ORIGINAL ARTICLE

Effectiveness of creatine supplementation among subjects with rheumatoid arthritis: a randomized controlled trial

Aamir Usman Memon[1*], Kumayl Abbas Meghji[2], Shahnaz Bano[3], Palwasha Abbasi[4], Sumayya Kazi[5], Muhammad Amir Memon[6]

Biomedica - Official Journal of University of Health Sciences, Lahore, Pakistan
Volume 40(4):159-163
https://doi.org/10.24911/BioMedica/5-1185

ABSTRACT

Background and Objective: Creatine supplementation has shown potential benefits in improving muscle mass and strength; however, its effect in patients with rheumatoid arthritis is still under investigation. The current study aimed to evaluate the effectiveness of Creatine supplementation on body composition and physical function in the subjects presenting with rheumatoid arthritis in the local population.

Methods: A double-blinded trial involving 30 patients with RA were assigned randomly in two groups each. One group received Creatine (Cr) supplementation (Cr group) and the other, a plain flavored drink (Control group) for 12 weeks. There was no difference in appearance, odor, and color between treatment and control intervention. Assessments were conducted at the initial (pre-supplementation), on the 6th day (after the loading phase), and 12th week (immediately after supplementation ended). Demographic and clinical data were required through interviews and reviewers of medical records. Body composition parameters such as muscle, fat, and bone mass were assessed using standardized methods. Knee extensor strength and objective physical functions were evaluated using validated tests. As the data were normally distributed independent sample *t* test was run for between-group analysis. $p < 0.05$ was considered statistically significant.

Results: The study outcomes included changes in body composition and physical functioning between Cr group and the control group. A significant improvement was noted for the 8 feet up and go (8^0UG) test with a mean difference of 1.14 ± 0.49 (p value = 0.029). The rest of the variables including isometric knee extensor strength, sit-to-stand-30, and 50-feet Walk (50^0W) test showed non-significant results ($p > 0.05$) with a mean difference of 2.66 ± 20.65, 0.62 ± 0.56, and 1.41 ± 1.06, respectively.

Conclusion: Our findings suggest more improvement in body mass, physical functions, and knee extensor strength parameters in the Creatine supplementation group. However, the statistically significant improvement was only seen in 8^0UG function in the Creatine group as compared to the control. Larger scale studies are required to explore the clinical benefits of creatine supplementation in patients with rheumatoid arthritis.

Keywords: Creatine, autoimmune disease, Arthritis, Rheumatoid, Body mass, muscle mass, Isometric knee extensor strength (IKES).

Received: 07 August 2024 **Revised:** 18 October 2024 **Accepted:** 02 December 2024
Correspondence to: Aamir Usman Memon
*Senior Registrar, Department of Orthopedics, Suleman Roshan Medical College, Tando Adam Khan, Pakistan.
Email: takatsu.aamiru@gmail.com
Full list of author information is available at the end of the article.

Introduction

Rheumatoid arthritis (RA) is identified by the inflammatory process that is chronic affecting joints and many other organs, such as heart, kidneys, lungs, digestion, eyes, skin, and nervous system [1-2]. Many kinds of arthritis have been researched and are divided into non-inflammatory (osteoarthritis) and inflammatory. The latter may be caused by crystal deposits (such as pseudogout, alkaline calcium phosphate disease, and gout), bacteria and viruses (such as *Staphylococcus aureus*, *Neisseria gonorrhoeae*, Lyme disease, parvovirus, and enterovirus), or may result from an autoimmune process [3]. According to the World Health Organization, in 2019, more than 18 million were living with rheumatoid arthritis globally. Approximately 70% of those affected had been identified as female, and 55% were over the age of 55 [4]. Of these, 13 million individuals experience moderate to severe symptoms posing benefits through rehabilitation [5]. Although RA is a systemic disease affecting multiple organs and systems at once, it most commonly impacts the hands including their small joints, wrists, feet,

ankles, knees, shoulders, and elbows [6]. RA is a multifactorial disease occurred by genetic, environmental, and stochastic factors The genetic risk for RA that has been approximated by scientific studies is about 50% [7].

Recent analysis highlights the importance of RA being a public health problem. Arthritis is the leading reason of work-related disability among adults in the United States [8]. In addition, many health studies have analyzed the economic impact of rheumatoid arthritis and shown that the costs associated with preventing rheumatoid arthritis by reducing the chances of risk or through early treatment are lower than those incurred in hospital and surgery [2].

Patients with RA have a high risk of sarcopenia (prevalence 25%) in addition to joint pain, falls, fractures and increased physical inactivity may also occur [9]. In recent years, there has been rising interest in nutritional and dietary supplementations alone or in conjunction with exercises to support or optimize clinically relevant functional and integrated rehabilitation programmes in those patients with significant muscle and strength loss [10,11]. When it comes to finding solutions, previous literature proves that a single nutritional intervention, in particular, creatine monohydrate supplementation, might facilitate and potentially enhance rehabilitation [10,11]. Creatine (Cr) supplementation is extensively studied for its impact on muscle performance and growth. It enhances the body's capacity to produce energy rapidly, which is beneficial for intensity which is high, short-duration activities. By enhancing the availability of phosphocreatine in muscles, creatine being helpful in regenerating adenosine triphosphate, the primary energy carrier in cells, more quickly. This results in greater strength increased lean muscle mass, and faster recovery times. Additionally, creatine supplementation has been discovered to be effective in stimulating muscle growth through increased water content within muscle cells and increased protein synthesis rates. Consequently, it is used to boost muscle power, size, and overall muscle performance [12-14].

This clinical experimental trial was therefore designed to evaluate the effectiveness of Creatine supplementation on body composition (body mass, muscle, and fat mass) and physical functions in the patients suffering from rheumatoid arthritis in the local population.

Methods

This double-blinded clinical trial was conducted over 12 weeks from November 2023 to January 2024 at Civil Hospital Hyderabad, Pakistan. A total of 30 patients with RA who did not change their medications in the last 3 months were included in each study group. Participants were recruited from outpatient clinics and were required to meet the following criteria including: American College of Rheumatology/ European League against Rheumatism 2010 clinical criteria of suffering from RA [15], being over 18 years of age, and having no known or other medical conditions, pregnancy, are not involved in strenuous physical activity and are not taking any sort of anabolic supplement. This study complies with the Declaration of Helsinki and had been approved by the Institutional Ethics Committee.

Randomization was performed independently via an online system to ensure groups were matched by gender and age. Both the researcher and the participants were blind to the assignment until the end of the study. Group 1 (Cr Group) was given a daily load of 20 g of creatine monohydrate (MyProtein) for the first five days (four doses of 5 g each), following a maintenance dose of 3 g per day for the remainder of the study [16]. The creatine was mixed with drink powder that was mango flavored (Foster Clark Products) to enhance the taste. The Group 2 (Control group) only received flavored drink. Supplements for both groups came in the same package and were mixed with water to create the drink. There was no difference in appearance, odor, and color between treatment and control. Participants were requested to maintain their usual fitness activity and healthy eating habits and to report any significant lifestyle changes to the researchers. Assessments were conducted at the initial (pre-supplementation), on 6th day (after the loading phase), and 12th week (immediately after supplementation ended). Participants took these measurements in fasting and abstained from physical activity, caffeine, and alcohol for 24 full hours. Demographic and clinical data were required through interviews and reviewership of medical records. Body mass (BM) was measured using a stadiometer, and total and regional lean, fat, and bone masses were estimated with skin calipers. Isometric maximum voluntary knee extensor strength was measured using an isokinetic dynamometer. Additionally, three objective measures of physical activity were administered to assess activities of daily living: 1) 30-second sitting to standing (STS-30), 2) the 8-feet up and go test (8^0UG), and 3) the 50-feet walk test (50^0W) records the time taken in seconds to walk 50 feet in a line as fast as possible.

Statistical analysis

The data were analyzed using SPSS version 23. Demographic information was collected using measures of central tendency and variance, i.e., mean and standard deviation. The skewness and kurtosis test was applied to identify the normality of data. As the data were normally distributed, independent sample *t* test was run for between-group analysis. *p*-value < 0.05 was considered statistically significant.

Results

A total of 30 patients each were randomly allocated into Cr group and the control group. The mean age of participants was 62.86 ± 6.73 and 59.33 ± 9.5 (p = 0.67), respectively. The baseline variables were found to be both significant and non-significant with mean value of 25.65 ± 3.21and 27.14 ± 5.05 (p = 0.045), 46.72 ± 6.45 and 48.23 ± 9.35 (p = 0.046), 21.77 ± 5.10, and 21.73 ± 6.33 (p = 0.694) for BM index, lean mass, and fat mass in creatine supplementation and control group, respectively (Table 1).

Table 2 shows the difference in the mean value of the knee-extensor strength and physical function measures after 6 days of intervention between the creatine and control group.

Table 3 shows the difference in mean value after 12 weeks of intervention between the creatine and control group. There was an improvement in terms of mean difference (MD) among all the variables in the creatine group with an MD of 2.66 ± 20.65, 0.62 ± 0.56, 1.14 ± 0.49, and 1.41 ± 1.06 for isometric knee extensor strength, sit to stand-30, 8^0UG, and 50^0W among patients in creatine group, respectively. However, only 8^0UG showed significant results for creatine supplementation.

Discussion

The findings of our study showed more improvement in terms of MD of variables in the experimental group receiving creatine supplementation for 12 weeks. The mean values were improved from 310.23 ± 54.44 to 339.27 ± 51.70 for knee extensor strength, 12.65 ± 3.0 to 15.76 ± 1.84 for 30-second sitting to standing test, 7.1 ± 1.3 to 9.85 ± 1.62 for 8^0UG test, and 10.67 ± 2.1 to 12.56 ± 1.70 for the 50^0W in Cr supplementation group. However, the p-value was only significant for 8^0UG test. A study conducted by Desai et al. on the efficacy and safety of Creatine in exercise, sports, and medicine revealed that is the most investigated supplement in literature and it was found to enhance the positive effect on Lean BM gain, muscle strength, and physical performance in both healthy and clinical subjects [17]. A study conducted by Hong et al. [18] on the impact of creatine levels on musculoskeletal health in the elderly involved 484,598 rheumatoid arthritis patients with 5,427 cases and 479,171 controls; the findings revealed significant

Table 1. *Baseline clinico-demographic profile of study groups.*

Clinical parameters		Creatine, *n* (30)	Control, *n* (30)	*p-value**
Age, years		62.86 ± 6.73	59.33 ± 9.51	0.67
Gender	Male	10 (33.3%)	10 (33.3%)	
	Female	20 (66.7%)	20 (66.7%)	
BMI, kg/m^2		25.65 ± 3.21	27.14 ± 5.05	0.045
Total LM, kg		46.72 ± 6.45	48.23 ± 9.35	0.046
Total FM, kg		21.77 ± 5.10	21.73 ± 6.33	0.694

**Independent sample T-test.*

Table 2. *Comparison of strength and physical function measures between the study groups after 6 days.*

Strength and physical function measures	Creatine, *n* (30)	Control, *n* (30)	*p-value**
Isometric knee extensor strength (Newtons)	310.23 ± 54.44	312.28 ± 57.64	0.953
Sit to stand-30, repetitions	12.65 ± 3.0	13.34 ± 1.49	0.015
8^0UG, seconds	7.1 ± 1.3	7.2 ± 1.1	0.825
50^0W, seconds	10.67 ± 2.1	8.11 ± 1.86	0.689

**Independent sample T-test.*

Table 3. *Comparison of strength and physical function measures between the study groups after 12 weeks.*

Strength and physical function measures	Creatine (*n* = 30)	Placebo (*n* = 30)	Mean difference	*p-value**
Isometric knee extensor strength (Newton)	339.27 ± 51.70	336.60 ± 61.05	2.66 ± 20.65	0.89
Sit to stand-30, repetitions	15.76 ± 1.84	15.13 ± 1.15	0.62 ± 0.56	0.27
8^0UG, seconds	9.85 ± 1.62	8.71 ± 1.0	1.14 ± 0.49	***0.029***
50^0W, seconds	12.56 ± 1.70	11.14 ± 3.75	1.41 ± 1.06	0.19

**Independent sample T-test.*

improvement in body mass and physical functions in patients with RA (OR = 0.99, b=-0.01, $p = 0.87$) [18]. In a double-blind randomized controlled trial conducted by Wilkinson et al. [16] on the effects of Cr supplementation on body composition and physical function were monitored on 40 patients with RA. The findings showed improvement in all outcome measures, i.e., BM index and muscle strength ($p < 0.05$) in the group receiving Cr [16]. Similar results were reported in a narrative review by Letarouilly et al. [19] on the effects of nutrition and physical training in patients with RA which included 18 studies. The findings showed creatine supplementation combined with progressive resistance training leads to a modest and short-term increase in lean mass [19].

In another study on 18 patients with mild to moderate osteoarthritis, the effects of creatine monohydrate supplementation on inflammation and cartilage degradation were analyzed and compared with the placebo group. The results were contrasting to the above-mentioned results of studies which showed after 12 weeks of intervention which showed a 12-week supplementation with creatine monohydrate has no impact on inflammatory biomarkers, cartilage degradation, Knee injury and Osteoarthritis Outcome Score, or muscle strength in individuals with mild to moderate knee osteoarthritis [20]. A separate systematic review and meta-analysis examining 33 randomized controlled trials involving 1076 participants investigated creatine supplementation's impact on functional disability risk. This analysis found that creatine supplementation enhanced sit-to-stand performance, muscle function, and lean tissue mass. However, these findings should be interpreted cautiously, as the evidence quality was rated low to very low due to significant bias concerns within the included studies [21]. The efficacy of Cr supplementation in improving muscle strength has been proven by many studies published in the literature. However, when it comes to RA patients, the literature has shown conflicting results. Hence, there is a need for further studies with large sample size and clinically validated follow-up for a better understanding of the creatine supplementation-based effects in patients with RA.

Limitations of the study

A significant advantage of this research is its double-blinded intervention plan which reduces bias and strengthens internal validity. While the study offers valuable insights, several constraints should be noted. The relatively small participant pool and brief 12-week timeframe potentially restricted the detection of enduring effects. The study's lack of rigorous control over participants' physical activity levels and dietary habits may have introduced unwanted variability in the results. Furthermore, the absence of biochemical marker analysis limited understanding of the underlying physiological mechanisms at work. The reliance on self-reported adherence to the supplementation protocol introduces possible reporting bias, emphasizing the importance of implementing objective compliance monitoring methods in subsequent research.

Conclusion

Our findings suggest an improvement in muscle strength and physical performance in patients with rheumatoid arthritis (RA) over 12 weeks. The observed increase in knee extensor strength, sit-to-stand, and walking tests suggests creatine may be an important treatment to reduce muscle weakness and functional impairment associated with RA. However, the between comparison showed non-significant findings for all variables except for the 8 feet up and go test. Creatine supplementation is promising for improving physical function and muscle strength, but more research is needed to establish a definitive treatment plan and improve treatment for its application on RA patients. Resolving this discrepancy will help ensure that RA patients can benefit from the therapeutic benefits of creatine.

Acknowledgement

The authors would like to acknowledge the administration of Isra University Hospital Hyderabad, Pakistan for provision of the logistic support during the execution of research work.

List of abbreviations

BM	Body mass
Cr	Creatine
IKES	Isometric maximum voluntary knee extensor strength
MD	Mean difference
RA	Rheumatoid arthritis
SD	Standard deviation
UG	Up and go
8^0UG	8 feet up and go
50^0W	50-feet Walk

Conflict of interest

None to declare.

Grant support and financial disclosure

None to disclose.

Ethics approval

The ethical approval of the study was granted by the Institutional Ethics Committee of Isra University Hospital, Hyderabad, Pakistan vide Letter no: IRB/24/105 dated 03 November, 2023.

Authors' contributions

AUM, SK, SB: Conception and design of study, acquisition of data, drafting of manuscript, critical intellectual input.

KA, SK, MAM: Data collection, analysis of data, drafting of manuscript, critical intellectual input.

All Authors: Approval and the responsibility of the final version of the manuscript to be published.

Authors' Details

Aamir Usman Memon[1], Kumayl Abbas Meghji[2], Shahnaz Bano[3], Palwasha Abbasi[4], Sumayya Kazi[5], Muhammad Amir Memon[6]

1. Department of Orthopedics, Suleman Roshan Medical College, Tando Adam Khan, Pakistan
2. Assistant Professor, Department of Physiology, Isra University, Hyderabad, Pakistan
3. Assistant Professor, Department of Pharmacology, Isra University, Hyderabad, Pakistan
4. Associate Professor, Department of Pharmacology, Suleman Roshan Medical College, Tando Adam Khan, Pakistan
5. Associate Professor, Department of Biochemistry, Isra University, Hyderabad, Pakistan
6. Associate Professor, Department of Pediatrics, Isra University Hospital, Hyderabad, Pakistan

References

1. Conforti A, Di Cola I, Pavlych V, Ruscitti P, Berardicurti O, Ursini F, et al. Beyond the joints: the extra-articular manifestations in rheumatoid arthritis. Autoimmun Rev. 2021;20(2):102735. https://doi.org/10.1016/j.autrev.2020.102735
2. Radu A-F, Bungau SG. Management of rheumatoid arthritis: an overview. Cells. 2021;10(11):2857. https://doi.org/10.3390/cells10112857
3. Joshi DC, Naskar A, Datta K, Sarkar U, Otia MK, KhatoonT. Rheumatoid arthritis: etiology, pathophysiology, and modern treatments. Int J Res Appl Sci Biotechnol. 2022;9(3):32–9. https://doi.org/10.31033/ijrasb.9.3.7
4. Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional, and national burden of rheumatoid arthritis, 1990–2017: a systematic analysis of the Global Burden of Disease Study 2017. Ann Rheum Dis. 2019;78(11):1463–71. https://doi.org/10.1136/annrheumdis-2019-215920
5. Cieza A, Causey K, Kamenov K, Hanson SW, Chatterji S, Vos T. Global estimates of the need for rehabilitation based on the Global Burden of Disease Study 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10267):2006–17. https://doi.org/10.1016/S0140-6736(20)32340-0
6. Long H, Liu Q, Yin H, Wang K, Diao N, Zhang Y, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Arthritis Rheumatol. 2022;74(7):1172–83. https://doi.org/10.1002/art.42089
7. Venetsanopoulou AI, Alamanos Y, Voulgari PV, Drosos AA. Epidemiology of rheumatoid arthritis: genetic and environmental influences. Expert Rev Clin Immunol. 2022;18(9):923–31. https://doi.org/10.1080/1744666X.2022.2106970
8. Theis KA, Steinweg A, Helmick CG, Courtney-Long E, Bolen JA, Lee R. Which one? What kind? How many? Types, causes, and prevalence of disability among US adults. Disabil Health J. 2019;12(3):411–21. https://doi.org/10.1016/j.dhjo.2019.03.001
9. Bennett JL, Pratt AG, Dodds R, Sayer AA, Isaacs JD. Rheumatoid sarcopenia: loss of skeletal muscle strength and mass in rheumatoid arthritis. Nat Rev Rheumatol. 2023;19(4):239–51. https://doi.org/10.1038/s41584-023-00921-9
10. Fairman CM, Kendall KL, Hart NH, Taaffe DR, GalvaoDA, Newton RU. The potential therapeutic effects of creatine supplementation on body composition and muscle function in cancer. Crit Rev Oncol Hematol. 2019;133:46–57. https://doi.org/10.1016/j.critrevonc.2018.11.003
11. Sagtaganov Z, Bekaryssova D. Complex rehabilitation of patients with rheumatoid arthritis. Rheumatol Int. 2024;44(9):1789–93. https://doi.org/10.1007/s00296-024-05669-3
12. Stares A, Bains M. The additive effects of creatinesupplementation and exercise training in an aging population: a systematic review of randomized controlled trials. J Geriatr Phys Ther. 2020;43(2):99–112. https://doi.org/10.1519/JPT.0000000000000222
13. Wu SH, Chen KL, Hsu C, Chen HC, Chen JY, Yu SY, et al. Creatine supplementation for muscle growth: a scoping review of randomized clinical trials from 2012 to 2021. Nutrients. 2022;14(6):1255. https://doi.org/10.3390/nu14061255
14. Wallimann T, Hall CH, Colgan SP, Glover LE. Creatinesupplementation for patients with inflammatory bowel diseases: a scientific rationale for a clinical trial. Nutrients. 2021;13(5):1429. https://doi.org/10.3390/nu13051429
15. Studenic P, Aletaha D, de Wit M, Stamm TA, Alasti F, Lacaille D, et al. American College of Rheumatology/EULAR remission criteria for rheumatoid arthritis: 2022 revision. Ann Rheum Dis. 2023;82(1):74–80. https://doi.org/10.1136/ard-2022-223413
16. Wilkinson TJ, Lemmey AB, Jones JG, Sheikh F, Ahmad YA, Chitale S, et al. Can creatine supplementation improve body composition and objective physical function in rheumatoid arthritis patients? a randomized controlled trial. Arthritis Care Res. 2016 Jun;68(6):729–37.
17. Desai I, Pandit A, Smith-Ryan AE, Simar D, Candow DG, Kaakoush NO, et al. The effect of creatine supplementation on lean body mass with and without resistance training. Nutrients. 2025;17(6):1081. https://doi.org/10.3390/nu17061081
18. Hong M, Wang J, Jin L, Ling K. The impact of creatinelevels on musculoskeletal health in the elderly: a mendelianrandomization analysis. BMC Musculoskelet Disord. 2024;25(1):1–6. https://doi.org/10.1186/s12891-024-08140-3
19. Letarouilly JG, Flipo RM, Cortet B, Tournadre A, PaccouJ. Body composition in patients with rheumatoid arthritis: a narrative literature review. Ther Adv Musculoskelet Dis. 2021;13:1–21. https://doi.org/10.1177/1759720X211015006
20. 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. https://doi.org/10.1016/j.nutres.2017.12.010
21. Davies TW, Watson N, Pilkington JJ, McClelland TJ, Azzopardi G, Pearse RM, et al. Creatine supplementation for optimization of physical function in the patient at risk of functional disability: a systematic review and meta-analysis. JPEN J Parenter Enteral Nutr. 2024;48(4):389–405. https://doi.org/10.1002/jpen.2607