Synergistic effects of creatine supplementation and resistance training in the management of knee osteoarthritis: A narrative review

Muhammad Osama,[1,2,3] Bruno Bonnechère,[4,5,6], Jean Mapinduzi,[4,7,8] Farooq Azam Rathore[9]

Abstract

Knee osteoarthritis (KOA) is a common joint disorder and a leading cause of disability. Although there is no cure, management strategies focus on conservative approaches such as pharmacotherapy, non-pharmacological supplementation, physical therapy (PT), and exercise. Pharmacological treatments are widely used for pain relief but carry risks of long-term adverse effects and do not enhance joint or muscle health. Non-pharmacological supplements, including glucosamine and chondroitin-sulphate, are frequently used, although their effectiveness remains debated. However, PT, particularly resistance training (RT), has shown significant benefits in improving muscle strength and function in KOA. Creatine supplementation (CS) has recently emerged as a promising non-pharmacological intervention, particularly when combined with RT. Studies indicate that while CS alone shows limited benefits in KOA, its combination with RT significantly enhances muscle strength, lean mass, physical function, and quality of life by replenishing phosphocreatine stores, which fuel high-intensity muscle contractions during RT. Additionally, CS appears to be safe in short and mid-term use according to the available studies. Even though evidence has shown positive effects of CS without any significant adverse effects, very few studies with small sample sizes have been published in the literature regarding KOA, reporting varying results. We recommend that future studies should include larger sample sizes and standardized measures to strengthen the evidence base.

Keywords: Creatine, exercise, physical therapy, physiotherapy, knee osteoarthritis.

DOI: https://doi.org/10.47391/JPMA.25-82

Introduction

Osteoarthritis (OA) is a common condition, with the knee being particularly susceptible due to its weight-bearing role and high-stress demands.[1,2] Knee osteoarthritis (KOA) represents a significant portion of OA related disability worldwide, making KOA one of the top contributors to disability, ranking 4th in women and 8th in men worldwide.[1-3] KOA has high prevalence in aging populations having doubled since the mid-20th century, reaching 80% among those over 65 in industrialized countries.[1]

Management of KOA

Currently, there is no definitive cure for KOA, and management focusses on prevention and early intervention through patient education, physical therapy (PT), and pharmacologic treatment.[2-4] Pharmacologic management typically includes acetaminophen and Non-Steroidal Anti-Inflammatory Drugs such as ibuprofen for pain relief. While effective, these medications may be associated with gastrointestinal, cardiovascular, and renal side effects, especially with prolonged use.[5]

In contrast, exercise therapy is a safe and important component of conservative management, offering benefits without significant adverse-effects.[4] It plays an important role in improving mobility, balance, and muscle strength, all of which contribute to reduced pain, and enhanced joint function and quality of life (QOL).[4] Resistance training (RT) is ideal for KOA as it involves fewer repetitions but effectively strengthens muscles, improving pain, function, and muscle strength, and possibly slowing OA progression. High-intensity RT (80% of 1-repetition maximum-RM) is reported to be most effective, though moderate intensity (60% of 1RM) may suffice for some individuals.[4] Moreover, PT modalities like joint mobilization, ultrasound, laser, heat and

[1]Department of Physical Therapy, Faculty of Allied Health and Biological Sciences, Ibadat International University Islamabad (IIUI), Pakistan. [2]Brainstorm Research (www.brainstormresearch.org), [3]Active Health Physio, South Canterbury, New Zealand, [4]REVAL Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium, [5]Technology-Supported and Data-Driven Rehabilitation, Data Sciences Institute, Hasselt University, Diepenbeek, Belgium, [6]Centre of expertise in Care Innovation, Department of PXL – Healthcare, PXL University of Applied Sciences and Arts, Hasselt, Belgium, [7]TechnoRehab Lab[2], Department of Physiotherapy and Rehabilitation, Department of Clinical Sciences, National Institute of Public Health (INSP), Bujumbura, Burundi, [8]Clinic of Physiotherapy and Orthopedic Equipment (CKAO-AMAHORO), Bujumbura, Burundi, [9]Department of Rehabilitation Medicine, Quetta Institute of Medical Sciences (QIMS) Quetta, Pakistan

Correspondence: Farooq Azam Rathore . **Email:** farooqrathore@gmail.com
ORCID ID: 0000-0002-4759-0453

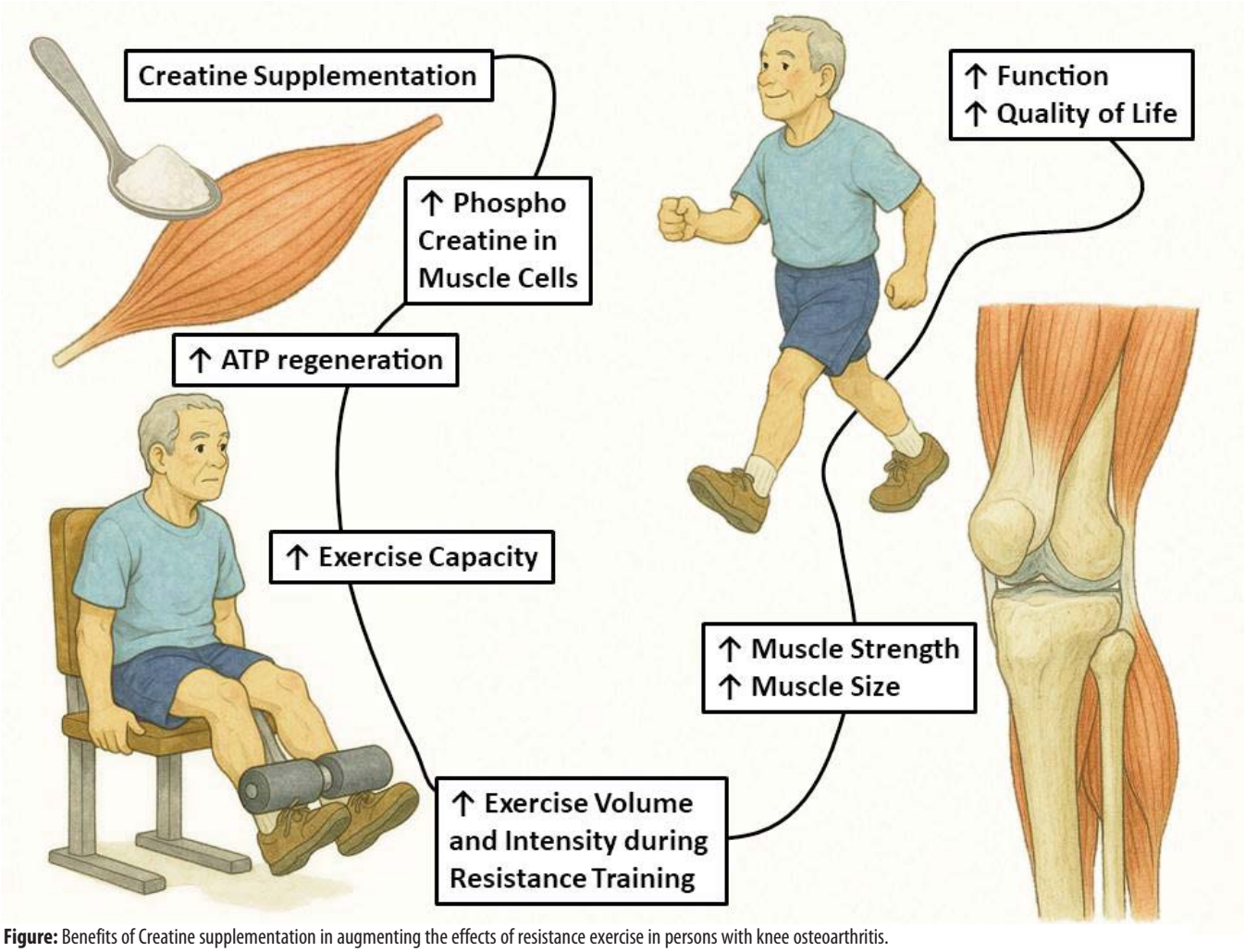

Figure: Benefits of Creatine supplementation in augmenting the effects of resistance exercise in persons with knee osteoarthritis.

electrotherapy support pain and functional improvement, especially when combined with exercise.[2,4]

Popular non-pharmacological supplements for KOA, like glucosamine and chondroitin-sulfate, have mixed clinical evidence,[2] and they have shown no added benefit when administered with exercise in KOA.[2] The need for alternative dietary supplements that can effectively enhance the impact of exercise in managing KOA is clear, as exercise remains one of the most essential and promising treatment approaches, and combining specific supplements with exercise could potentially amplify therapeutic outcomes in KOA. This is where creatine supplementation (CS) serves as valuable option with its potential to amplify the effects of resistance training and high-intensity exercise.

Creatine's role in augmenting the effects of RT

Creatine is synthesized from amino acids, 95% of which is stored in skeletal muscles, and exists as phosphocreatine (PCr) and free creatine. In muscles, 1-2% of creatine is broken down daily and excreted in urine, with stores replenished through diet or supplementation.[6,7] Creatine is stored in muscles as PCr, where it serves as a readily available energy source, especially during high-intensity, short-duration exercises. In skeletal muscle, creatine enhances adenosine triphosphate (ATP) regeneration through its conversion to phosphocreatine via creatine kinase as shown in the equation below:

$$Cr + ATP \rightleftharpoons PCr + ADP$$

PCr serves as an energy-rich compound, acting as a rapid-access energy source within muscles.[6,7] By increasing PCr levels, the muscles' ability to produce ATP is increased, which in turn supports greater force generation, prolonged effort and additional repetitions thus resulting in greater workload and training volume within a session.[6,7] Over time, this increased exercise volume

optimizes strength and muscle development via hypertrophy and hyperplasia.[6,7] Thus, individuals using creatine can exercise at higher intensities, do more repetitions, and build more muscles (Figure).[6,7] Typically, skeletal muscle can store ATP and PCr to fuel muscle contraction for up to 10 seconds. Short-term CS can raise total creatine by 10-30% and PCr by 10-40%.[6,7] In addition to enhancing energy availability, creatine may aid muscle repair and growth by increasing satellite cell signalling and intracellular-water (ICW) content, promoting muscle cell volume expansion.[6,7] Creatine also helps reduce muscle breakdown, potentially supporting muscle mass growth by lowering protein myostatin levels, which can otherwise restrict new muscle formation. Figure. Studies suggest that creatine aids in muscle recovery, injury prevention, and neuro-protection and has shown potential benefits in aging, pregnancy, and conditions like OA, muscular-dystrophy, Parkinson's, and stroke.[6-8] Some studies even suggest creatine having anti-inflammatory properties.[6,7]

Creatine and KOA: Efficacy and mechanisms from current evidence

Based upon the literature review, four studies were identified (Table) focusing on effects of creatine in KOA. Only Neves et al (2011) combined creatine with lower-extremity (LE) RT and reported the most positive results,[8] demonstrating the combination to be effective in enhancing physical functioning, LE lean mass, quality of life (QOL), and muscle strength.[8] Additionally, CS when combined with RT was found to be more effective than RT alone in terms of physical-functioning, LE lean mass and QOL.[8]

Two studies showed no significant improvement in patients receiving CS compared to placebo.[9,10] However, it is important to point out that CS was not combined with RT in those studies.[9,10] This suggests that CS is only effective when combined with RT. This, hypothesis can be supported by the fact that CS boosts the PCr energy-system, which provides energy during initial few seconds of muscle contraction and is explicitly important in fuelling explosive and high-intensity contractions for RT. It is perhaps for this reason, that when CS is accompanied with RT, significant improvements in muscle strength and lean mass are observed, sequentially resulting in an improvement in physical-functioning and QOL in KOA.

However, a study conducted by Peeler J et al showed that CS improves QOL even in absence of LE-RT.[11] This is perhaps because of the fact that performance fatigability is a known phenomenon in KOA,[3,12] and by increasing muscle creatine reserves the muscle PCr energy-system reserves are increased which may decrease performance and perceived fatigability in short-bouts of activity, thus resulting in overall improvement in QOL. Nonetheless, this hypothesis is still up for debate as there is no current evidence to support this claim, and studies need to be carried out in terms of the effects of CS in KOA.

Moreover, literature has shown that in the absence of loading protocol it may take as long as 12-weeks to observe improvements in muscle size and strength.[6,7] In three of the studies loading protocol was followed and CS was carried out for 12-weeks. Conversely, no loading protocol was followed in Roy BD et al's study, and CS was carried out for 40-days only, 10-days before and 30-days after surgery, and perhaps that is the reason no significant improvements were observed in terms of lean muscle mass and muscle strength.[10]

Despite the variations in the findings of published studies, it is notable that only one study combined CS with RT, which also showed the most promising results.[8] Furthermore, it is also imperative to point out that in addition to a limited number of studies regarding CS in KOA, the existing studies consisted of small sample sizes, lack of RT in combination with CS and heterogeneity in the grade of KOA. It is thus suggested that future studies with larger sample sizes, standardized measures and inclusion criteria, appropriate follow up with loading protocol and combination of RT with CS should be conducted to strengthen the evidence base.

Creatine formulations and dosage recommendations

Creatine supplements come in various formulations, with creatine-monohydrate (CM) being the most widely used due to its cost-effectiveness and efficacy.[6,7] While newer formulations offer limited added benefits, combining CM with β-alanine has shown superior effects.[6,7] This combination is effective as β-alanine supports prolonged exercise (>60 sec), while CM enhances short, high-intensity performance.[6,7] The International Society of Sports Nutrition suggests a "loading protocol" of 20g/day (5gx4/day) or 0.3g/kg of body weight for 5-7 days to boost muscle creatine stores by 20-40%.[6,7] To maintain these levels, a daily dose of 3-5g is recommended with consistent exercise. If skipping the loading phase, 3g/day for 28 days can also elevate muscle creatine, while 6g/day may be necessary for up to 12-weeks to see increases in muscle size and strength.[6,7]

Adverse effects of CS

It is suggested that CS may result in weight gain, however the increase is in muscle mass, and not fat mass.[7]

Table : Summary of studies published on effects of Creatine supplementation in knee osteoarthritis.

Author	Study Design	Sample	Duration	Treatment Protocol	Inclusion Criteria	Outcome Measures	Results
Cornish SM & Peeler JD, 2018 [9]	Double Blind RCT	18	12 wk	1. Creatine Supplementation(20 grams/ day for 1 week.5g/day for 11 weeks of creatine monohydrate).2. Control/ Placebo(20 grams/ day for 1 week.5g/day for 11 weeks of maltodextrin)	45-65 years, Grade II-III Knee OA[a], BMI over 25kg/m^2 and knee pain on ADLs.	Inflammatory Markers (c-reactive protein, interleukin-1β, interleukin-6, s100 A8/A9, tumour necrosis factor-α), Cartilage degeneration markers (serum COMP), KOOS, Isometric muscle/thigh strength (isokinetic dynamometer).	No significant differences were observed between CS and placebo.
Neves M JR et al., 2011.[8]	Double Blind RCT	26	12 wk	1. Creatine supplementation (20 grams/ day for 1 week.5g/day for 11 weeks of creatine monohydrate + lower limb resistance exercise2. Control(Lower limb Resistance exercise only)(Use of up to 3g/day of paracetamol was allowed ifnecessary)	Post-menopausal women, 50-65 years with knee OA[b]	Physical Function (timed stand test), lean mass, QOL (Lequesne Index), WOMAC, pain, stiffness, muscle strength.	CS significantly improves physical function, LE lean muscle mass and QOL. No Significant differences were observed in terms of muscle strength and whole body lean muscle mass between the two groups.
Peeler J et al., 2019[11]	Single blind RCT	26	12 wk	1. LBPP supported treadmillwalking exercise2. Creatine supplementation(20 grams/ day for 1 week.5g/day for 11 weeks of creatine monohydrate)3. Control. Placebo(20 grams/ day for 1 week.5g/day for 11 weeks of maltodextrin)	45-65 years, Grade II-III Knee OA[a], BMI over 25kg/m^2 and knee pain on ADLs.	Body anthropometry, knee ROM, knee joint function and QOL (KOOS) , pain, Inflammatory biomarker (S100A8/A9) and cartilage degeneration biomarkers (COMP)	Significant improvements seen in sports and recreation function subscale of KOOS in LBPP group and in QOL subscale in CS group. No significant effects were observed in terms of S100 A8/A9 levels in all the groups. Moreover, SCOMP levels had a significant positive correlation with knee pain and KOOS (joint symptoms and ADL subscales).
Roy BD., 2005[10]	Double blind RCT	37	40 days	1. Creatine supplementation(5 g creatine monohydrate + 4 g dextrose twice a day, for 10 days before surgery and once a day after surgery for 10 days.2. Control. Placebo(7 g of dextrose per day for 40 days)	Knee OA undergoing TKA	Body composition, muscle metabolite concentrations, muscle histo-morphometry, quadriceps, ankle DF and handgrip strength, functional capacity.	No positive effects of CS on body composition, muscle strength and recovery.

Moreover, CS also increases water intake in muscles, resulting in greater ICW, which may also contribute to overall body mass.[6] This increase in ICW, has led to a belief that CS causes water retention, however creatine itself is an osmotically active substance and causes short-term increase in ICW.[6] This serves as a stimulus for muscle growth and is associated with higher strength and functional capacity.[13] No increase in total body-water in

relation to muscle mass occurs over the long-term, suggesting CS does not cause water-retention.[6] In fact, a meta-analysis published by Forbes et al in 2019 has shown that CS, in combination with RT reduces fat mass in the elderly.[14]

Anecdotal claims have been made regarding side-effects of CS including kidney damage, but no supporting evidence has been identified.[6] Additionally, studies have shown no significant effects of CS on renal or hepatic toxicity.[8,15,16] A meta-analysis published in 2019 showed that CS does not induce renal damage, and neither serum-creatinine levels nor plasma urea levels are significantly altered with CS.[15] Moreover, in terms KOA, Neves et al also reported no significant difference in terms of creatinine clearance between CS and placebo group.[8] Considering the current available literature, we can conclude that CS is safe in terms of renal or hepatic toxicity.

Conclusion

Creatine supplementation, particularly in combination with resistance training, presents a theoretically grounded and emerging adjunctive strategy for the management of knee OA. However, the limited number of high-quality studies necessitates further research to determine its effectiveness, optimize dosages, investigate long-term effects, and explore its mechanisms in pain-relief, muscle strengthening and functional improvement.

Acknowledgement: None.

Disclaimer: Individual images in Figure 1 were created using ChatGPT and then compiled and labelled using Adobe Photoshop.

Conflict of Interest: None.

Source of Funding: None.

References

1. Rodriguez-Veiga D, González-Martín C, Pertega-Díaz S, Seoane-Pillado T, Barreiro-Quintás M, Balboa-Barreiro V. Prevalence of osteoarthritis of the knee in a random population sample of people aged 40 and older. Gac Med Mex. 2019;155:37-43.
2. Osama M, Babur MN, Siddiqi FA, Tassadaq N, Tareen A. Effects of glucosamine and chondroitin sulfate supplementation in addition to resistance exercise training and manual therapy in patients with knee osteoarthritis: A randomized controlled trial. J Pak Med Assoc. 2022;72:1272-7.
3. Osama M, Babur MN, Siddiqi FA. Walking related performance fatigability in persons with knee osteoarthritis; an important yet neglected outcome. J Pak Med Assoc. 2021;71:1513-4.
4. Li Y, Su Y, Chen S, Zhang Y, Zhang Z, Liu C, et al. The effects of resistance exercise in patients with knee osteoarthritis: a systematic review and meta-analysis. Clinical Rehabil. 2016;30:947-59.
5. Vonkeman HE, van de Laar MA, editors. Nonsteroidal anti-inflammatory drugs: adverse effects and their prevention. Semin Arthritis Rheum. 2010;39:294-312.
6. Antonio J, Candow DG, Forbes SC, Gualano B, Jagim AR, Kreider RB, et al. Common questions `and misconceptions about creatine supplementation: what does the scientific evidence really show? J Int Soc Sports Nutr. 2021;18:13.
7. Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, et al. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr. 2017;14:18.
8. Neves Jr M, Gualano B, Roschel H, Fuller R, Benatti FB, PINTO ALDS, et al. Beneficial effect of creatine supplementation in knee osteoarthritis. Med Sci Sports Exerc. 2011;43:1538-43.
9. Cornish SM, Peeler JD. No effect of creatine monohydrate supplementation on inflammatory and cartilage degradation biomarkers in individuals with knee osteoarthritis. Nutr Res. 2018;51:57-66.
10. Roy BD, de Beer J, Harvey D, Tarnopolsky MA. Creatine monohydrate supplementation does not improve functional recovery after total knee arthroplasty. Arch Phys Med Rehabil. 2005;86:1293-8.
11. Peeler J, Zhang P, Cornish S, Ghavami S. S100A8/A9, Exercise, and Creatine in Knee Osteoarthritis. The FASEB Journal. 2019;33(1_supplement):769.4-.4.
12. Waqar A, Saif M, Osama M, Nasir R, Fayyaz A. Walking related performance fatigability in patients with knee osteoarthritis as compared to healthy controls. Physiother Pract Res. 2023;44:211-5.
13. Serra-Prat M, Lorenzo I, Palomera E, Yébenes JC, Campins L, Cabré M. Intracellular water content in lean mass is associated with muscle strength, functional capacity, and frailty in community-dwelling elderly individuals. A cross-sectional study. Nutrients. 2019;11:661.
14. Forbes SC, Candow DG, Krentz JR, Roberts MD, Young KC. Changes in fat mass following creatine supplementation and resistance training in adults≥ 50 years of age: a meta-analysis. J Funct Morphol Kinesiol. 2023;8:30. doi: 10.3390/jfmk8010030. PMID: 36976127. 2019;4(3):62.
15. e Silva AdS, Pertille A, Barbosa CGR, de Oliveira Silva JA, de Jesus DV, Ribeiro AGSV, et al. Effects of creatine supplementation on renal function: a systematic review and meta-analysis. J Ren Nutr 2019;29:480-9.
16. Baracho NCdV, Castro LPd, Borges NdC, Laira PB. Study of renal and hepatic toxicity in rats supplemented with creatine. Acta Cir Bras 2015;30:313-8.