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The Role of Creatine Supplementation in Cardiovascular Health: A Comprehensive Review

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ABSTRACT

Background

Creatine is a compound synthesized in the human body, but it can also be obtained from food sources. Research demonstrates that creatine supplementation is safe, provides long-term benefits, and has therapeutic potential.

Aim

This study aims to present current knowledge regarding the role of creatine in the human body, with a particular focus on the effects of creatine supplementation on the cardiovascular system.

Materials and Methods

A comprehensive literature review was conducted across PubMed, Google Scholar, and relevant academic texts. Keywords included "creatine," "supplementation," "cardiovascular diseases," and "heart failure."

Results

In the human body, creatine is transported through the bloodstream and absorbed by energy-demanding cells. It supports muscle recovery and increases lean body mass, making it beneficial in tendon injury rehabilitation. Regarding cardiovascular health, some studies suggest that creatine supplementation lowers systolic blood pressure, enhances microcirculation, reduces homocysteine levels, and decreases inflammation by inhibiting markers like TNF-α and CRP. However, other studies indicate minimal impact on blood flow, lipid profiles, and hemodynamic parameters.

Conclusions

Creatine exhibits wide-ranging properties, positioning it as a strong candidate for further research and a potential therapeutic agent, though further research is needed to clarify its cardiovascular effects.

Keywords: creatine, supplementation, cardiovascular diseases, heart failure.

1. Introduction

Creatine is a chemical compound consisting of guanidine and acetic acid. In the human body, it is found mainly in the muscles, while smaller amounts of creatine are also present in the brain, liver and kidneys. Creatine kinase is an enzyme that enables the formation of phosphocreatine from creatine and has a very important role. This compound is an energy substrate in muscle cells [1]. Creatine is really important in the human body, primarily as a store that releases energy in the muscles during their functioning. Therefore, it is necessary for basic muscle function, especially during physical exercise [2].

Creatine supplementation (CrS) can be an adjunct to treatment for people suffering from muscle diseases such as Duchenne myopathy or infectious disease. Additionally, there are benefits from CrS in metabolic disorders such as type II diabetes or bone diseases, such as osteoporosis [3].

Preliminary research has also shown that CrS increases creatine concentration in the brain, leading to alleviation symptoms of depression, concussion, and symptoms of traumatic brain injury [4]. The beneficial effect of creatine can also be seen during its supplementation in Parkinson's, Alzheimer's and Huntington's diseases. Studies have shown that the use of creatine

improves cognitive functions, especially in patients whose cognitive functions are impaired due to lack of sleep or chronic pathological conditions, such as deficiencies of creatine synthesis enzymes, aging, and mental or neurological diseases [5].

Creatine was discovered by the French scientist Michael Eugenia Chevereul in 1832. Its name comes from the Greek word “kreas” which means meat, because in meat the greatest amount of creatine is found [6]. Creatine in the body is partially synthesized in the kidneys, pancreas and liver (1–2 g/day) and also supplied with food (1–5 g/day). Transport in the human body takes place mainly to skeletal muscles but also to the brain and testicles [3].

In 1992, research showed that several days of CrS significantly increased the concentration of both free creatine and phosphocreatine in skeletal muscles. Taking 20 to 25 g of creatine daily for 5 to 7 days has also been proven to attenuate the normal loss of strength during short-term but demanding exercise. Therefore it can be concluded that this significantly improves training efficiency and consequently, increases physical performance [1].

There are evidences that CrS increases fat-free body mass, but the significant impact of diet must be also taken into account. It may provide similar, if not greater, benefits. In 2001, there was conducted research in which it turned out that people supplementing creatine and undergoing resistance training (RT) for 8 weeks had a similar increase in muscle strength and mass compared to people who underwent the same training and were on an isoenergetic and appropriately nitrogen-balanced diet [3].

CrS is becoming more and more popular and widespread. The main reason is to increase its muscle concentration, which improves physical performance, especially in high-efficiency training. Studies have also shown that post-exercise regeneration and thermoregulation improve, the effectiveness of rehabilitation during injuries increases and the severity of injuries decreases. Among the many benefits of using creatine as a supplement, there is also a positive effect on the nervous system. According to research, CrS used both short and long term is safe. It has been documented that greater benefits result from low creatine intake (approx. 3g/day) throughout life than from higher doses (up to 30g/day) for 5 years [7].

The aim of this study is to review the current state of knowledge about the role of creatine in the human body and above all, the impact of CrS on the cardiovascular system. This analysis will allow us to better understand the mechanisms of action of creatine, its impact on cardiovascular performance and cardiovascular diseases. The safety of its use will also be taken into account. Additionally, the work aims to indicate possible directions for future research in

this increasingly common field of CrS in medicine.

2. Research materials and methods

2.1 Data collection and analysis

A review of the literature was carried out using the following databases: PubMed, Google Scholar and the books. The key words such as creatine, supplementation, cardiovascular diseases, heart failure were used. The analysis was based on research on the role of creatine in the functioning of the circulatory system, with particular attention paid to its effect on blood pressure, lipid profile and its importance in the treatment of heart failure.

3. Research results

3.1 Creatine mechanisms of action.

Creatine synthesis takes place in two stages. In the first phase, the amidino group of L-arginine is transferred to the N-amino group of L-glycine. As a result of this reaction, L-ornithine and guanidinoacetate are formed, which is methylated with the participation of S-adenosyl-L-methionine. The catalyst for this process is the GAMT enzyme (guanidinoacetate N-methyltransferase). The product of this reaction, in addition to S-adenosyl-L-cysteine, is creatine [8].

Creatine is transported in the body via the blood. From there, it is taken up by cells with high energy demand using the SLC6A8 transporter. It belongs to a broad group of transmembrane carriers that mediate the transport of amino acids and neurotransmitters. SLC6A8 expression is important in organs such as skeletal muscle, brain, and heart, where energy expenditure is significant [9].

Skeletal muscles, as cells with high energy requirements, have several metabolic pathways that allow for the production of ATP, both in aerobic and anaerobic conditions. One of the most important of these is the breakdown of phosphocreatine. This process is particularly important in the case of short, intense efforts lasting seconds (e.g. jumping, sprinting) [10].

Phosphocreatine is produced in muscle cells by reversible phosphorylation of creatine using the enzyme creatine kinase. This metabolite is broken down during muscle contraction, which results in the synthesis of ATP, which is readily available to the cell. In 1962, researchers Cain and Davis inhibited creatine kinase, and consequently the enzymatic breakdown of phosphocreatine to creatine. A notable decrease in ATP levels in cells was observed at that time,

which significantly reduced the ability of muscle tissue to contract. [11, 12].

The end product of creatine metabolism is creatinine. It is formed in the process of non-enzymatic creatine anhydration. This reaction is irreversible in vivo and occurs depending on pH and temperature. Creatinine is eliminated from the body via the kidneys [13].

3.2 The effect of creatine supplementation on the cardiovascular system.

In a 2016 study, the authors noted changes in systolic blood pressure (SBP) throughout the study, such that at time 0, SBP was higher than at 0.5 hours and 1 hour after CrM (creatine monohydrate) supplementation ($p<0.05$). Moreover, the assessment at 1 hour was significantly lower than SBP at 0, 2, 3, 4, and 5 hours post-supplementation (all $p < 0.01$). No correlation between SBP and diastolic blood pressure (DBP) was observed [14].

Another group of researchers in 2004 found differences in blood pressure between placebo and creatine groups, as well as between genders. DBP decreased in both groups during each exercise session. Men had higher SBP than women in both cases, and these differences were attributed to the higher baseline blood pressure in men. In the mentioned study, the blood pressure response to exercise was normal and did not differ between the groups [15].

However, most studies on this topic show no statistically significant changes in blood pressure [16, 17, 18, 19, 20, 21].

In the article from 2022 the authors theorize that physical exercise increases blood flow to muscles, potentially enhancing creatine transport, absorption, and retention in skeletal muscles [22, 23]. Therefore, combining exercise with CrS may be beneficial. However, timing is crucial, as it must account for the digestion, absorption, and peak concentration of creatine in the bloodstream, as well as the intensity and duration of muscle blood flow. Creatine plasma concentration typically peaks within ≤ 2 hours after a 5 g dose and remains elevated for about 4 hours [24]. Blood flow usually returns to resting levels within 30 minutes post-exercise, but can sometimes stay elevated longer [25]. According to the authors, taking creatine before RT, which lasts around 70 minutes [26], could theoretically align increased blood flow with elevated creatine levels, promoting better uptake and retention in muscles compared to post-workout supplementation [27].

Researchers monitored blood flow and found that increased creatine uptake was likely due to insulin's effect on creatine kinetics in muscles. Additionally, insulin may also increase Na+-K+ pump activity, which in their opinion could further facilitate creatine transport [27,

28].

When it comes to vessels, the functional density of skin capillaries (p=0.0496) and capillary recruitment during post-occlusive reactive hyperemia (p=0.0043) increased after CrS. There was also an increase in microcirculatory vasodilation in the skin induced by post-occlusive reactive hyperemia (p=0.0078) [29]. These findings suggest that CrS may improve microvascular responses, potentially contributing to better tissue perfusion and overall vascular health.

There are also cases where CrS did not modify blood flow in the legs after exercise nor did it affect vascular function [30, 31].

Another study showed that CrS significantly increased blood flow in the calf and forearm. However, these changes were only observed in the group receiving creatine combined with RT, not in the groups supplemented with creatine alone or given a placebo. The authors suggested that the results indicate a synergistic or "additive" effect between creatine and RT. However, we cannot conclude that creatine alone impacts vascular function [32, 33].

There are also articles proving the counterargument: intense exercise immediately increases arterial stiffness [34]. Sanchez-Gonzalez et al. studied the effect of CrS (10 g/day for 3 weeks) on this response after intense knee extension. They found that CrS attenuated the increase in arterial stiffness compared to placebo. The authors attributed this to creatine's influence on increased sympathetic activity, blood pressure, and vasoconstriction. Nevertheless, with repeated intense exercise, arterial stiffness and blood pressure continue to rise [35].

Galvan E. et al. proved that five hours after CrM supplementation, an increase in HDL-C (p=0.001) and a decrease in triglycerides (p=0.01) were observed [14]. De Moraes R. et al. observed significant changes in total cholesterol (p = 0.0486) and LDL cholesterol (p = 0.0027) levels during CrS [29]. All of this positively impacts human health.

On the contrary, no significant changes in lipid profiles were observed, regardless of the period of CrS [36].

At the beginning of the study, there were no significant differences in the lipid profile between the groups. Both groups showed an increase in HDL cholesterol levels after 8 weeks of aerobic training compared to 4 weeks (p = 0.01), indicating an improvement in the beneficial lipid profile over time. Both groups also experienced a decrease in VLDL triglycerides after 4 and 8 weeks of aerobic training (p = 0.02 and p = 0.01), suggesting a positive effect of time on lowering these lipids. However, CrS had no significant effect on any of the measured lipid

variables, indicating no additional effect of creatine on the lipid profile (no interaction effect). These findings suggest that the duration of the study positively impacted the improvement of the lipid profile, but CrS did not produce any additional effect in this regard [37].

The findings from various studies suggest that CrS has a mixed impact on lipid profiles. Therefore, while creatine may have some beneficial short-term effects, its long-term influence on lipid metabolism remains uncertain.

The study indicates that CrS had minimal impact on hemodynamic variables, with the only significant change being a decrease in SBP [14]. No significant differences were observed between the creatine and placebo groups across various cardiovascular measures, such as SBP, DBP, mean arterial pressure (MAP), and heart rate (HR) throughout the CrS period [38].

Maximum HR (HRmax) was significantly lower after 28 days of CrS, while resting HR remained unchanged. The increased blood flow observed in the Doppler study after 28 days of supplementation was not statistically significant, which the authors suggest may explain the reduction in HRmax [39].

Among the variables assessed in the cardiopulmonary exercise test, peak oxygen consumption, anaerobic threshold, and oxygen pulse showed no significant differences between the groups ($p > 0.05$). No significant difference in distance covered was observed in the 6-minute walk test [40].

Echocardiographic studies revealed no changes in heart structure or function before and after CrS, suggesting that creatine does not significantly influence cardiac health or performance in the context of this study [39].

3.3 Creatine supplementation and cardiovascular performance.

CrM is currently considered the most effective dietary supplement for increasing lean body mass and improving anaerobic performance [41].

Additionally, it is suggested that increasing creatine levels in the body (in the form of creatine phosphate (CrP)) through supplementation may accelerate the recovery of ATP stores, thereby improving short-term exercise performance [42].

In contrast, no significant differences in exercise performance were found between the creatine groups and the control groups [20].

Muscle-tendon stiffness under a load of 200% body weight decreased by 13% after CrS. The control group remained unchanged ($p<0.05$) [43]. In another study, this hypothesis was

refuted. No increase in muscle tension or stiffness was observed under any load. It was hypothesized that increased intracellular fluid concentration, resulting from creatine consumption, could increase muscle-tendon unit stiffness, potentially increasing the risk of injury. However, the results clearly show that 28-day CrS does not raise the risk of muscle damage associated with increased stiffness of the muscle-tendon system [43].

The aim of the study was to assess the effect of CrS on markers of oxidative stress and antioxidant mechanisms after exhaustive cycling exercise. 18 active men performed two cycling trials, separated by a one-week break. For 5 days before the second trial, participants received creatine or the placebo. Heart rate, oxygen uptake, and blood markers were measured before, after, and 24 hours after exercise. Hydroperoxide concentration increased after exercise, but CrS had no effect on lipid peroxidation, antioxidant levels, heart rate, or oxygen uptake. Short-term CrS did not enhance antioxidant defenses or protect against oxidative stress [44].

CrS positively influenced the increase in the range of motion 24 hours after training compared to the placebo group, suggesting better muscle recovery. The CrS group exhibited higher values of maximal voluntary muscle contractions at key time points post-training (0, 48, 96, 168 hours), indicating less strength impairment after exertion. The CrS group experienced a reduction in muscle circumference at 48, 72, 96, and 168 hours post-training, which may indicate a quicker reduction in post-exercise swelling. The shear modulus was also reduced at 96 and 168 hours post-training, suggesting a beneficial effect on muscle stiffness. No changes were observed in the levels of the N-terminal fragment of titanium in urine or in subjective muscle soreness ratings. The CrS group experienced less muscle fatigue compared to the placebo both immediately after exertion and at 168 hours post-training, which may suggest better recovery and muscle performance following CrS. To conclude, CrS may support muscle recovery, reduce fatigue, and improve range of motion and muscle strength after intense exertion [45].

Novel research has been presented regarding the impact of CrS on recovery during rehabilitation after tendon injuries in young fin swimmers. The results indicate that the combination of therapy with CrS effectively supports the rehabilitation of tendinopathy, alleviating muscle and strength loss, reducing pain, and significantly shortening recovery time. Authors mention that a limitation of the study was the small sample size; however, the data obtained provide a promising basis for further research [46].

Human studies have shown that CrS may positively influence satellite cells. It was found

that the combination of CrM supplementation with RT increases the number of these cells more than training alone. Therefore, creatine may support muscle regenerative capabilities, which is another mechanism through which supplementation may help protect against age-related declines in muscle mass and function [47].

In another study conducted by Louis M. et al. participants consumed 21g of creatine daily for a week before starting exercises, and around 21g of maltodextrin + 6g of creatine/hour for 3 hours after resistance exercises. CrS increased the total creatine content in muscles by around 21% ($p<0.01$) [30].

It is proven that CrM significantly increases workload, peak power, average power, and average speed ($p = 0.001$) [14].

The findings from Peeters B.M. et al. highlight the positive effects of CrM and CrP supplementation on physical performance. After 6 weeks of supplementation with CrM and CrP, both groups significantly increased lean body mass and strength, particularly in the bench press. The placebo group, during this time, decreased its body weight. The CrM and CrP groups improved their leg press performance by 32.6 kg and 27.5 kg, respectively, compared to 21.2 kg in the placebo group. The number of repetitions in bicep exercises was also higher in the CrS groups. This demonstrated that with creatine, more repetitions can be performed before fatigue sets in, allowing for the use of greater loads during training. Although statistically significant changes were only seen in lean body mass and bench press performance, CrS supported greater gains in strength and lean body mass compared to placebo, making it a valuable ergogenic aid for athletes [18].

In another study, it was shown that 7 days of CrS (20 g/day) did not improve performance in a 2-minute push-up test, confirming that creatine supports strength in exercises lasting <60 seconds but not endurance [20].

The authors of the study demonstrated that the responder (R) group increased their maximum strength in the incline leg press by 25.8 kg after 5 days of CrM supplementation, while the partially responsive (QR) and non-responsive (NR) subgroups recorded minimal changes (2.5 kg and 2.0 kg, respectively). The NR group exhibited significantly lower maximum strength in both the bench press and angled leg press compared to either the R or QR groups [48].

The study conducted by Dalton RL et al. found a significant interaction between creatine type, time, and sex in leg press performance. Women taking 3g of creatine nitrate (CNL) for 5

days showed improved endurance, though no group differences were found overall. The group taking 6g of creatine nitrate (CNH) for 6 days showed increased bench press strength and less strength loss during recovery, as well as improved leg press strength after 5 days. CNL improved endurance in bench press and leg press, though not significantly. In summary, CNH aids strength gains and recovery, while CNL may benefit endurance, suggesting both forms support different athletic goals.[21].

3.4 Creatine and cardiovascular diseases.

Heart failure (HF) is a heterogeneous clinical syndrome resulting from cardiac overload and injury, which is a significant contributor to high mortality, morbidity, and reduced quality of life. [49, 50] Shein et.al [51] conducted a study on dogs, in which chronic right ventricular stimulation was used to induce cardiac dysfunction and heart failure. They observed a reduction in both ATP and creatine levels, with creatine depletion occurring at a faster rate, suggesting that creatine may serve a compensatory role by mitigating the depletion of purines in the failing heart. The authors hypothesized that phosphocreatine supplementation in the early stages of heart failure could be utilized to replenish ATP, thereby slowing its decline through the creatine kinase reaction, which modulates ADP and AMP concentrations.

In a study performed by Gordon et al. [52], 17 patients aged 43 to 70 years, with an ejection fraction below 40%, were supplemented with creatine (20g/day) for 10 days. The results showed that one week of CrS in patients with chronic heart failure did not improve the ejection fraction, but it did increase the phosphagen content in skeletal muscles, leading to enhanced performance in terms of both strength and endurance.

Aron et al. [53] conducted a study involving men aged 55 to 80 years who were randomly assigned to three groups: a CrS group (Creapure Creatine Powder, Alzchem Trostberg, Germany) receiving 20g/day, a placebo group (Maltodextrin Powder, Nutricost, USA) also receiving 20g/day, and a control group (no supplementation). The results indicated that 7 days of CrS significantly improved vascular parameters related to arterial stiffness and atherosclerosis, suggesting its potential clinical application in the treatment of cardiovascular pathologies. CrS may represent a safe, effective, and cost-efficient adjunct to standard therapy.

Homocysteine is considered an independent risk factor for atherosclerotic diseases affecting coronary, cerebral, and peripheral vessels, with higher plasma levels correlating to increased risks of conditions such as coronary heart disease and cerebrovascular disease [54].

Oral supplementation of creatine may effectively lower the risk of developing conditions such as coronary artery disease and cerebrovascular disease by reducing the production of homocysteine [55].

CrS is gaining increasing recognition in the context of treating and managing inflammatory conditions associated with cardiovascular diseases. As a natural compound found in the body, creatine plays a crucial role in the energy metabolism of cells, and its supplementation may significantly impact inflammatory processes [2, 56, 57]. CrS shows beneficial effects on the levels of TNF-α (tumor necrosis factor alpha) and C-reactive protein (CRP). Research suggests that a 7-day creatine regimen may inhibit the rise in TNF-α and CRP levels, indicating its anti-inflammatory properties. Additionally, CrS may also impact LDH (lactate dehydrogenase). A reduction in LDH activity following CrS may indicate decreased tissue degradation in response to intense physical exercise, further supporting the potential benefits of its use in protection against inflammatory conditions [57].

In a study conducted by Hemati et al. [58], 100 patients were randomly assigned to two groups: an intervention group that received 5 grams of CrM daily and engaged in exercise for 8 weeks, and a control group with no interventions. Key inflammatory markers, including interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), were measured. The results demonstrated that levels of hs-CRP and IL-6 significantly increased in the control group, while they decreased in the intervention group. Levels of P-selectin and ICAM-1 rose in the control group but decreased in the intervention group. However, the level of VCAM-1 did not show any significant change in the intervention group. The results indicate that CrS combined with regular physical activity significantly reduces inflammatory markers and improves endothelial function in patients with heart failure.

Unfortunately, there is a limited number of studies investigating the effects of creatine on inflammation in cardiovascular diseases. Despite promising results in some research, further investigations are necessary to gain a deeper understanding of the mechanisms of action of creatine and its potential benefits in reducing inflammatory conditions and improving cardiovascular health.

3.5 Safety of Creatine use.

In the world of easy access to unverified information, depending on the intentions and

profits of the authors, one can find many advantages and disadvantages of using CrS.

There are many suggestions in the literature about water retention or dehydratation connected to CrS - creatine as an osmotically active substance is taken up into muscle due to sodium-dependent creatine transporter [59]. Although some evidence indicates that CrS can lead to short-term water retention by increasing intracellular volume, other studies suggest it does not affect total body water (either intracellular or extracellular) over longer durations. Therefore, CrS may not necessarily cause water retention - there is no such medical proof [60]. Mentioning water retention, we need to look closer at thermoregulatory responses.

Some studies [61, 62, 63, 64] have investigated thermoregulation changes connected to creatine-supplemented individuals but the data do not support any confirmed conclusions. Another potential side effect mentioned by many authors - kidney damage/renal dysfunction. Clinical studies investigating serum creatinine levels in relation to supplementation have shown that serum creatinine either remains unchanged or increases, but stays within the normal range (adult norm) [7, 65] In summary: studies suggest that taking creatine supplements at recommended dosages does not lead to kidney damage or renal dysfunction in healthy individuals [60].

Creatine - correctly connected with muscles, sometimes in general flow of information is connected to muscle crampings. Some studies reported similar frequency of muscle dysfunction (such as cramping, muscle tightness, strains, injuries, etc.) among both creatine and non-creatine users, or fewer cases of muscle dysfunction in those who used creatine [66,67].

Next appearing in public information and literature, potential side effects of creatine use such as hair loss, increased fat mass are also not supported by scientific studies [68]. Currently, there appears to be no empirical evidence linking creatine to any of mentioned potential pathologies.

Creatine synthesis/changes catalyzed for example by L-arginine: glycine amidinotransferase (AGAT) and guanidinoacetate N-methyltransferase (GAMT) mainly take place in kidney and liver - like many substances used in cardiology or other medical areas [69, 70]. Unfortunately, there is not enough data, reliable studies or other information that allow conclusions on the interaction of ingested creatine with drugs used in cardiovascular disease. Due to its promising results for use in the field of cardiology, new information or reliable studies on a wider group of patients can be expected in the near future.

Aging is associated with a number of changes in the body, among them are: a decrease

in creatine and phosphocreatine levels (the largest percentage decrease in skeletal muscle) [71]. Recent review described meta-analysis of the role of CrS in the aging population. All in all, the majority of them suggest an overall beneficial effect on aged individuals especially in gaining muscle mass which has a positive impact on day-to-day functioning [72]. Also, supplementation of creatine in elderly which comes with reduced physical activity increases bone mineral density [73]. Due to the relative safety of creatine in the elderly, attempts have been made to include CrS in numerous diseases that are more common in the elderly, for example:

Parkinson's disease (PD): among the symptoms of this neurodegenerative disease are resting tremors, loss of muscle mass, loss of strength, increased fatigability, bradykinesia. In September 2013, the National Institute of Neurological Disorders and Stroke NINDS announced that the phase III clinical trial for creatine use in PD was halted because the study would result in an observable significant difference. In many others diseases like: stroke, amyotrophic lateral sclerosis, Alzheimer's disease, memory loss there are some promising indications of the desirability of CrS, however, either these studies were on too few patients or the mechanisms of action of creatine have not been clarified, further research is needed [71].

Creatine is a cost-effective and safe dietary supplement with effects on both peripheral and central systems. For older adults, its benefits can significantly enhance quality of life and potentially lessen the impact of sarcopenia and cognitive decline [73].

4. Discussion

Creatine plays a key role in supporting muscle energy metabolism and recovery, with additional potential benefits for cardiovascular health. Supplementation appears to enhance muscle regenerative processes, reduce fatigue, and improve functional performance, making it valuable in both athletic and clinical contexts.

Evidence for cardiovascular effects is promising but not conclusive. Creatine may support vascular function, improve microcirculation, and modulate inflammatory responses, particularly when combined with exercise. However, its long-term impact on blood pressure, lipid metabolism, and cardiac performance remains unclear, highlighting the need for further investigation.

Creatine is generally well-tolerated across populations, including older adults, with minimal risk of adverse effects. Concerns such as renal dysfunction, dehydration, or muscle issues are not supported by current evidence. In aging individuals, supplementation may help maintain

muscle mass, functional capacity, and overall quality of life.

Limitations of the current literature include small sample sizes, short supplementation periods, heterogeneity in protocols, and limited long-term studies in cardiovascular populations. Confounding factors such as diet, physical activity, and baseline fitness are often inadequately controlled.

Future research should focus on larger, well-designed trials to clarify cardiovascular benefits, particularly in patients with heart failure or other cardiovascular risks. Studies combining CrS with exercise interventions may elucidate synergistic effects on vascular function and muscle metabolism. Mechanistic investigations are also needed to understand creatine's influence on inflammation, endothelial function, and energy metabolism in both healthy and clinical populations.

In summary, creatine supplementation is a safe, cost-effective intervention with demonstrated benefits for muscle performance, recovery, and select cardiovascular markers. While evidence indicates potential positive effects on vascular function and inflammation, further research is needed to define its therapeutic potential, especially in chronic cardiovascular disease and aging.

5. Conclusions

CrS demonstrates potential benefits across multiple aspects of cardiovascular and musculoskeletal health, but its effects vary in duration and scope. While it can temporarily reduce systolic blood pressure shortly after intake, it does not seem to produce lasting changes in blood pressure levels. Combined with resistance training, creatine improves blood flow, particularly in the lower limbs, highlighting a synergistic benefit with physical activity for vascular health. In heart failure management, phosphocreatine supplementation supports the heart by slowing ATP and creatine depletion, though it does not improve ejection fraction with short-term use.

Creatine's influence on cardiovascular risk factors, such as arterial stiffness and homocysteine levels, suggests its potential in reducing risks of coronary and cerebrovascular diseases. Its impact on lipid metabolism is less consistent; while some studies show improvements in HDL-C and triglycerides, findings are mixed.

Creatine also exhibits anti-inflammatory effects, decreasing TNF-α, CRP, and other markers linked to tissue damage and chronic inflammation, thus offering protection in conditions associated with cardiovascular diseases. In the musculoskeletal system, creatine effectively

enhances performance in short, high-intensity activities, aids in muscle recovery, and supports tendon regeneration, making it beneficial for athletic rehabilitation. Further research is needed to establish consistent long-term effects and optimize therapeutic use in cardiovascular and musculoskeletal applications.

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Author contributions

Conceptualization, J.D. and P.M.; Methodology, J.D.; Software, J.D.; Validation, J.D., P.M., M.L., M.P., A.O., H.D., B.L.; Formal Analysis, J.D., P.M., M.L., M.P., A.O., H.D.,; Investigation, P.M.; Resources, J.D., P.M., M.L., M.P., A.O., H.D., B.L.; Data Curation, J.D., P.M., M.L., M.P., A.O., H.D., B.L.; Writing – Original Draft Preparation, J.D., P.M., M.L., M.P., A.O., H.D., B.L.; Writing – Review & Editing, J.D. and P.M.; Visualization, J.D.; Supervision, A.O.; Project Administration, J.D..

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Conflict of interest

The authors declare there are no conflicts of interest.

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