 cells.

Again, a beneficial combination of resistance training and Cr supplementation is capable to benefit patients with neuropathies46 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.51-53 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 patients.5

As presented by Gualano et al.45 Cr supplementation have already been studied showing benefits undoing some of the unfavorable changes for the majority of those
COMCLUSION

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


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