SPORT SUPPLEMENTATION: BENEFICIAL EFFECTS OF VITAMIN E AND CREATINE ON EXERCISE PERFORMANCE

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Abstract. Most athletes use food supplements to obtain a well-trained, athletic, and healthy looking body. Supplementation practices vary between sports and individual athletes. Many athletes take food additives, containing vitamin E and food additives with creatine because of their favorable effects on muscle mass. Vitamin E deficiency leads to serious damage to the body, especially the muscles. Antioxidant supplementation with Vitamin E is likely to provide beneficial effects against exercise-induced oxidative tissue damage. Many studies have examined the effects of creatine supplementation on exercise performance. This article reviews the literature on vitamin E and creatine supplementation in sport and shows their beneficial effect on exercise performance.

Key words: Vitamin E, creatine, sport, food supplements.

Introduction
I. Vitamin E: function and metabolism.

Vitamin E is a term that encompasses a group of potent, lipid-soluble, chain-breaking antioxidants. Structural analyses have revealed that molecules having vitamin E antioxidant activity include four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ) (Fig. 1.). The most abundant form in nature is α-tocopherol, which has the highest biological activity based on fetal resorption assays, and reverses vitamin E deficiency symptoms in humans. The molecular functions fulfilled specifically by α-tocopherol have yet to be fully described, but it is unlikely they are limited to general antioxidant functions [1].

In 1922 Evans and Bishop discovered vitamin E – a micronutrient essential for reproduction in rats. It was rediscovered in the 1950 as factor 2 by Klaus Schwarz and placed in the context of cellular antioxidant systems, together with sulfur amino acids (factor 1) and selenium (factor 3). Vitamin E subsequently has proved to be effective in preventing lipid peroxidation and other radical-driven oxidative events. Vitamin E prevents loss of spermatogenesis in males and the failure to retain zygotes in female rats [1].

The antioxidant activity of vitamin E has persuaded many groups to study its ability to prevent chronic diseases especially those believed to have an oxidative stress component such as cardiovascular diseases and atherosclerosis. Epidemiological studies have reported that high vitamin E intakes are correlated with a reduced risk of cardiovascular diseases [2, 3]. Vitamin E is essential for proper functioning of muscles. In humans severe vitamin E deficiency leads to neuromuscular abnormalities characterized by spino-cerebellar ataxia [4, 5, 6].

Vitamin E is important for normal neurological function in man. This is proved by the following data:

1) the neuropathological changes observed in vitamin-E-deficient states in man (such as abetalipoproteinemia, chronic liver disease and cystic fibrosis) are similar to those reported in vitamin-E-deficient rats and monkeys; 2) in abetalipoproteinemia early therapy with vitamin E delays and may prevent the development of neurological complications, and in patients with established lesions treatment can arrest or reverse the neuropathy; 3) neurological manifestations can be improved by vitamin E in other chronic disorders of fat absorption with severe vitamin E deficiency [7].
II. Vitamin E supplementation in sport.

Physical exercise may be associated with a 10- to 20-fold increase in whole body oxygen uptake. During exercise oxygen flux in the active peripheral skeletal muscle fibres may increase by as much as 100- to 200-fold. Studies from the past 2 decades suggest that strenuous exercise lead to oxidative stress because the generation of reactive oxygen species (ROS) is elevated to a level that overwhelms tissue antioxidant defense systems. The magnitude of the stress depends on the ability of the tissues to detoxify ROS. Antioxidants produced by the body and dietary taken exogenous antioxidants protect against reactive oxygen and nitrogen species. Antioxidant supplementation provide beneficial effects against exercise-induced oxidative tissue damage [8]. A great number of human studies have shown that supplementation with antioxidant vitamins has favorable effects on the process of lipid peroxidation [9].

Rokitzki et al. have made a very interesting study to evaluate the effects of 5 months of alpha-tocopherol supplementation on physical performance during aerobic exercise training in 30 top-class cyclists. Plasma α-tocopherol concentration is increased significantly in the vitamin E-supplemented group, whereas the placebo group shows a trend toward decrease. Physical performance did not improve in the α-tocopherol-supplemented group compared to the placebo group. Heart rates were also not significantly different. The findings indicate a protective effect of α-tocopherol supplementation against oxidative stress induced by strenuous exercise [10].

Tsakiris et al. have investigated Paraoxonase 1/arylesterase (PON 1/Aryl) activities in basketball players with or without Vitamin E supplementation pre- and post-training. Vitamin E (α-tocopherol) reduces lipid peroxidation. Paraoxonase 1/arylesterase activities are closely related to oxidation and athrogenesis. In this study blood is obtained from 10 players pre- (group A), post-exercise (group B) and after 1 month on Vitamin E (200 mg/24 h/orally) supplementation pre- (group C) and post-exercise (group D). Lactate, pyruvate, muscle enzyme activities, creatine kinase, lactate dehydrogenase and total antioxidant status are measured with commercial kits. Catecholamines and Vitamin E are determined with high-performance liquid chromatography methods and PON 1/Aryl activities – spectrophotometrically.
The obtained results show that lactate, pyruvate, muscle enzyme activities and catecholamines are increased in all groups post-training. Total antioxidant status is decreased in all the groups post-training. PON 1/Aryl activities are significantly decreased post-exercise (group B) (PON1: 65 U/ml, Aryl: 58 U/ml) as compared to those pre-exercise (group A) (PON1: 142 U/ml, Aryl: 114 U min/ml). It is concluded that Vitamin E supplementation may result in protection of the enzyme PON 1/Aryl activities from free radical production [9].

III. Vitamin E Deficiency.

Vitamin E has been shown to be required by a large number of species of animals and people. The most common deficiency signs are reproductive difficulties and degeneration of the skeletal muscle. The latter condition, referred to as nutritional muscular dystrophy [1]. In humans vitamin E deficiency can be caused by: genetic abnormalities, chronic liver disease, fat malabsorption [11] or abetalipoproteinemia [12]. Patients with familial isolated vitamin E deficiency, an inborn genetic defect in the gene for the α-tocopherol transfer protein, have dramatically reduced plasma vitamin E levels and neurological disorders characteristic of vitamin E deficiency such as cerebellar ataxia, dysarthria, absence of deep tendon reflexes, vibratory and proprioceptive sensory loss, positive Babinski sign [1] and retinitis pigmentosa due to free radical mediated neuronal damage. The deficiency symptoms can be ameliorated when these patients are given doses of vitamin E of up to 2000 mg per day [12].

It is described that after from 6 to 13 months treatment with a purified diet without vitamin E, monkeys develop acute vitamin E deficiency, characterized with the following signs: slowness of movement, loss of muscle tissue, difficulty in breathing, muscular dystrophy, elevated urinary excretion of creatine, allantoin and free amino acids, decreased urinary excretion of creatinine, anemia and granulocytosis. All these signs are reversed by treatment with α-tocopherol. The physical signs of vitamin E deficiency, muscular dystrophy are observed after from 167 to 391 days of treatment. The influence of vitamin E therapy on the excretion of creatine, allantoin and free amino acids by an initially dystrophic monkey is illustrated in Fig. 2. [13].

The hemogram of vitamin E-deficient monkeys is given in Table 1. The vitamin E-deficient monkeys exhibited granulocytosis and in most cases a lymphopenia [13].

<table>
<thead>
<tr>
<th>Vitamin deficiency</th>
<th>Monkey No</th>
<th>Erythrocytes</th>
<th>Hemoglobin</th>
<th>Hemato-crit value</th>
<th>Neurophils</th>
<th>Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>millions/μl</td>
<td>gm/100 ml</td>
<td>per cent</td>
<td>thousands/μl</td>
<td>thousands/μl</td>
</tr>
<tr>
<td>None</td>
<td>1-89</td>
<td>4.8 ± 0.2*</td>
<td>15.5 ± 0.4</td>
<td>44 ± 2*</td>
<td>4.7 ± 0.5</td>
<td>10.7 ± 1.2</td>
</tr>
<tr>
<td>&quot;</td>
<td>1-94</td>
<td>2.9</td>
<td>6.4</td>
<td>30</td>
<td>25.7</td>
<td>1.1</td>
</tr>
<tr>
<td>&quot;</td>
<td>1-91</td>
<td>1.6</td>
<td>4.0</td>
<td>15</td>
<td>6.0</td>
<td>4.4</td>
</tr>
<tr>
<td>&quot;</td>
<td>1-97</td>
<td>3.3</td>
<td>9.2</td>
<td>32</td>
<td>11.7</td>
<td>3.6</td>
</tr>
<tr>
<td>&quot;</td>
<td></td>
<td>0.7</td>
<td>2.9</td>
<td>12</td>
<td>42.8</td>
<td>11.9</td>
</tr>
<tr>
<td>E and B&lt;sub&gt;6&lt;/sub&gt;</td>
<td>1-85</td>
<td>2.6</td>
<td>8.1</td>
<td>28</td>
<td>10.7</td>
<td>4.2</td>
</tr>
<tr>
<td>&quot;</td>
<td>1-86</td>
<td>3.2</td>
<td>9.5</td>
<td>34</td>
<td>18.6</td>
<td>3.8</td>
</tr>
<tr>
<td>&quot;</td>
<td>1-81</td>
<td>2.5</td>
<td>6.7</td>
<td>26</td>
<td>20.0</td>
<td>1.6</td>
</tr>
<tr>
<td>&quot;</td>
<td>1-88</td>
<td>3.4</td>
<td>9.0</td>
<td>31</td>
<td>18.0</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Fig. 2. The effect of α-tocopherol on the excretion of urinary nitrogenous constituents [13].
Creatinuria associated with vitamin E deficiency may arise either as a result of an impaired retention of creatine by muscle or as a result of an imbalance between extramuscular creatine synthesis and creatine uptake by muscle. In rats maintained on a vitamin E-deficient diet for 20 weeks a creatinuria is observed. In experiments creatine-2-C14 is injected intraperitoneally into normal, vitamin E-deficient and previously deficient rats treated with α-tocopheryl acetate. Creatine is isolated after various time intervals from different skeletal muscles, heart, brain, kidney, liver, blood serum, erythrocytes, retroperitoneal fat, urine, and its specific activity and quantity are determined. In vitamin E-deficient rats an increase in the ratio of specific activities of “free” creatine to muscle creatine is observed. After treatment with α-tocopheryl acetate this ratio returned to normal values [14].

Supplementation with vitamin E may antagonize vitamin K in healthy adults. Regular consumption of more than 1000 mg (1500 IU) of tocopherols per day may be expected to cause hypervitaminosis E, with an associated risk of vitamin K deficiency and consequently of bleeding problems [15].

IV. Importance of Creatine.
Sports and physical activity are very important for the complex therapy of diabetes [16] and dysfunction of neuro-muscle systems [17,18] and for prevention of osteoporosis in women [19] and of obesity among children and adolescents [20]. Creatine (Fig. 3.) is the object of growing interest in the scientific literature. This is because of the widespread use of creatine by athletes, on the one hand, and to some promising results regarding its therapeutic potential in neuromuscular disease on the other. Creatine was discovered in 1835 by the French scientist Chevreul, and named after the Greek word kreas (flesh). The first creatine supplementation studies in animals and humans began in the early 1900 [21]. Because of the widespread use of creatine by athletes, promising results with regard to the clinical therapeutic potential of creatine in neuromuscular, neurological [22] and cardiovascular diseases, and the effects of creatine analogues as anticancer agents, interest in creatine supplementation has grown exponentially over recent years, mainly...
with respect to using the compound as an ergogenic aid. It seems therefore opportunity to review the ergogenic use of creatine [21].

Creatine is a nitrogenous amino acid compound with a net positive charge and a molecular weight of 131 Da [21]. Arginine is often applied in multisupplements [23] like Tonotyl® [24], because is precursor of nitric oxide [25] and is involved in metabolic pathways, such as protein degradation and synthesis of creatine [23].

The endogenous synthesis of creatine (Fig. 4.) involves three amino acids: glycine, arginine and methionine [26]. In the kidney L-arginine-glycine amidinotransferase catalyses the reaction of the transfer of the amidino group of arginine to glycine to yield L-ornithine and guanidinoacetate. In the hepatocyte, a methyl group from S-adenosyl-L-methionine is transferred to the nitrogen atom by S-adenosyl-L-methionine-N-guanidinoacetate methyltransferase, yielding creatine and S-adenosyl-L-homocysteine [21].

The daily demand for creatine is met both by intestinal absorption of dietary creatine and by the novo creatine biosynthesis [21].

**V. Creatine in sport supplementation.**

From the bloodstream creatine is taken up from specific transporters: creatine transporter 1 (CRT1) and choline transporter 1 (CHOT1) [21]. CRT1 is expressed in cardiac and skeletal muscle, brain, kidney and placenta [27] and belongs to the superfamily of Na\(^+\) and Cl\(^-\) dependent neurotransmitter transporters [28]. In muscle cells creatine is phosphorylated by creatinekinase to form phosphocreatine within 25 min. upon arrival (Fig. 5.). ATP formed by glycolysis and oxidative phosphorylation reacts with creatine. All creatinekinase isoenzymes catalyse the reversible transfer of the γ-phosphate group of ATP to the guanidino group of creatine to yield ADP, phosphocreatine and H\(^+\). Large negative charges on phosphocreatine prevent diffusion across biological membranes thus locking phosphocreatine in the muscle cell. During exercise, when muscle ATP is being consumed, the high-energy phosphoryl group of phosphocreatine is transferred to ADP to restore ATP. Creatine is then recycled or transformed to creatinine, which cannot be reutilised and is excreted in the urine. Phosphocreatine (at a rate of 2.6 %) and creatine (at a rate of 1-2 %) are degraded daily to creatinine by spontaneous non-enzymatic reactions [21].

Creatinine production totals 2 g/d based on a 70 kg men. The creatinine turnover is proportional to the muscle mass and increases with high-intensity physical exercise. Creatinine enters the circulation by diffusion and is eliminated from the body through glomerular filtration. Vegetarians have marginally lower urinary creatinine excretion rates than individuals on normal diets, suggesting that creatine biosynthesis rates and muscle creatine contents are also marginally lower than in individuals ingesting creatine containing diets. The daily demand for creatine is met...
both by intestinal absorption of dietary creatine (1-2 g) and by de novo creatine biosynthesis (1-2 g). Because muscle has virtually no creatine-synthesising capacity, creatine has to be taken up from the blood against a large concentration gradient by a saturable $[\text{Na}^+]$ and $[\text{Cl} –]$ dependent creatine transporter that spans the plasma membrane. Muscular creatine and phosphocreatine are nonenzymatically converted at an almost steady rate (~2% of total creatine per day) to creatinine, which diffuses out of the cells and is excreted by the kidneys into the urine [21].

Creatine is a legal substance consumed by athletes as an ergogenic aid, being the most widespread, effective and safe ergogenic aid in the world. Its use is extended to trained and untrained individuals, men and women, adolescent and elderly individuals. Creatine supplementation has been advocated to improve high-intensity exercise, intermittent high-intensity exercise, and even endurance exercise (mainly in non-weight-bearing endurance activities). There is no scientific evidence of any adverse effect following creatine supplementation in healthy individuals, even during long-term administration. In Table 2. and Table 3. are summarized some studies about creatine supplementation and benefits in sport.

The researchers show that the benefits from the use of creatine in sports are undeniable. The athletes who practice bodybuilding appreciate creatine supplementation. It has often been reported that short-term creatine ingestion is accompanied by a 1-2 % increase in body mass [29,34].

Some side effects of creatine supplementation have been described. The Mayo Clinic states that creatine has been associated with asthmatic symptoms and warns against consumption by persons with known allergies to creatine. A 2009 systematic review discredited concerns that creatine supplementation could affect hydration status and heat tolerance and lead to muscle cramping and diarrhea [35]. Recent reports suggest that creatine may enhance performance in hot and humid conditions by maintaining haematocrit, aiding thermoregulation and reducing exercising heart rate. Compound may positively influence plasma volume during the dehydration [36]. Although studies have shown little or no adverse impact on kidney or liver function from oral creatine supplementation, there are reports that liver function may be altered and kidney damage such as interstitial nephritis may occur [37]. In 2004 the European Food Safety Authority (EFSA) published a record which stated that oral long-term intake of 3 g pure creatine daily is risk-free. In a study in 2003 on athletes, taking creatine for 21 months, is proved that no significant changes in markers of renal function are found [38]. After application on athletes of creatine for 3 months no evidences of kidney damage are observed [39]. Long-term administration of large quantities of creatine (20 g/daily) is reported to increase the production of formaldehyde (Fig. 6.) [21], which has the potential to cause serious unwanted side effects. Methylamine is transformed to formaldehyde and hydrogen peroxide by semicarba-

<table>
<thead>
<tr>
<th>Purpose of study 1 [29]</th>
<th>To examine the effect of creatine supplementation in conjunction with resistance training on physiological adaptations including muscle fiber hypertrophy and muscle creatine accumulation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Nineteen healthy resistance-trained men are treated with creatine capsules (25 g daily) for 1 week followed by a maintenance dose (5 g daily) for the remainder of the training.</td>
</tr>
<tr>
<td>Results</td>
<td>After 12 week creatine supplementation significantly increases the body mass and fat-free mass, enhances physical performance and muscle morphology in response to heavy resistance training, mediated via higher quality training sessions.</td>
</tr>
<tr>
<td>Purpose of study 2 [30]</td>
<td>To evaluate the effects of 3, 5 or 7 days of creatine loading (at 20 g daily) on strength gains and body composition during resistance training.</td>
</tr>
<tr>
<td>Design</td>
<td>Twenty men, age 19-22 years, randomized to creatine or placebo group (n = 10).</td>
</tr>
<tr>
<td>Results</td>
<td>It is demonstrated a benefit between baseline and 3 days creatine supplementation for bench press strength, back squat strength, arm curl strength and standing long jump distance. Creatine shows a benefit between baseline and 5 days creatine supplementation for 45 m sprint time.</td>
</tr>
</tbody>
</table>
zide-sensitive amine oxidase. This risk is largely theoretical because urinary excretion of formaldehyde, even under heavy creatine supplementation, does not exceed normal limits [40].

Even the few reported cases with side effects of creatine supplementation, this is the one of the most safe supplement used in sport. There is no scientific evidence of any adverse effect following creatine supplementation in healthy individuals, even during long-term administration. Nevertheless, renal and liver monitoring must be performed in individuals with previous pathology in these organs [21].

Conclusion.

Many athletes use supplements to improve their performance. One of the safest additives include vitamin E and creatine. Both individually and in combination they contribute to better working muscles, increase endurance and shorten recovery time. During training the muscles are exposed to extreme oxidative stress, this is of utmost importance to athletes take daily vitamin E. The combination of vitamin E and creatine will contribute to better health of athletes and better sporting achievements.

Table 3. Researches about supplementation with creatine.

<table>
<thead>
<tr>
<th>Purpose of study 3 [31]</th>
<th>To determine whether oral creatine loading could enhance single and repeated short sprint performance.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>After treatment of athletes with 5 g of creatine 4 times daily for 5 days before repeating the cycle sprint tests is recorded significantly greater scores in total work (kJ) completed over the 6 sprints.</td>
</tr>
<tr>
<td>Results</td>
<td>Creatine supplementation can enhance both single and repeated short sprint performance.</td>
</tr>
<tr>
<td>Purpose of study 4 [32]</td>
<td>To investigate the alterations in creatine and creatinine concentrations following lower dosages.</td>
</tr>
<tr>
<td>Design</td>
<td>The athletes ingested 6 g of creatine 2 times daily for 5 days.</td>
</tr>
<tr>
<td>Results</td>
<td>Creatine supplementation is found to have no influence on the cardiovascular system, oxygen uptake and blood lactate concentration. The fall in blood glucose during the exercise test was significantly reduced after consumption of creatine. Interval power performance is significantly increased by 18 %.</td>
</tr>
<tr>
<td>Purpose of study 5 [33]</td>
<td>To evaluate the effects creatine supplementation on muscle strength and weightlifting performance.</td>
</tr>
<tr>
<td>Design</td>
<td>22 studies are reviewed.</td>
</tr>
<tr>
<td>Results</td>
<td>Creatine supplementation during resistance training is more effective at increasing muscle strength (8 %) and weightlifting performance (14 %) than resistance training alone.</td>
</tr>
</tbody>
</table>

References


19. Каснакова П, Чаушев Г, Блажев Д. Възможности на спорта и физическата активност за профилактика на остеопорозата при жени на работното място в Медицински колеж към Медицински университет – Пло...


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