Section A -Research paper

Role of Creatine and Heart Health: A Review

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Abstract

Creatine is a very important compound for heart contraction and energy metabolism in our body. It has been proven in many pieces of research that Creatine supplementation (throughout the paper, only supplementation with creatine monohydrate will be reviewed, as this is by far the most used and best-known way of supplementing creatine) increases creatine level in the body and promote a healthy and safe heart. In heart failure, the expression of the creatine transporter is low and phosphocreatine fails to prevent ATP exhaustion because creatine and phosphocreatine content decrease. According to the research data available about creatine at this time, creatinesupplementation is very effective for heart failure patients because it helps to increase muscle strength and endurance of the heart. Creatine hasenergy-boosting properties which is why it is the strongest favorable organic compound to treat heart ischemia because heart ischemia is the condition in which the heart either reduces or loses the ability to synthesize ATP. Creatine has antitumor and anti-cancer properties. It works to prevent tumor and cancer growth by enhancing antitumor and anti-cancer activity in the body, so it is not only good for cardiac health but also beneficial for cancer patients. In this review paper, the available knowledge related to creatine and creatine supplementation has been collected and summarized so far and explores its heart health-related beneficial effects.

Keywords: Creatine, ATP, Phosphocreatine, Heart failure, anti-cancer properties.

Metabolism and the Role of Creatine

Functions of Creatine

Creatine is a significant amino acid that is mostly found in the body's muscles and brain in the form of phosphocreatine to be used for energy. It is reversibly phosphorylated to phosphocreatine by the enzyme creatine kinase. When phosphocreatine is converted back to creatine, its phosphate link then breaks, and this release of energy enables the phosphorylation of an adenosine diphosphate (ADP) molecule to anadenosine triphosphate (ATP) molecule. As a result,

phosphocreatine serves as an energy store quickly and without oxygen synthesizes ATP. The reaction is the following:

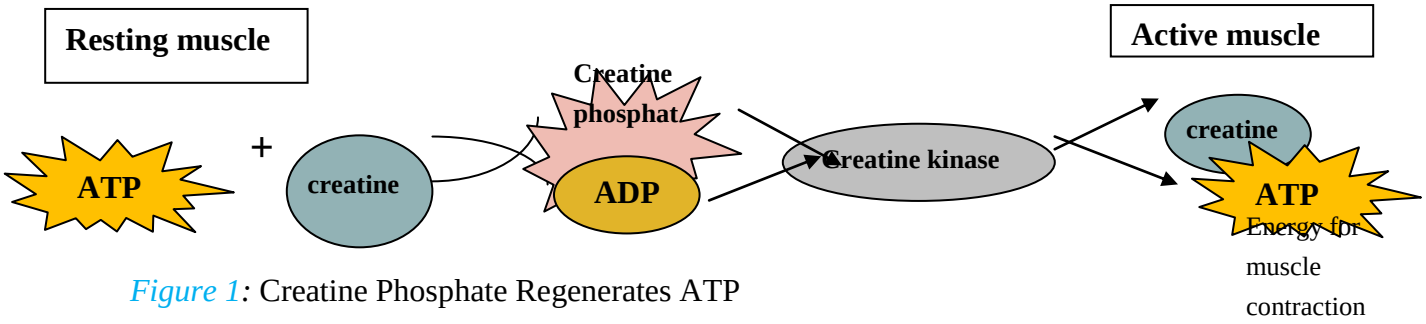
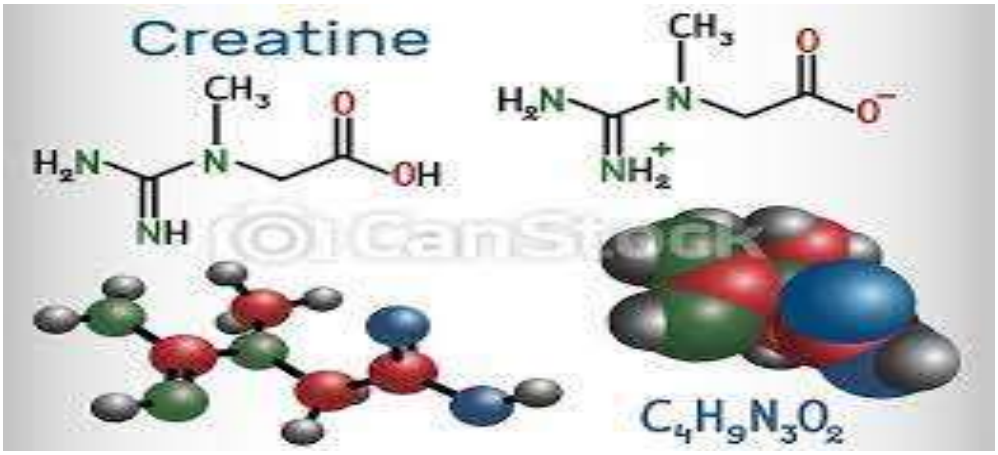


Figure 1: Creatine Phosphate Regenerates ATP

The contraction of the heart is significantly impacted by this reaction. Its roles have been reviewed elsewhere and are, in summary:

(1) transfer of ATP from its source (mitochondria) to its destination (cytoplasm or the membrane of a nerve cell). This procedure is also known as "the ATP shuttle". Creatine first absorbs the phosphate from ATP near the mitochondria to become phosphocreatine, which then performs this transport (or "shuttle") of ATP energy. It then dissipates to the cell's edge via its gradient of concentration. It lends its phosphate to ADP close to the cytoplasmic ATPase, producing ATP outside of the mitochondria and delivering it precisely where and when it is needed. As a result, it changes back to creatine and diffuses back to the mitochondrion along its gradient of concentration to restart the cycle. The fact that ATP is a huge molecule and that its diffusion through the cytoplasm of an organism filled with organelles is sluggish and laborious is the reason why the cell needs this intricate process to transport energy between mitochondria and cytoplasmic ATPase.Contrarily, because phosphocreatine is a much smaller molecule, it diffuses through the cytoplasm more quickly.



(2) In situations of increasing energy demand and in disorders with a decreased blood or oxygen supply, phosphocreatine can restore ATP concentration. In the first case, the amount of ATP consumed is more than the cell's capacity to produce it. For instance, a muscle subjected to an

especially hard exertion rapidly consumes more ATP than it can create, depleting its supply. In the second case, an organ is unable to make enough ATP due to a lack of blood (ischemia) or oxygen (anoxia). For example, in the event of infarction of the myocardium, phosphocreatine transfers its phosphoric group to ADP to produce ATP at a time when the heart is unable to synthesize it due to ischemia. The biochemical process that begins with the creatine/phosphocreatine system is the one that buffers ATP levels at times of elevated energy expenditure the fastest among all those that our cells use to synthesize ATP. This explains why scientists are interested in this chemical, whose administration has been suggested in numerous physiological and pathological circumstances.

Creatine Acquisition by the Organism with Particular Reference to the Heart

The body's creatine reserves are typically steadily depleted as creatine is routinely converted to creatinine. Consuming creatine with food and endogenous synthesis both contribute to the replenishment of the creatine reserve.

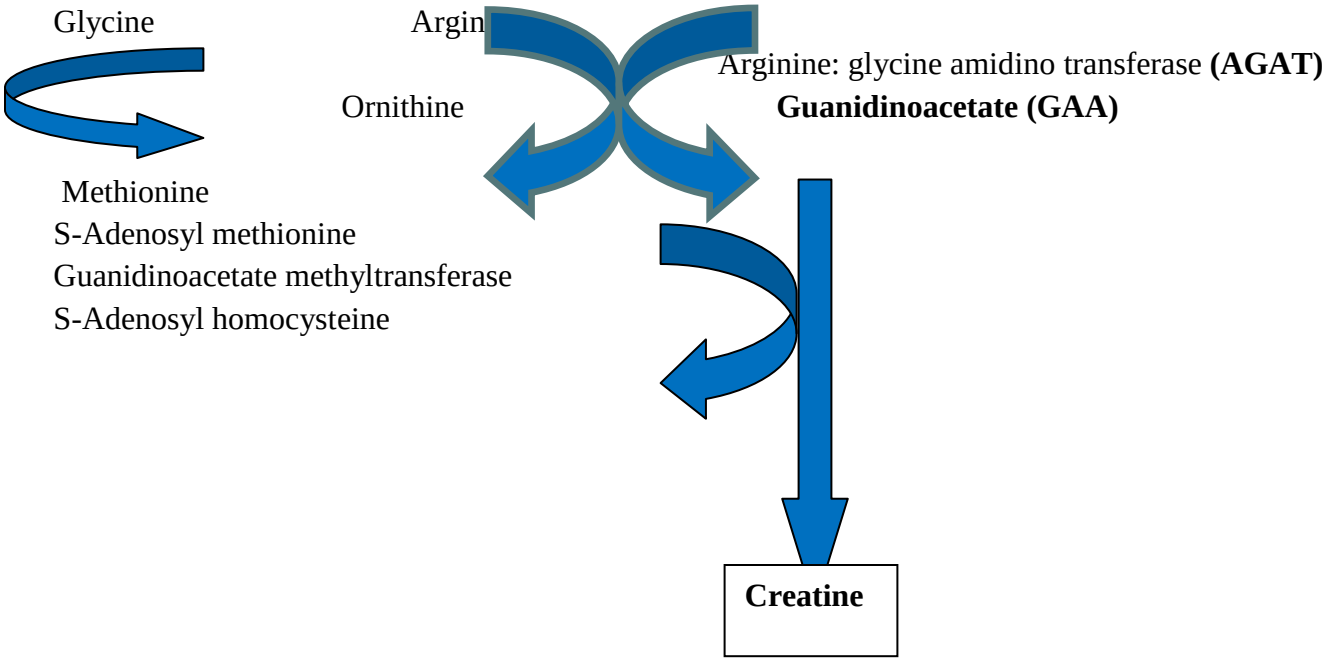


Figure 2: Endogenous Creatine Synthesis

Endogenous Synthesis of Creatine

Creatine is produced in the liver and kidney throughout the entire body. Particularly, the kidney completes the initial stage of production by converting arginine and glycine into hepatic acid. liver. acid is then taken to the liver, where, with the help of the methyl donor S-adenosyl-methionine, it is transformed into creatine. Additionally, some organs, like the brain and testicles, can synthesize creatine for self-use. It is commonly accepted that cardiomyocytes cannot synthesize creatine in the heart. The fact that cardiomyocytes may synthesize creatine similarly to other organs suggests that

such synthesis may, in fact, take place. In actuality, arginine-glycine amidino transferase (AGAT), the initial enzyme of creatine production, is expressed in the heart Under normal circumstances, the heart's expression is similar to that of other tissues, but it increases significantly under pathological conditions. Additionally, research revealed that adding arginine, a precursor to creatine, to the toad hearts' incubation medium prevented the loss of creatine during in vitro incubation as if arginine were metabolized to creatine. Additionally, arginine increased the amount of creatinine (the end result of creatine cyclization) in isolated rabbit hearts. Both of these latter studies provided compelling evidence that arginine is actually turned into creatine in the isolated heart, just as it is in other organs. However, there hasn't been much research done on the potential for creatine synthesis by the heart, and more is absolutely needed.

Uptake of Creatine from Dietary or Supplement Sources

The body typically consumes and absorbs around half of the creatine it requires from food sources. Vegetables do not contain creatine; instead, meals of animal origins do. Therefore, those who don't regularly eat meat or fish are more likely to have a creatine shortage, and they should add more of it to their diets. Additionally, exogenous supplementation of creatine enables the administration of large doses of this substance and an increase in its content above baseline values. Only supplementation with creatine monohydrate will be discussed throughout the paper as it is by far the most popular and well-known method of getting creatine. Creatine raises the intracellular pool of both creatine and phosphocreatine when it is given in this manner at suitable dosages. For the muscle tissue, such an increase is very important. Athletes use the ability of the muscles to contract more forcefully and for longer periods of time due to creatine supplementation to enhance their performance.Similar to the way it works in muscles and other tissues, creatine is metabolized and used in the heart.

The following are some specific processes through which supplementing with creatine benefits the body:

1. Restoring normal creatine concentration when it is lower than usual due to a condition (such as heart failure, see below) or a lifestyle choice (such as in vegetarian or vegan people).
2. An increase in energy availability (obtained by raising the tissue's phosphocreatine concentration) when the ratio of available to needed energy is constrained by either decreased energy production (as in hypoxia or ischemia) or increased demand (such as the muscle of athletes during competition).

Last but not least, it should be noted that creatine does not enter cells on its own; rather, it requires a particular transporter to cross plasma membranes. The same thing occurs in the heart, where the creatine transporter, which must be present for creatine to enter myocardial cells, is found on the plasma membrane of the myocytes.

Creatine Supplementation in Heart Failure

The European Society of Cardiology defines heart failure as "a clinical syndrome that features by prominent symptoms (breathlessness, swelling, and fatigue) that can also be associated with signs (such as elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused

by an underlying structural and/or operational cardiac abnormality, leading to in a reduced output of the heart and/or increased intracardiac pressures at rest or during stress." Thus, one of the main symptoms of heart failure is the heart's inability to pump blood effectively enough to maintain bodily activities. Heart failure is a serious condition for which there is frequently no cure.

Creatine Levels Drop in Heart Failure

This section will present a wide range of evidence spanning a considerable amount of time that demonstrates how creatine, phosphocreatine, or both, reduce heart failure. Feinstein found that, in guinea pig hearts treated to various experimental circumstances, there was a drop in phosphocreatine, total creatine (i.e., creatine + phosphocreatine), and adenosine triphosphate (ATP), which affected the function of the heart in vivo. The latter situations included ouabain therapy, experimental congestive heart failure, and severe hypoxia. This scholar came to the conclusion that the primary factor causing heart failure is a lower rate of synthesis of high-energy moleculesIn line with this theory, it was eventually learned that one of creatine's primary functions is to enable quick re-synthesis of ATP at the locations of its use. A few years later, Fox et al. demonstrated that phosphocreatine and total creatine were reduced by roughly 33–43% compared to controls in dogs suffering from experimental pulmonary artery stenosis-induced chronic heart failure, but ATP was reduced to a lower level (by about 12%). Shen et al. investigated experimental heart failure caused by continuous right ventricular pacing in living dogs and discovered that both ATP and creatine were lowered, with creatine decreasing earlier than ATP. Those authors made the logical assumption that phosphocreatine was used to restore the ATP stock in the early stages of heart failure, reducing the loss of ATP. More recently, Ten Hove et al. established that experimental rat heart failure had a lower creatine concentration and linked it to the concomitant decline in creatine transporter that they also discovered.

As previously stated, it has been shown that the downregulation of the creatine transporter occurs in failing hearts in both rodents and humans. This is assumed to be the cause of the decreased creatine level of the failing heart. It is interesting that while ATP levels in the failing heart are steady or just slightly reduced, phosphocreatine levels typically decline considerably more dramatically, which results in a decrease in the phosphocreatine/ATP ratio. This seems to point to a mismatch between the mitochondrion's production of ATP and the cytoplasm's need for ATP. It is therefore highly likely that phosphocreatine is used to quickly resynthesize ATP, thereby reducing the rate at which ATP is lost in a failing heart. In addition to decreased creatine transporter expression, this is another cause of phosphocreatine depletion in heart failure.

These preclinical findings imply, in summary, that (1) a decrease in creatine absorption caused by down-regulation of the creatine transporter and (2) consumption of phosphocreatine, which is used to prevent or prolong ATP exhaustion, cause the creatine concentration in the failing heart to drop.In studies of heart failure patients, Nascimento et al. discovered that both creatine kinase activity and creatine dropped, and they proposed that this decline hampered the capacity of cardiomyocytes to quickly transfer energy to the systems that required it. According to Neubauer et al., coronary artery ligation-induced heart failure causes a drop in creatine levels in both human

patients and a mouse experimental model. They also discovered a contemporaneous decline in creatine transporter in humans, which they determined was the root cause of the decline in creatine.With the aid of magnetic resonance spectroscopy, Winter et al. discovered that individuals with non-ischemic heart failure had lower total creatine levels. In order to look at the phosphocreatine/ATP ratio in healthy human volunteers and heart failure patients, Neubauer et al. used in vivo 31P-MR spectroscopy. They discovered that patients with heart failure not only had a lower average ratiothan controls but that this decline was also a statistically significant predictor of mortality for specific individuals. A different team later used in vivo proton magnetic resonance spectroscopy to confirm these results.In subsequent studies, the same group revealed a positive association between myocardial creatine content and left ventricular ejection fraction in addition to further confirming the decreasing creatine content of the failing human heart due to a wide range of causes. The notion that heart failure is caused by a reduction in energy availability was supported by these data, which also suggested that one potential treatment for it might have involved reversing and restoring the decreased phosphocreatine content of failing hearts.

Reduced Creatine's Effects on Cardiac Function

In fact, lowering cardiac creatine has a negative impact on contractility. Saks et al. demonstrated in the hearts of frogs that a drop in myocardial creatine concentration resulted in a decrease in contraction force. Ten Hove et al. devised a plan to lessen the amount of creatine found intracellularly in the hearts of the animals. They discovered that these hearts did not exhibit any notable abnormalities while at rest, but that when exposed to a sympathomimetic substance, their ability to contract was reduced. They could not effectively raise cardiac output in response to stimulation because of a diminished contractility reserve. They also demonstrated a greater susceptibility to ischemia injury. Capello et al. demonstrated that isolated rat hearts depleted of creatine through treatment with Capello acid, an antagonist of the creatine transporter, had nearly normal cardiac output when subjected to a submaximal pressure load, but displayed a 43% decrease in pressure-volume work at a maximal pressure load. According to these two latter studies, decreasing heart creatine content prevented enhanced cardiac output when contractility was more crucial, but did not have significant impacts at rest or during low levels of stimulation.

Since there is no indication that creatine drops below the Km of the creatine kinase enzyme in heart failure, Field made the intriguing observation that creatine content is typically sufficient to maintain creatine metabolism at a level of efficiency. This opinion, while intriguing, is at odds with the aforementioned findings, which in later years would have shown that the decline in creatine in heart failure is in fact clinically relevant, as it correlates with left ventricular ejection fraction and is a predictor of mortality in specific patients.

The aforementioned data demonstrate that decreasing creatine content in failing hearts and its association with decreased contractility strength are both sound discoveries, and they give justification for further research into the benefits of creatine supplementation in heart failure patients.

Effects of Creatine Supplementation in Heart Failure Patients

The goal of creatine supplementation for the failing heart is to restore the normal level of creatine, which has been documented to decrease in this state as mentioned above. A few preclinical or clinical trials have looked into the effects of creatine supplementation on heart failure.

Faller et al. employed mice that overexpressed the creatine transporter in a preclinical study on the effects of ribose supplementation in the failing heart. They chose the mice that just slightly increased their creatine levels, had coronary artery ligation operations to cause chronic myocardial infarction, and added ribose to their diets. They discovered that the heart function was not improved by this medication. Although pertinent, this study used over-expression of the creatine transporter rather than creatine supplementation. Additionally, it required the administration of ribose, the effects of which might have prevented the increase in creatine.

Fumagillin et al. examined the effects of supplementation with coenzyme Q10 and creatine (320 and 340 mg daily, respectively, for 8 weeks) on heart failure patients in the New York Heart Association functional class II to III in a randomised, placebo-controlled experiment. They discovered a greater peak oxygen intake in the treated group without any negative side effects. It is interesting that the trial's relatively modest creatine dosage (340 mg daily) was used. This discovery sparked speculation that the medication may have improved skeletal muscle performance rather than myocardial function as a result of this finding. Using a randomised, placebo-controlled approach, Carvalho et al. examined the effects of creatine supplementation (5 g/day for 6 months) in people with heart failure (New York Heart Association functional classes II to IV). Interestingly, they discovered a substantial positive association between peak oxygen consumption and the distance walked during the six-minute walk test solely in the creatine-treated group, but they observed no effect on any of the other measures they investigated. In theory, this result suggests that the creatine-treated group only utilised oxygen more effectively.

Additionally, several research revealed that creatine supplementation can enhance muscle performance in people with heart failure, resulting in an overall functional improvement. In a double-blind, placebo-controlled trial, Gordon et al. discovered that giving heart failure patients creatine supplements increased their muscle strength and endurance. Creatine supplementation (20 g/day for 5 days) considerably enhances muscular function, according to research by Andrews et al. They reported that creatine improved muscle endurance, which was measured as the quantity of contractions made up to exhaustion at 75% of maximum voluntary strength, and decreased the formation of ammonia and lactate under the same circumstances. These results generated curiosity, but an accompanying editorial [caused confusion when it stated that "only patients with low muscle creatine levels benefit from the therapy". Actually, Andrews et al. did not take measurements of the levels of creatine in their patients; instead, they cited earlier research that had found that "In individuals with severe chronic heart failure, dietary creatine supplementation results in a reduction in total skeletal muscle creatine content as well as a notable increase in the levels of phosphocreatine and creatine in the muscles." Therefore, the proper interpretation of those authors' data should be that creatine supplementation is beneficial for all patients with heart failure as a population. The same editorial also sparked doubts regarding the safety of long-term creatine

supplementation, doubts that subsequent studies would have allayed. Finally, Kathe et al. discovered that supplementing with creatine (4 g five times per day) improved muscle strength in patients with severe heart failure. This study was double-blind, placebo-controlled, and crossover-designed. In conclusion, these studies show that while creatine supplementation may have some beneficial effects on cardiac function in patients with heart failure, its more significant effects are on skeletal muscle endurance and strength, which theoretically should improve the quality of life for these largely incurable patients.

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