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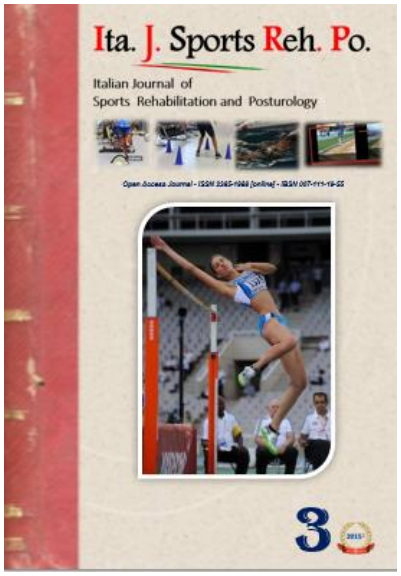

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Progress in the field of tissue engineering in the past decade has allowed the development of new types of treatment also in the Sports Traumatology sector. These new treatments include the use of growth factors and stem cells. It has now been widely shown that the growth factors contained in the PRP (platelet rich plasma) obtained through centrifugation of autologous blood, applied onto the site of tissue damage, give rise to the activation and acceleration of the tissue healing physiological processes. We are using this technique in the treatment of lesions of the shoulder rotator cuff, in subcutaneous lesions of the Achilles tendon and we are also experimenting the use of this membrane in the reconstruction of the anterior cruciate ligament with artificial ligament. As far as stem cells are concerned, their use is limited almost exclusively to the treatment of cartilaginous lesions. Adult mesenchymal stem cells are obtained by aspiration of bone marrow during surgery. There are numerous sites from which it is appropriate to remove the bone marrow, but usually the iliac crest is chosen, by aspiration with a suitable device. Following removal , the stem cells are placed on a hyaluronic acid scaffold and applied onto the site of cartilaginous lesion. The cells obtained from the bone marrow can thus constitute a valid alternative in the treatment of chondral lesions smaller than 2 centimeters. To conclude, tissue engineering and gene therapy currently enjoy a considerable appeal in the scientific community and will certainly represent the future. In our experience, we are highly motivated to pursue research and experimentation in this fascinating field, while bearing in mind the potential risks associated with this type of engineering

Prof . Enrico Castellacci
Emeritus Editor Ita J. Sports Reh. Po.
Head of the Medical Staff Italian National Football Team – Italy

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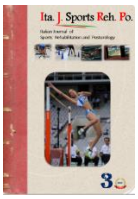

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Evaluative Analysis of Citrulline Supplementation Among Athletic Populations

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Abstract

The fundamental purpose of this article is to chronicle the endogenous mechanisms which drive the conversion of citrulline into nitric oxide and examinethe efficacy and applicability of citrulline supplementation among healthy and compromised populations. Citrulline, anantecedent of the conditionally essential amino acidarginine, has grown increasingly popular among athletic populations and bodybuildersin recent years for its ostensiblepossession of ergogenic andanabolic capacities. The purported benefits of citrulline supplementation and associated clinical applications will beintroduced and subsequently examined through an unbiased review of existing scientific literature.

Key words : Citrulline, Sports supplementation, Sports nutrition, Amino acids

Introduction

An endogenous constituent of the conditionally essential amino acid, arginine, citrulline was initially extracted and isolated from watermelon rind and subsequently identified as an integral catalyst in the urea cycle, the pathway by which ammonia is excreted from the body. Citrulline is also secreted from the upper and middle regions of the intestinal villi and proximal small bowel where it is synthesized from glutamine (12) through a cascade of enzymatic activity and later converted to arginine within the endothelial cells contained within the lumen of the gastrointestinal tract. Citrulline is also converted to arginine via enzymatically enriched nephritic pathways. Arginine, which is composed of arginase and synthase enzymes, combines with nitrous oxide synthase and is oxidized to nitric oxide, a pneumatic chemical transmitter which is deeply rooted in multiple physiological and pathological processes and dually influences the function of the central and peripheral nervous systems through the intonation of neurotransmission, systemic perfusion, and immunological responses (11). Lauded by medical and sports science professionals for its robust vasodilatory characteristics, nitric oxide has been speculated to burgeon the delivery of oxygen and nutrients to active musculature, plausibly bolstering tolerance to physical activity and staging enhanced recovery (21).

Citrulline Metabolism

Preliminary research suggests that citrulline bypasses splanchnic extraction, thereby amplifying its bioavailability and resultant effect on muscle protein synthesis and endogenous nitrogen balance (7,8,20). Nutritional intake accounts for trace quantities of citrulline, unless watermelon, and more specifically, the protective rind which encases the fruit, is regularly consumed.

Since citrulline does not enter hepatic metabolic pathways and is capable of surviving within the intestine, from where it originates, consumption of watermelon rind and exogenous citrulline supplementation may warrant consideration in the treatment of conditions, of which the end product of arginine oxidation, nitric oxide, is intimately involved. In states of prolonged physiologic stress, nitric oxide synthase activity increases, however, if this activity is nullified by compromised endothelial functioning and heightened oxidative stress, the synthase will uncouple and shift from nitric oxide generation to the production of nitrites which render widespread cellular damage and toxicity (31). Knowing that citrulline is readily converted to arginine, which is comprised of enzymes specific to the creation of nitric oxide, citrulline supplementation has been theorized as a possible antidote in the management of acute respiratory distress syndrome and sepsis (9).

Clinical Application

Citrulline administration has demonstrated discernible improvements among individuals suffering from a continuum of ailments and medical conditions. Six weeks of watermelon extract supplementation containing a 6g blend of citrulline and arginine elicited a collective reduction in

systolic and diastolic blood pressure at brachial and ankle landmarks and conjoining carotid wave reflection amid prehypertensive and stage 1 hypertensive adults (10). A daily dose of 3g of citrulline taken by thirty-five stabilized heart failure patients for four months, increased resting and peri-exercise left ventricular ejection fraction by 20.3% and 12.7%, respectively (1). Citrulline supplementation may provide some value among obese pregnant women, as the level of asymmetric dimethylarginine (ADMA), a nitric oxide synthase uncoupling agent, and independent cardiovascular disease risk, is markedly elevated during obesity. Citrulline is thought to neutralize the inhibitory effects of ADMA, by prompting the conversion of citrulline into arginine, thus boosting the arginine to ADMA ratio, which is associated with improved vascular functioning. Powers and colleagues administered 3g of citrulline to healthy obese pregnant women at 16 weeks of gestation for three weeks, which resulted in improved vascular function, lower blood pressure, and improved arginine to ADMA ratio (23). The findings of this study affirm that of an earlier investigation conducted by Schwedhelm and colleagues who revealed a daily 3g dose of citrulline improved the arginine to ADMA ratio while reinforcing flow-mediated vasodilation, as well as nitrate and urinary cyclic guanosine clearance rates (24).
Citrulline levels may serve as a bioindicator of alimentary health and supplementation may be specified for individuals will malabsorption issues or following invasive procedures, which may include small bowel transplantation (5). As it relates to gut health, citrulline may attenuate the effects splanchnic hypoperfusion. Splanchnic hypoperfusion is characterized by inadequate blood flow often stemming from trauma, vascular disease, and shock, which corrodes the intestinal mucosal barrier and invites endotoxemia and systemic inflammation (29). Exhaustive and intensive physical activity also increases the susceptibility to splanchnic hypoperfusion.

Researchers attempted to replicate splanchnichypoperfusion via cycling protocols at submaximal workloadsin a randomized, double-blind crossover study while evaluating the effect of a 10g dose of citrulline consumed prior to exercise. In addition to elevated plasma citrulline and arginine levels, the onset of splanchnic hypoperfusion was prevented in the citrulline group. In earlier studies, citrulline administration was found to mitigate complications noted among endotoxemic subjects (13, 15, 26, 30). A purported mechanism is accelerating the shuttling of ammonia into the urea cycle where it is eliminated from the body (3, 18). It should also be noted that lower ammonia levels will limit the activation of phosphofructokinase (26), a rate-limiting enzyme which is heavily invested in the regulation of glycolytic pathways, and prevents oxidation of pyruvate to acetyl coenzyme-A, thus reducing the onset of fatigue. Since glycolytic functioning may be streamlined by citrulline supplementation, a consequent reduction in the manufacture of acidic metabolites may result.

Performance Benefits

Citrulline has gained traction in the sports nutrition, fitness, and performance training communities on the supposed premises that it is capable of enhancing muscle protein synthesis and work capacity. The capacity to increase serum arginine levels has been well documented in the literature (5,20), which cite its aptitude in elevating nitric oxide signaling even more efficiently than equivalently matched arginine. The bioavailability of exogenous arginine is diminished due to

hepatic clearance, whereas this process is averted completely by citrulline. Recent literature suggests that citrulline when coupled with arginine, is capable of elevating plasma arginine concentration and subsequent hastening the conversion to nitric oxide (19).
Citrulline supplementation has demonstrated a34% increase rate of oxidative phosphorylation (14, 22), the mechanism which accounts for the greatest amount of adenosine triphosphate produced in cellular respiration (2). Improvements were noted in isometric muscular contraction efficiency by reducing the oxidative and phosphagen energetic costs of contraction by 32% and 28% respectively (14). Although a single dosage of a citrulline at 1g and 6g consumed prior to exercise elicited no perceptible improvements in the number of repetitions performed, time to exhaustion, oxygen uptake, anaerobic threshold, or flow-mediated vasodilation (6), a dosage of 8g taken before repeated bouts of multiple lower-body resistance exercises performed to failure at 60% of 1 RM, demonstrated a significant difference in anaerobic work capacity, although no such differences were noted in blood lactate levels and heart rate between the citrulline and placebo groups (33). A randomized, counterbalanced, and double-blind study involving 14 resistance-trained male subjects, demonstrated significant improvements in chin-up, reverse chin-up, and push-up performance following one week citrulline supplementation dosed at 8g per day (32). A dose of 6g of citrulline consumed 2 hours prior to an extensive aerobic bout, consisting of a 137 km stage, elicited greater growth hormone levels, amino acid utilization, and nitrogen sparing effect versus the control group (25).

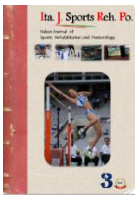
Citrulline supplementation evoked a concurrent improvement in number of repetitions performed and reduction in muscle soreness at the 24 and 48 hour marks following exercise (22). Watermelon juice containing 6g of citrulline consumed prior to exercise reduced recovery heart rates and alleviated delayed onset muscle soreness (27).
Citrulline may also tender anabolic effects by stimulating muscle protein synthesis by activating and regulating the mammalian target of rapamycin (mTOR) pathway (7, 8, 17) as arginine has demonstrated (28). In the presence of a low protein diet, additive citrullineenhanced protein synthesis by way of increasing arginine and ornithine plasma concentrations without any noticeable effect on endocrinological functioning (16). Further, citrulline supplementation may serve as a viable treatment strategy for men coping with mild erectile dysfunction as it is capable of directly prompting nitric oxide-mediated vasodilation and endothelial functioning sans involvement of the presystemic metabolism. A daily dose of 1.5g of citrulline per day administered for one month elicited improved scores in erection hardness and reported number of intercourses (4).

Evaluation of Ergogenicity and Anabolism and Practical Considerations

While it is convenient and tempting to extrapolate efficacy and multifaceted virtues based on the existing body of literature, there lies a comparative dearth of scientific data supporting citrulline supplementation for use among healthy, athletic populations. (Table 1) Citrulline, when combined with other amino acids, namely arginine and ornithine, and when embedded in proprietary pre workout blends,which are often composed of creatine and stimulants,may evoke a synergistic effect on nitric oxide production.

Table 1

Based on the presented literature, recommended dosage amounts and the intended purpose and accompanying benefit(s) are listed below:
• 1.5g per day: Treatment of mild erectile dysfunction
• 3g per day: Improved resting and peri-exercise left ventricular ejection fraction, enhanced visceral perfusion, lowered blood pressure, and elevated ammonia clearance rates, improved arginine to ADMA ratio
• 6g per day (including arginine): collective reduction in systolic and diastolic blood pressure at brachial and ankle landmarks and conjoining carotid wave reflection
• 6g prior to exercise: temperate improvements in aerobic and anaerobic work capacity
• 8g prior to exercise: moderate improvements in strength-endurance



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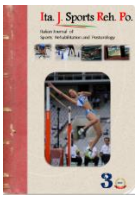

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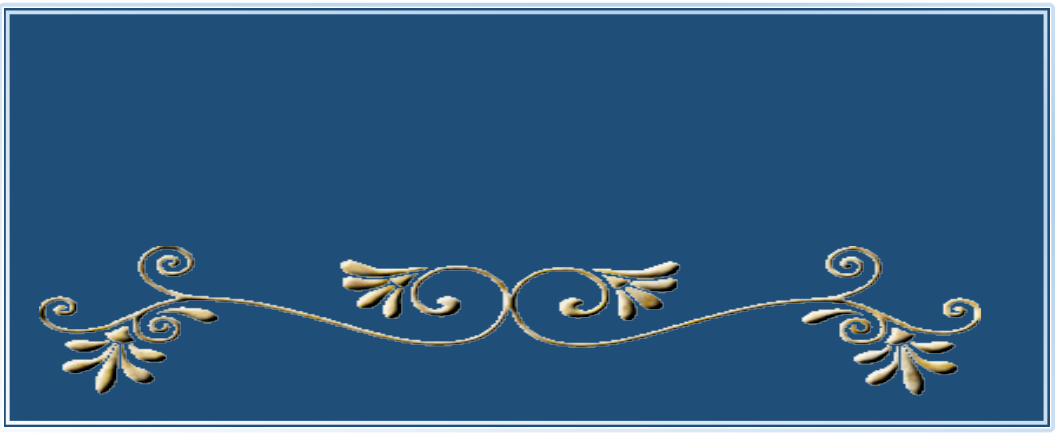

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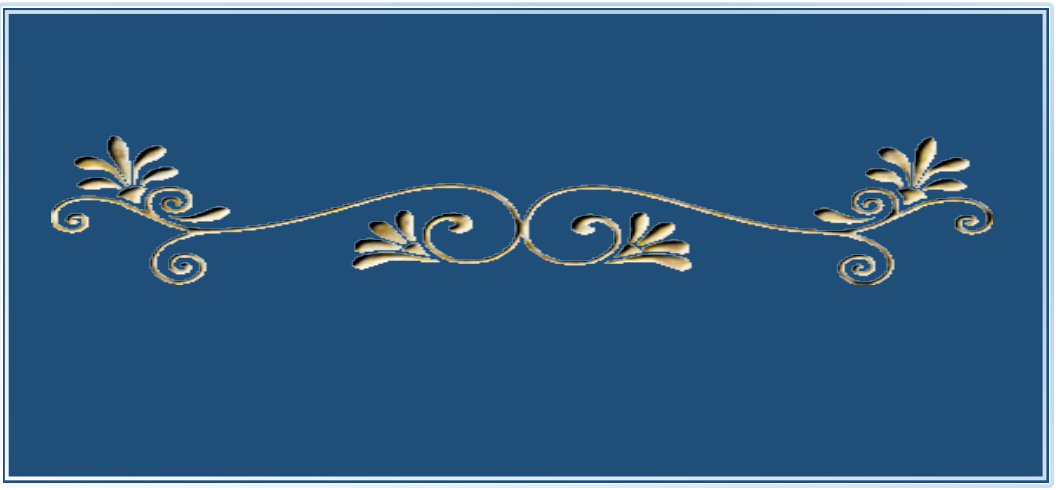

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