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Role of creatine and creatine precursors supplementation on cardiovascular system physiology and pathophysiology

Abstract

This essay aims to show the state of the art in the use of creatine supplementation and precursors in the physiology and pathophysiology of the cardiovascular system. Also, show the prospects and plausibility of using the aforementioned supplements to prevent and improve the prognosis of heart disease patients.

Keywords: creatine; heart; cardiomyocite; X–linked disease; guanidinoacetic acid, betaine

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Introduction

In recent decades, a significant increase in scientific research, labels, and consumption of creatine supplementation can be observed. Initially (end of the 18th century and beginning of the 19th) the little attention given to this molecule was almost exclusively therapeutic.[1-3] However, in the 1980s some sports results were attributed in part to the use of creatine supplementation by victorious athletes, mainly the positive results of the English athletics team in speed and strength tests. The results achieved and the advanced physical appearance of athletes like Linford Christie boosted the market, both athletes and non–athletes who saw nutritional resources as a way to accelerate gains in muscle mass.[4]

Over time, creatine supplementation has come to be expected as a resource for increasing performance gains and improving physical appearance through muscle hypertrophy.[4,5] However, boosting consumption also stimulated an increase in curiosity about the properties of creatine (metabolism, cell signaling, pharmacokinetics, etc.), leading several researchers to observe the relationship between dietary consumption and supplementation in different tissues and organs.[3,6] Hence, the relationship between the lack or reduction in creatine concentrations and the etiology of several diseases (main mutations in the genes Guanidinoacetate N–methyltransferase [GAMT], Arginine: glycine amidinotransferase[AGAT], and solute carrier family 6 member 8 [SLC6A8] and myodegenerative diseases), as well as the use of creatine supplementation as an adjuvant in the treatment of these as well as other diseases.[3,7-9]

Creatine supplementation started to be used with different levels of success in neurology, geriatrics and gerontology, orthopedics, physiatry, endocrinology, and other specialties.[7-10] The results found encouraged researchers from other specialties to start testing creatine supplementation, especially after the strengthening of evidence of the essential actions of creatine in mitochondria. Among these specialties, cardiology could not be left out.[11-13]

Therefore, this essay is intended to show the state of the art in the use of creatine supplementation, without intending to be an exhaustive review of research results (without ignoring them of course).

Discussion

Creatine can be produced endogenously or ingested through the food of animal origin (mainly meat, fish, chicken, and pork).[3] The heart is an organ that cannot produce its creatine, thus depending on what reaches it via the bloodstream. Entry into cardiomyocytes occurs exclusively (as far as is known) by facilitation of a group of transmembrane proteins known as creatine transporters (CrT) which is encoded in the SLC6A8 gene (solute carrier family 6 member 8) located on Xq28 (X chromosome position q28).[3,9,14]

It is not difficult to deduce that defects in the SLC6A8 gene disable the carrier's cardiomyocytes from receiving a sufficient amount of creatine to maintain the functioning of these cells and, consequently, the heart itself.

About 80 mutations in this gene are known to be found in patients with X–linked creatine deficiency (Table 1). These mutations mainly induce intellectual disability, behavioral problems, seizures, and muscle weakness, as they affect more skeletal muscle tissues and the brain.[15,16]

The main disease linked to mutations on the X chromosome is dilated cardiomyopathy, which is etiologically linked to another gene (DMD or dystrophin) and is not directly related to creatine. Mutations in the SLC6A8 gene, on the other hand, lead to a decrease in the cross–sectional area of muscle fibers, a decrease in the number of muscle fibers, and a deficiency in the ability to regenerate damaged fibers. These effects are more evident in skeletal muscle, however, they also happen in cardiomyocytes.[17]

As creatine plays a vital role in cardiomyocytes, it is speculated that there are protective mechanisms against the reduction of intra–cardiomuscular creatine stores. One of the hypotheses is that the cardiomyocyte may come to produce the two key enzymes in the synthesis of creatine (mainly GAMT and possibly AGAT). The very lack of adequate concentrations of creatine would induce gene expression, but this mechanism still lacks solid evidence, especially in humans. It is believed that as the consequences in the brain and skeletal muscles are more evident clinically, cardiac problems tend to be underreported. Decreased creatine levels have also been shown to correlate with heart failure, increased prevalence of ventricular arrhythmias, and ischemia.[9,18,19]

To better understand the pathophysiology of X–linked heart disease and how supplementation can eventually be a coadjuvant in the treatment, we need to understand how CrT works. Creatine transport is a symport, meaning that it uses the sodium ion concentration differential to co–transport creatine (Figures 1-2).

However, intracellular and extracellular concentrations of creatine interfere with the efficiency of the transporter. Cardiomyocytes are especially sensitive to low concentrations, as they are vitally dependent on creatine metabolism. When creatine stores are low, there is an increase in the efficiency of creatine transport in an attempt to stabilize physiological concentrations.[3,9,14] This mechanism occurs, for example, in vegetarians and vegans, who do not consume foods rich in creatine and depend exclusively on endogenous production (which is insufficient). Thus, the hearts of vegetarians and vegans do not present diseases related to a creatine deficiency, and the transport of the metabolite is increased to supply the subphysiological concentrations. Similarly, cardiomyocytes may seek creatine homeostasis by enhancing transport.[20]

Table 1 Main mutations of the SLC6A8 gene[5,16]

Variant	Clinical phenotype
P31L	Seizures, speech and motor delay, and thalamus atrophy
G87R	Intellectual disability
G132V	Intellectual disability
R207W	Global developmental delays, hypotonia, intellectual disability, and language apraxia
G253R	Mild intellectual disability and language delay
N331K	Speech delay, seizures, and hyperactivity
C337W	Intellectual disability
G356V	Epilepsy and mild intellectual disability
G381R	Intellectual disability, seizures, speech, and behavioral disturbance, hypotonia, and gastrointestinal problems
P382L	Severe intellectual disability, speech delay, behavioral problems, and epilepsy
P390L	Intellectual disability, learning difficulties, seizures, hyperactive and impulsive behavior
R391W	Seizures, hyperactivity, aggressiveness, and hyperphagia
T394K	Intellectual disabilities, severe developmental delay and speech impairment, seizures, and mild scale autism
A404P	Mild psychomotor retardation and language impairments
G424D	Speech and language delay, learning difficulties, mild autistic features, social anxiety and attention deficit, aggressiveness, impulsiveness, and hyperactivity
G466R	Developmental delay, dystonia, no speech, and epilepsy
D474G	Mild intellectual disability and occasional febrile seizures
C491W	Generalized tonic-clonic seizures
M510K	Moderate intellectual disability, antiepileptic drug-responsive seizures, hypotonia, and dysarthria
P544L	Moderate intellectual disability, generalized hypotonia, delayed language, and speech skills, and multifocal epileptic waves
P554L	Intellectual disability, hypotonia, intellectual disability, severe speech delay, seizures, autism, and epilepsy
G561A	Intellectual disability
F315del	Intellectual disability, epilepsy, autism, and speech delay
N336del	Intellectual disability, seizures, and motor dyspraxia
1347del	Moderate intellectual disability, aggressive behavior, and seizures
F354del	Intellectual disability
F360del	Intellectual disability, epilepsy, autism, and speech delay
F408del	Intellectual disability, epilepsy, autism, seizure, speech and language delay and a reduced interest in the surroundings

Figure 1 Linford Christie (born 1960), former British athlete, 100 meters 1982 Barcelona's Olympic gold medal and recordist.

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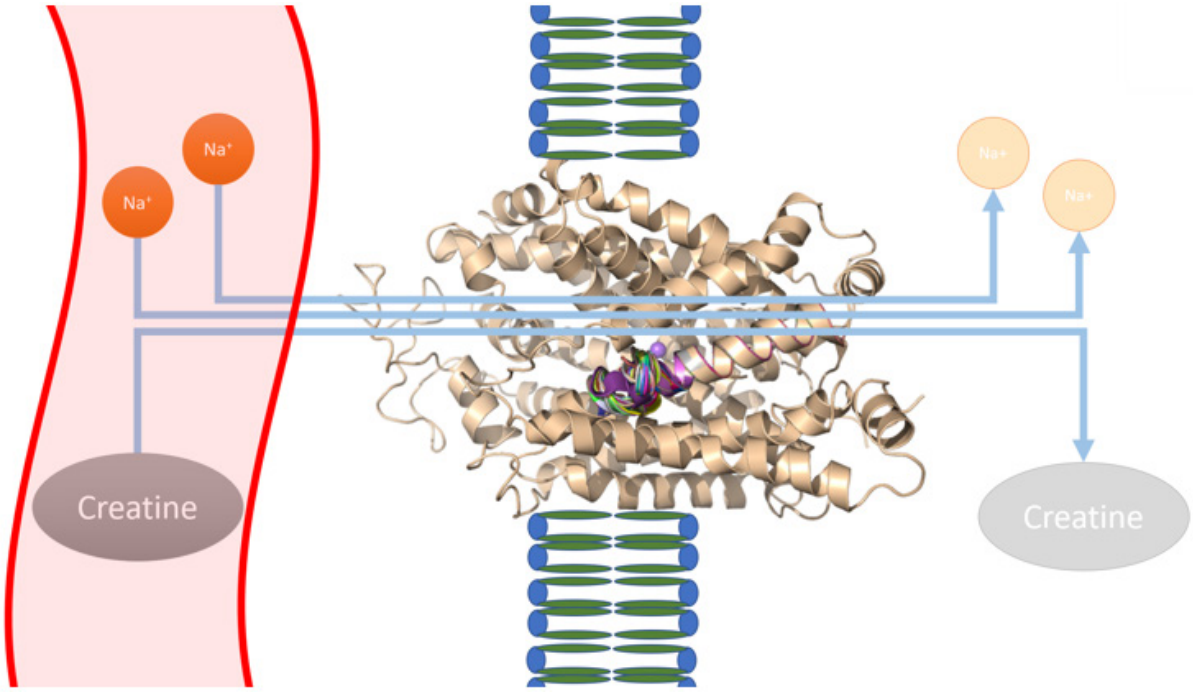

Figure 2 Creatine transport. In the center of the image, it is possible to observe the molecular structure of CrT and the sarcolemma; on the left, the bloodstream (wavy red image) carries the sodium ion (orange circular image) and creatine (gray elliptical image); the blue arrows represent the transport path; on the right, the cytosol of the cardiomyocyte is represented. Colors and proportions are for illustrative purposes only.[3,9,14]

In addition to the cases of vegetarians and vegans, murines carrying the disease linked to the X chromosome carry out similar mechanisms, however, the evidence in humans is still insufficient.

It is important to emphasize that creatine is available in various formulations such as creatine monohydrate, creatine–pyruvate, creatine–citrate, creatine–malate, creatine–taurinate, creatine–phosphate, creatine–orotate, creatine–ethyl ester, creatine–pyroglutamate, creatine–gluconate, and magnesium–creatine chelate.[21] However, the overwhelming majority of scientific studies use creatine monohydrate, in addition, comparative clinical trials reinforce that creatine monohydrate is the most efficient means of supplementation for ingestion, absorption, half–life, and health safety.

Regarding the safety of creatine supplementation for health, several randomized clinical trials were carried out and demonstrated that, regardless of the age group and gender of the patient, there are no significant side effects.[1,22-25] Recently, studies with pregnant women[25,26] and patients with chronic kidney disease have benefited from this supplementation without showing deleterious health effects.[27] There are rare (<5%) reported cases of cramping and gastrointestinal discomfort (usually appearing at doses above 20 g/day). Thus, when prescribed correctly, within the parameters of individual needs, and by trained professionals, evidence shows that creatine is safe for health.[1,28]

With the progress of scientific research on creatine, new study hypotheses were opened, including the use of creatine precursors and metabolites. Guanidinoacetic acid (GAA) and Betaine (N–trimethylglycine) have been the most successful cases of applications with promising outcomes.

GAA is a precursor of creatine synthesis that has been very successful in the treatment of metabolic diseases such as inborn errors in the production of the enzyme AGAT and renal failure. Studies that began in the 1950s showed positive effects of GAA in patients with decompensated heart failure, anxiety (which increases sympathetic activity, overloading the cardiovascular system), and depression.[29,30]

Animal studies have shown slight increases in homocysteine, which is proposed as a risk factor for cardiovascular disease. However, the studies were not able to demonstrate the appearance of atherosclerosis or other cardiovascular impairments. More animal and human studies need to be performed to verify the safety of GAA for the heart and arteries. In time, a few human studies did not show significant differences in homocysteine levels, but it is important to emphasize that homocysteine assessment was not a primary outcome of these studies.[31,32]

Betaine (N–trimethylglycine) is another creatine precursor that has been studied more recently. Betaine degradation functions as a transmethylator of homocysteine into methionine (giving up its methyl group). In this way, it fulfills 3 functions: reduction of homocysteine, an increase of methionine for protein synthesis, and production of SAM (S–adenosylmethionine) which is a universal donor of methyl groups for several metabolic functions contributing to homeostasis. At least 10 studies to date[33-42] have shown cardiovascular benefits in betaine supplemented compared to controls.

Interest in studies on betaine supplementation arose from findings on the correlation of betaine deficiency in patients who suffered acute myocardial infarction, heart failure, and secondary acute myocardial infarction. Another study also showed low betaine levels correlated with elevated homocysteine levels and other risk factors for heart failure.[43,44]

Betaine supplementation has also been negatively correlated with levels of atherogenic lipids and lipoproteins, in addition to reducing the area of atherosclerotic lesions and reducing the production of aortic TNF–alpha.[45,46]

A more current outcome of interest regarding creatine and precursor supplementation is its antioxidant effect on cardiomyocyte mitochondria. Several studies have shown a direct relationship between the concentration of creatine and the concentration of ROS (reactive oxygen species). the reduction of oxidative stress in cardiomyocytes is efficient in preventing ischemic outcomes in the myocardium.[47]

Elevated heart rate, stroke volume, and sympathetic action associated with exercise and stress increase ROS production. Recent findings show that creatine supplementation induces overexpression of the mitochondrial creatine kinase gene, which acts to maintain the ATP/ADP rate at normal levels in hypertensive patients, with a reduction in ROS production, preventing heart attacks and other vascular accidents.[46,48]

Evidence of control effects on oxidative stress induced by GAA supplementation is incipient, but there is physiological plausibility to speculate that increases in GAA concentration induce the expression of SOD (superoxide dismutase), which turns out to be one of the most important antioxidant agents, future research will demonstrate whether the outcomes will be as expected.[49,50]

Conclusion

The present essay showed the evidence and expectations of the use of creatine supplements and precursors in several outcomes related to the prevention and treatment of cardiovascular diseases. Some of these outcomes are already useful as adjuvants in treatment and prevention, others still lack evidence despite the results in animals and the physiological plausibilities that allow responsible speculation so that future tests will demonstrate (or not) empirical evidence that allows a better prognosis for cardiac patients.

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