

Alzchem Group AG
Human Nutrition Department

Selection of Scientific Studies of Prominent Creatine Topics

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1. Basics about Creatine

1.1. Metabolic Basis of Creatine in Health and Disease: A Bioinformatics-Assisted Review

Author: Bonilla, D.A.; Kreider, R.B.; Stout, J.R.; Forero, D.A.; Kerksick, C.M.; Roberts, M.D.; Rawson, E.S.

Publication: 2021, Nutrients, 13, 1238.

Link: <https://www.mdpi.com/2072-6643/13/4/1238>

Miniconclusion: this study explains the underlying roles and mechanism of creatine for the cellular energy metabolism.

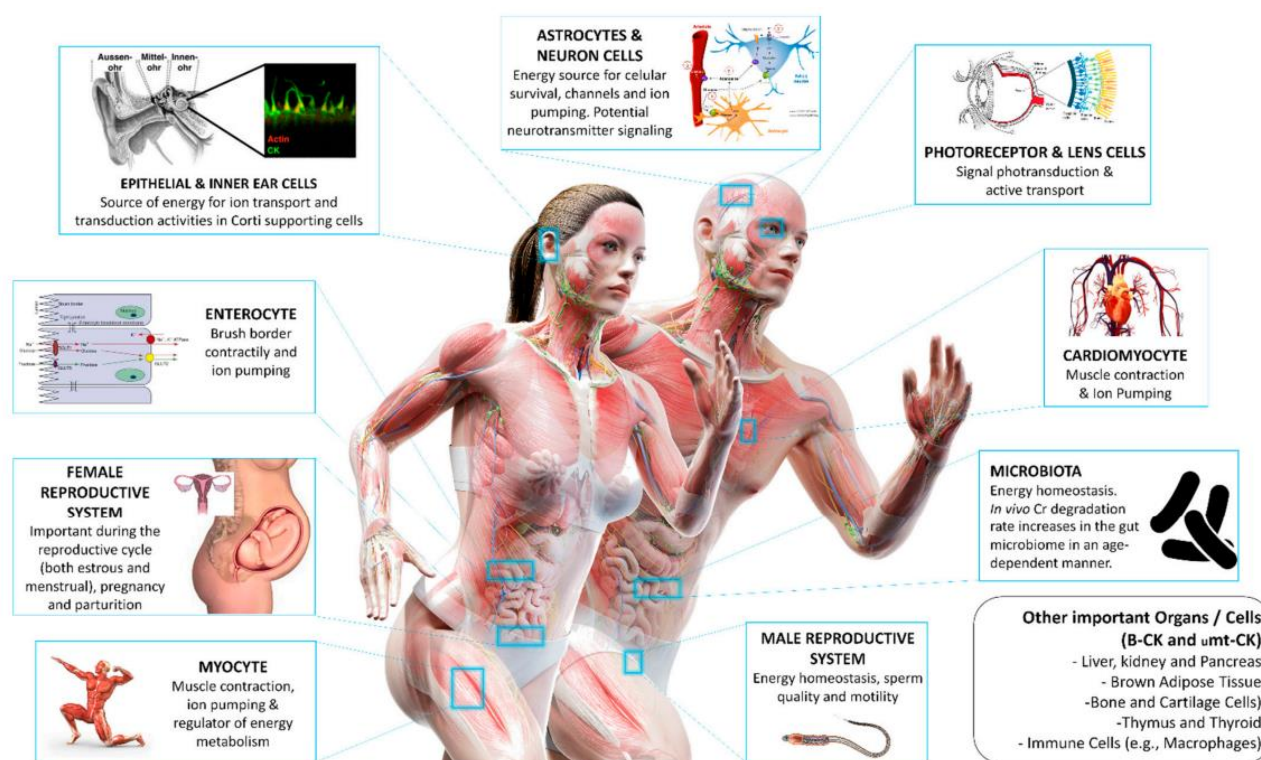


Figure 4. Importance of Cr metabolism in whole-body physiology. The CK/PCr system is essential for the chemo-mechanical energy transduction of cells/tissues with high, fluctuant, and constant energy demands. Source: designed by the authors (D.A.B.) using an anatomy template developed by 3dMediSphere (<https://www.turbosquid.com/>), licensed 3D standard Vray 3.60. accessed on 14 February 2020.

Figure 1: Bonilla et al. 2021

1.2. Creatine in Health and Disease

Author: Kreider, R.B.; Stout, J.R.

Publication: 2021, Nutrients, 13, 447

Miniconclusion: Assessment of peer-reviewed scientific and medical evidence related to creatine's role in promoting general health as we age and how creatine supplementation has been used as a nutritional strategy to help individuals recover from injury and/or manage chronic disease.

Link: <https://www.mdpi.com/2072-6643/13/2/447>

1.3. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show?

Author: Antonio, J., Candow, D.G., Forbes, S.C. et al.

Publication: 2021, J Int Soc Sports Nutr 18, 13

Miniconclusion: Most misunderstandings about creatine are either wrong (anabolic steroid, kidney damage, hair loss, dehydration, cramping, risk for adolescents, increase of fat mass, loading requirement, risk for elderly, works only in men, superior forms of creatine compared to monohydrate) or only true for very specific situations (water retention, lower efficiency in resistance sports).

Link: <https://www.tandfonline.com/doi/full/10.1186/s12970-021-00412-w>

1.4. Bioavailability, Efficacy, Safety, and Regulatory Status of Creatine and Related Compounds: A Critical Review

Author: Kreider, R.B.; Jäger, R.; Purpura, M.

Publication: 2022 Nutrients , 14, 1035

Miniconclusion: CrM continues to be the only source of creatine that has substantial evidence to support bioavailability, efficacy, and safety. Additionally, CrM is the source of creatine recommended explicitly by professional societies and organizations and approved for use in global markets as a dietary ingredient or food additive.

Link: <https://www.mdpi.com/2072-6643/14/5/1035>

1.5. The creatine kinase system and pleiotropic effects of creatine

Author: Wallimann, T., Tokarska-Schlattner, M. & Schlattner, U.

Publication: 2011, Amino Acids 40, 1271–1296

Miniconclusion: Creatine has three roles – temporal energy buffer, spatial energy buffer, metabolic regulator. Based on these roles, creatine has many positive roles on body functions.

Link: <https://link.springer.com/article/10.1007/s00726-011-0877-3>

2. Sarcopenia & Older Adults

2.1. Meta-Analysis Examining the Importance of Creatine Ingestion Strategies on Lean Tissue Mass and Strength in Older Adults

Author: Forbes, S.C.; Candow, D.G.; Ostojic, S.M.; Roberts, M.D.; Chilibeck, P.D.

Publication: 2021, Nutrients, 13, 1912.

Miniconclusion: Overall, creatine (independent of dosing strategy) augments lean tissue mass and strength increase from resistance training vs. placebo. Previous loading phases improved the results.

Link: <https://www.mdpi.com/2072-6643/13/6/1912>

2.2. Current Evidence and Possible Future Applications of Creatine Supplementation for Older Adults

Author: Candow, D.G.; Forbes, S.C.; Kirk, B.; Duque, G.

Publication: 2021, Nutrients, 13, 745.

Miniconclusion: Creatine (especially when combined with resistance training) has some favourable effects on aging muscle, bone and fat mass, muscle and bone strength, and physical performance, primarily in healthy populations

Link: <https://www.mdpi.com/2072-6643/13/3/745>

2.3. Efficacy of Creatine Supplementation Combined with Resistance Training on Muscle Strength and Muscle Mass in Older Females: A Systematic Review and Meta-Analysis.

Author: dos Santos, E.E.P.; de Araújo, R.C.; Candow, D.G.; Forbes, S.C.; Guijo, J.A.; de Almeida Santana, C.C.; Prado, W.L.d.; Botero, J.P

Publication: Nutrients 2021, 13, 3757.

Miniconclusion: Sarcopenia, the age-related muscle loss, particularly affects older females' quality of life. Resistance training (RT) is effective against sarcopenia, and combining creatine supplementation (Cr) with RT enhances muscle strength, especially in the upper body.

Link: <https://doi.org/10.3390/nu13113757>

3. Brain Health & Cognitive Function

3.1. Creatine Supplementation and Brain Health

Author: Roschel, H.; Gualano, B.; Ostojic, S.M.; Rawson, E.S.

Publication: 2021, Nutrients, 13, 586.

Miniconclusion: There is a potential for creatine supplementation to improve cognitive processing, especially in conditions characterized by brain creatine deficits, which could be induced by acute stressors (e.g., exercise, sleep deprivation) or chronic, pathologic conditions (e.g., creatine synthesis enzyme deficiencies, mTBI, aging, Alzheimer's disease, depression).

Link: <https://www.mdpi.com/2072-6643/13/2/586>

3.2. Effects of Creatine Supplementation on Brain Function and Health

Author: Forbes, S.C.; Cordingley, D.M.; Cornish, S.M.; Gualano, B.; Roschel, H.; Ostojic, S.M.; Rawson, E.S.; Roy, B.D.; Prokopidis, K.; Giannos, P.; et al.

Publication: Nutrients 2022, 14, 921.

Miniconclusion: The review discusses research on creatine's effects on the brain, indicating its potential to increase brain creatine content. It shows promise in alleviating symptoms of concussion, mild traumatic brain injury, and depression. The review explores creatine's impact on cognition during sleep deprivation and its effects on various neurological and mental health conditions. Additionally, recent advances in using creatine as a neuroprotective supplement after traumatic brain injury or concussion are outlined.

Link: [Nutrients | Free Full-Text | Effects of Creatine Supplementation on Brain Function and Health \(mdpi.com\)](#)

3.3. Creatine for the Treatment of Depression

Author: Kious, B.M.; Kondo, D.G.; Renshaw, P.F.

Publication: 2019, Biomolecules, 9, 406.

Miniconclusion: Clinical studies in neurological conditions such as PD have indicated that creatine might have an antidepressant effect, and early clinical studies in depressive disorders—especially MDD—indicate that creatine may have an important antidepressant effect.

Link: <https://www.mdpi.com/2218-273X/9/9/406>

3.4. "Heads Up" for Creatine Supplementation and its Potential Applications for Brain Health and Function

Author: Candow, D.G., Forbes, S.C., Ostojic, S.M. et al.

Publication: Sports Med (2023) (no open access)

Miniconclusion: The review discusses the increasing interest in the positive effects of creatine supplementation on brain health. Creatine can enhance cognition, memory, and health outcomes, particularly in aging adults and during stress like sleep deprivation. It also shows promise in conditions such as muscular dystrophy, traumatic brain injury, depression, and anxiety. However, potential sex- or age-related differences in the response to creatine remain unclear. The review aims to provide an updated discussion on current research in this area, including exploration of possible variations based on sex and age concerning brain bioenergetics, health measures, and neurological diseases.

Link: ["Heads Up" for Creatine Supplementation and its Potential Applications for Brain Health and Function | Sports Medicine \(springer.com\)](#)

4. Post Viral Fatigue Syndrome (PVFS)/Long-COVID

4.1. Diagnostic and Pharmacological Potency of Creatine in Post-Viral Fatigue Syndrome

Author: Ostojic, S.M.

Publication: 2021, Nutrients, 13, 503

Miniconclusion: Findings from initial trials on the metabolic substrate of PVFS, along with promising results from interventional studies, show that creatine is rightfully on the list of the German Medical Doctors list of potentially helpful Dietary Supplements.

Link: [Nutrients | Free Full-Text | Diagnostic and Pharmacological Potency of Creatine in Post-Viral Fatigue Syndrome \(mdpi.com\)](#)

4.2. Effects of six-month creatine supplementation on patient- and clinician-reported outcomes, and tissue creatine levels in patients with post-COVID-19 fatigue syndrome.

Author: Slankamenac, J., Ranisavljev, M., Todorovic, N., Ostojic, J., Stajer, V., & Ostojic, S. M.

Publication: 2023 Food Science & Nutrition, 11, 6899–6906.

Miniconclusion: Taking creatine for 6 months appears to improve tissue bioenergetics and attenuate clinical features of post-COVID-19 fatigue syndrome; additional studies are warranted to confirm our findings in various post-COVID-19 cohorts.

Link: <https://doi.org/10.1002/fsn3.3597>

4.3. Reduced tissue creatine levels in patients with long COVID-19: A cross-sectional study.

Author: Ranisavljev, M; Todorovic, N; Ostojic, J; Ostojic, SM

Publication: Journal of Postgraduate Medicine 69(3):p 162-163, Jul-Sep 2023.

Miniconclusion: We found that long COVID population is characterized by reduced creatine levels in energy-demanding organs, with lower creatine levels in the skeletal muscle linked with severe muscle pain. Creatine depletion could thus be a newly discovered metabolic footprint of long COVID, perhaps as an end result of supraphysiological energy utilization in this perplexing condition.

Link: [Reduced tissue creatine levels in patients with long COVID-1... : Journal of Postgraduate Medicine \(lww.com\)](#)

4.4. Creatine supplementation combined with breathing exercises reduces respiratory discomfort and improves creatine status in patients with long-COVID

Author: Slankamenac J, Ranisavljev M, Todorovic N, Ostojic J, Stajer V, Ostojic SM

Publication: Journal of Postgraduate Medicine Dec 7 2023.

Miniconclusion: Supplementation with 4 g of creatine per day alongside breathing exercises significantly increased tissue total creatine levels and improved time to exhaustion compared to breathing exercises alone. These preliminary findings suggest that creatine may be an effective adjunct therapy for managing clinical symptoms in long-COVID patients.

Link: [Creatine supplementation combined with breathing exercises reduces respiratory discomfort and improves creatine status in patients with long-COVID - PubMed \(nih.gov\)](#)

4.5. Exploring Creatine Intervention in Long COVID Patients with ME/CFS: A 6-Week Case Study

Author: Ziaja CP, Young S, Schaeffler H, Sadre-Chirazi-Stark M

Publication: Prof. Stark Institute Hamburg, 2024

Miniconclusion: The positive effects observed suggest that creatine may help modulate intracellular ATP levels and support the regenerative phase of ADP conversion. These findings propose a potential treatment approach and pave the way for future therapeutic interventions for individuals with ME/CFS and Long COVID.

Link: ask us for the poster

5. Cardiovascular Health

5.1. Role of Creatine in the Heart: Health and Disease

Author: Balestrino, M.

Publication: 2021, Nutrients, 13, 1215.

Miniconclusion: Creatine effectiveness in this case may be because anthracyclines reduce expression of the creatine transporter, and because of the pleiotropic antioxidant properties of creatine. Moreover, creatine may also reduce concomitant muscle damage by anthracyclines.

Link: <https://www.mdpi.com/2072-6643/13/4/1215>

5.2. The Potential Role of Creatine in Vascular Health

Author: Clarke, H.; Hickner, R.C.; Ormsbee, M.J.

Publication: 2021, Nutrients, 13, 857.

Miniconclusion: There is evidence to suggest that creatine may possess unique properties that may impart novel benefits upon the vasculature, further clinical research is needed.

Link: <https://www.mdpi.com/2072-6643/13/3/857>

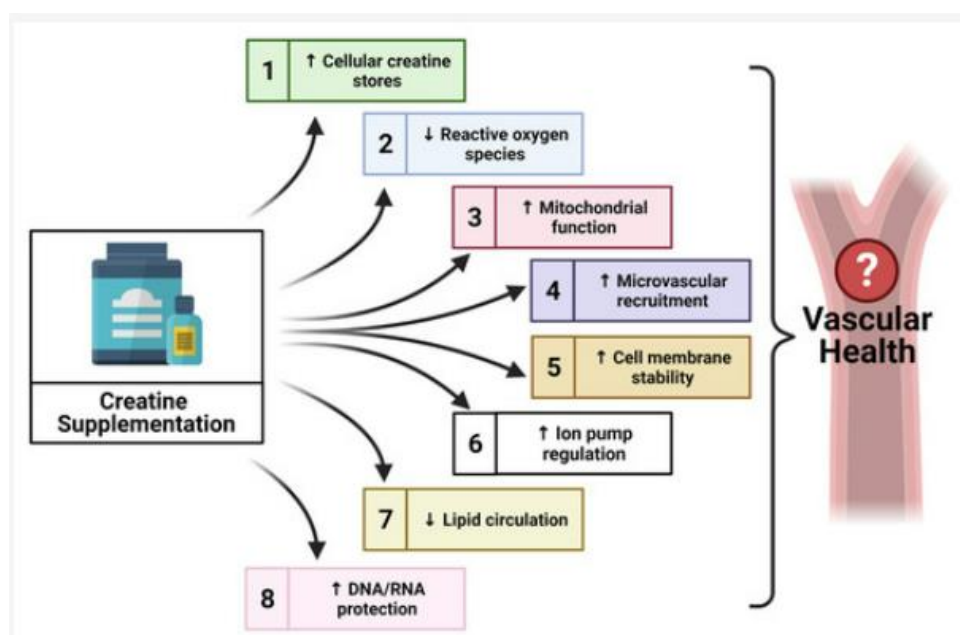


Figure 2: Clarke et al. 2021

5.3. The Evolving Applications of Creatine Supplementation: Could Creatine Improve Vascular Health?

Author: Clarke, H.; Kim, D.-H.; Meza, C.A.; Ormsbee, M.J.; Hickner, R.C.

Publication: Nutrients 2020, 12, 2834.

Miniconclusion: Creatine, a natural compound, not only enhances cellular energy but also shows promise in therapeutic applications for conditions like myopathies, neurodegenerative disorders, metabolic issues, and inflammatory diseases. With its antioxidant and anti-inflammatory properties, creatine supplementation may also have potential in improving vascular health, particularly in at-risk populations like older adults or those with cardiovascular disease.

Link: <https://doi.org/10.3390/nu12092834>

6. Special Nutrition

6.1. The Application of Creatine Supplementation in Medical Rehabilitation.

Author: Harmon, K.K.; Stout, J.R.; Fukuda, D.H.; Pabian, P.S.; Rawson, E.S.; Stock, M.S.

Publication: Nutrients 2021, 13, 1825.

Miniconclusion: Creatine monohydrate, known for its anabolic effects, has been studied as a supplement to mitigate muscle loss and dysfunction in various health conditions. The literature review highlights promising results in preserving muscle mass and function during rehabilitation. Despite its potential, more research is needed to address gaps in knowledge within medical rehabilitation.

Link: <https://doi.org/10.3390/nu13061825>

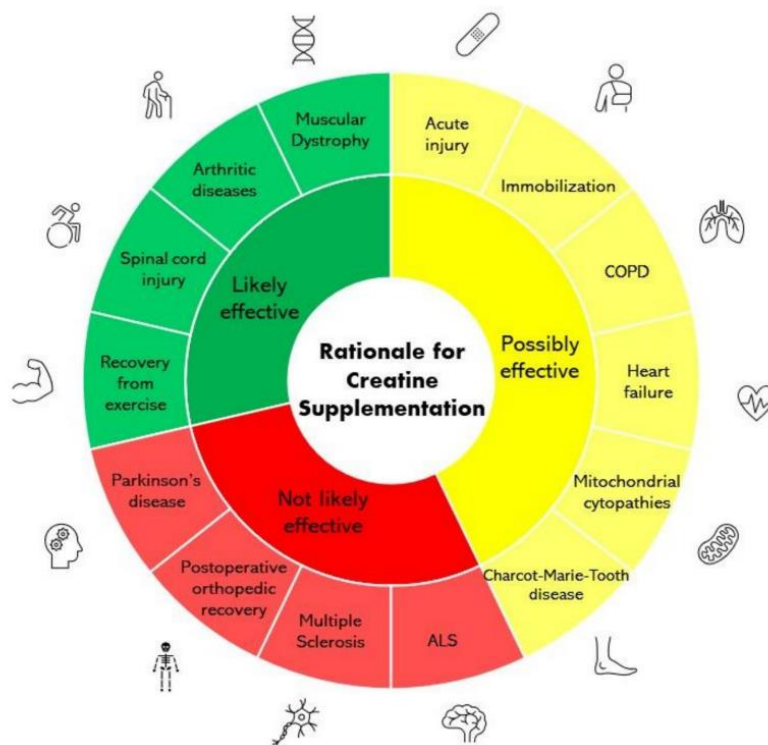


Figure 1. Rationale for examination of creatine supplementation as a rehabilitative aid. Abbreviations defined from clockwise: COPD = chronic obstructive pulmonary disease; ALS = amyotrophic lateral sclerosis.

Figure 3: Harmon et al. 2021

6.2. Creatine Supplementation: An Update.

Author: Hall, Matthew DO, CAQSM; Manetta, Elizabeth MD; Tupper, Kristofer DO.

Publication: Current Sports Medicine Reports 20(7):p 338-344, July 2021.

Miniconclusion: Creatine is a widely used dietary supplement among athletes, known for consistently increasing lean muscle mass and exercise capacity, especially with short-duration, high-intensity exercise. Beyond strength gains, research indicates additional benefits such as improved postexercise recovery, injury prevention, rehabilitation, and potential neurological advantages relevant to sports. Studies affirm the safety and good tolerance of both short- and long-term creatine supplementation in healthy individuals and various patient populations.

Link: [Creatine Supplementation: An Update : Current Sports Medicine Reports \(lww.com\)](#)

7. Longevity

See 2. Basics about Creatine for additional information of Creatine and Energy.

More specifically:

Kreider & Stout 2021 Creatine in Health and Disease

Miniconclusion: Assessment of peer-reviewed scientific and medical evidence related to creatine's role in promoting general health as we age and how creatine supplementation has been used as a nutritional strategy to help individuals recover from injury and/or manage chronic disease.

Link: <https://www.mdpi.com/2072-6643/13/2/447>

Bonilla et al. 2021

Metabolic Basis of Creatine in Health and Disease: A Bioinformatics-Assisted Review

Miniconclusion: this study explains the underlying roles and mechanism of creatine for the cellular energy metabolism.

Link: <https://www.mdpi.com/2072-6643/13/4/1238>

7.1. Genetic Depletion of Adipocyte Creatine Metabolism Inhibits Diet-Induced Thermogenesis and Drives Obesity

Author: Lawrence Kazak, Edward T. Chouchani, Gina Z. Lu, Mark P. Jedrychowski, Curtis J. Bare, Amir I. Mina, Manju Kumari, Song Zhang, Ivan Vuckovic, Dina Laznik-

Bogoslavski, Petras Dzeja, Alexander S. Banks, Evan D. Rosen, Bruce M. Spiegelman

Publication: 2017, Cell Metabolism, Volume 26, Issue 4, Pages 660-671.e3

Miniconclusion: These results provide strong in vivo genetic support for a role of GATM and creatine metabolism in energy expenditure, diet-induced thermogenesis, and defense against diet-induced obesity.

Link: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5629120/>

8. Male Fertility

8.1. Creatine as a Promising Component of Paternal Preconception Diet

Author: Ostojic, S.M.; Stea, T.H.; Engeset, D.

Publication: Nutrients 2022, 14, 586

Miniconclusion: Creatine, a conditionally essential nutrient, has caught attention as a male fertility-promoting candidate due to its role in sperm energy metabolism. As energy-demanding cells, spermatozoa can suffer from deficient creatine metabolism, with poor sperm count and motility are often associated with low creatine levels. A provision of supplemental creatine appears to positively affect sperm quality in pilot trials, suggesting a potential for using creatine to attenuate sub-fertility.

Link: [Nutrients | Free Full-Text | Creatine as a Promising Component of Paternal Preconception Diet \(mdpi.com\)](#)

8.2. Creatine Semen Creatine and Creatine Kinase Activity as an Indicator of Sperm Quality

Author: Nasrallah F, Hammami MB, Omar S, Aribia HB, Sanhaji H, Feki M..

Publication: Clin Lab. 2020 Sep 1;66(9). (no open access)

Miniconclusion: Semen contains high amounts of Cr and increased CK activity. Low semen Cr is associated with reduced sperm motility while high CK activity is associated with poor sperm quality. The findings suggest that Cr is of importance for sperm metabolism and that Cr supplementation could be useful in males with poor quality sperm.

Link: [Semen Creatine and Creatine Kinase Activity as an Indicator of Sperm Quality - PubMed \(nih.gov\)](#)

9. Female Health

9.1. Creatine Supplementation in Women's Health: A Lifespan Perspective.

Author: Smith-Ryan, A.E.; Cabre, H.E.; Eckerson, J.M.; Candow, D.G.

Publication: Nutrients 2021, 13, 877.

Miniconclusions: Research on creatine use in females suggests potential benefits, especially for improved strength and exercise performance in pre-menopausal stages. Post-menopausal females may also see benefits in muscle function and bone health with high doses and resistance training. Positive effects on mood and cognition are noted. Overall, creatine supplementation appears effective for females across different life stages.

Link: <https://doi.org/10.3390/nu13030877>

See a short and great video here: [Creatine Supplementation in Women's Health | Prof. Abbie Smith-Ryan, PhD \(youtube.com\)](#)

9.2. Creatine Metabolism in Female Reproduction, Pregnancy and Newborn

Author: Muccini, A.M.; Tran, N.T.; de Guingand, D.L.; Philip, M.; Della Gatta, P.A.; Galinsky, R.; Sherman, L.S.; Kelleher, M.A.; Palmer, K.R.; Berry, M.J.; Walker, D.W.; Snow, R.J.; Ellery, S.J.

Publication: 2021, Nutrients, 13, 490.

Miniconclusion: Initial promising findings supporting creatine supplementation during reproductive cycle, pregnancy, parturition and gestation. No risks have been found when using high quality creatine.

Link: [Creatine Metabolism in Female Reproduction, Pregnancy and Newborn Health - PMC \(nih.gov\)](#)

9.3. Creatine for women: a review of the relationship between creatine and the reproductive cycle and female-specific benefits of creatine therapy.

Author: Ellery, S.J., Walker, D.W. & Dickinson, H.

Publication: Amino Acids 48, 1807–1817 (2016). (no open access)

Miniconclusion: The creatine system is crucial for cellular energy regulation. Studies on creatine supplementation, focusing on its role in exercise and energy-related diseases,

suggest potential sex-specific responses. This review explores hormonal influences on creatine metabolism during reproductive stages, highlighting its impact on women's health. Changes in creatine synthesis, transport, and kinase expression during pregnancy and menopause are discussed. Recent findings indicate potential benefits of creatine supplementation for women, particularly in conditions like depression. Understanding these pathways is key to optimizing reproductive health outcomes for women using creatine as a dietary supplement.

Link: <https://doi.org/10.1007/s00726-016-2199-y>

9.4. Creatine metabolism in the uterus: potential implications for reproductive biology.

Author: Philip, M., Snow, R.J., Gatta, P.A.D. et al.

Publication: Amino Acids 52, 1275–1283 (2020). (no open access)

Miniconclusion: This review examines adaptations in uterine creatine metabolism during the reproductive cycle, pregnancy, and parturition, emphasizing links to fertility. It addresses changes in creatine levels, transport, synthesis, and kinase expression in uterine layers and cell types, also discussing the effects of dietary creatine. The upregulated creatine metabolism appears significant in supporting healthy uterine function, embryo implantation, and labor performance.

Link: <https://doi.org/10.1007/s00726-020-02896-3>

9.5. A 2-Year Randomized Controlled Trial on Creatine Supplementation during Exercise for Postmenopausal Bone Health

Author: Chilibeck, Philip D.; Candow, Darren G.; Gordon, Julianne J.; Duff, Whitney R.D.; Mason, Riley; Shaw, Keely; Taylor-Gjevre, Regina; Nair, Bindu; Zello, Gordon A.

Publication: May 5, 2023, Medicine & Science in Sports & Exercise,

Miniconclusions: Two years of creatine supplementation and exercise in postmenopausal women had no effect on bone mineral density, yet improved some bone geometric properties at the proximal femur.

Link: [https://journals.lww.com/acsm-
msse/Abstract/9900/A_2_Year_Randomized_Controlled_Trial_on_Creatine.273.aspx](https://journals.lww.com/acsm-msse/Abstract/9900/A_2_Year_Randomized_Controlled_Trial_on_Creatine.273.aspx)

10. Vegan and Vegetarian Diets

10.1. Changing to a vegetarian diet reduces the body creatine pool in omnivorous women, but appears not to affect carnitine and carnosine homeostasis: A randomised trial

Author: Blancquaert, L., Baguet, A., Bex, T., Volkaert, A., Everaert, I., Delanghe, J., Derave, W.

Publication: 2018, British Journal of Nutrition, 119(7), 759–770

Miniconclusion: the body creatine pool declined over a 3-month vegetarian diet in omnivorous women, which was ameliorated when accompanied by low-dose dietary creatine supplementation. Carnitine and carnosine homeostasis was unaffected

Link: <https://doi.org/10.1017/S000711451800017X>

10.2. The influence of creatine supplementation on the cognitive functioning of vegetarians and omnivores

Author: Benton, D., & Donohoe, R.

Publication: 2011, British Journal of Nutrition, 105(7), 1100–1105.

Miniconclusion: This double blind placebo controlled study in young females (n=128) creatine supplementation improved memory. Irrespective of dietary style, the supplementation of creatine decreased the variability in the responses to a choice reaction-time task.

Link: <https://doi.org/10.1017/S0007114510004733>

10.3. Effects of dietary supplementation with creatine on homocysteinemia and systemic microvascular endothelial function in individuals adhering to vegan diets.

Author: Van Bavel, D., de Moraes, R. and Tibirica, E

Publication: (2019), Fundam Clin Pharmacol, 33: 428–440. (no open access)

Miniconclusion: The study revealed that strict vegan diets may elevate hyperhomocysteinemia, negatively impacting vascular reactivity. However, three weeks of creatine supplementation effectively reduced homocysteine levels, increased folic

acid levels, and improved skin microvascular function in hyperhomocysteinemic individuals.

Link: <https://doi.org/10.1111/fcp.12442>

If you have any questions, comments, or desire for further information, please do not hesitate to contact us.

Contact: Ronja.maurer@alzchem.com