PERSPECTIVE

Perspective: Creatine, a Conditionally Essential Nutrient: Building the Case

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ABSTRACT

Creatine is a major component of energy metabolism that is abundant in human skeletal muscle, brain, and heart. Either synthesized internally or provided via an omnivorous diet, creatine is required for normal growth, development, and health. Recent advances in creatine nutrition and physiology suggest that the quantity of creatine the body naturally synthesizes is not sufficient to meet human needs. As a result, humans have to obtain enough creatine from the diet, which nominates creatine as an essential nutrient in certain circumstances. In this article, we summarize arguments that creatine should be considered a conditionally essential nutrient for humans and propose several questions that should be addressed in future research. *Adv Nutr* 2022;13:34–37.

Statement of Significance: The adequate provision of dietary creatine can be considered indispensable for optimal health and growth, as such we propose that creatine should be considered conditionally essential.

Keywords: creatine, food, meat, deficiency, growth, vegetarians

A classical definition describes an essential nutrient as a substance that provides structural or functional components to the human body and cannot be synthesized endogenously, and thus must be obtained from food sources. In fact, humans can produce several essential nutrients, but the amount that the body naturally synthesizes appears insufficient to meet the increased requirements in certain conditions, such as neonatal growth, catabolic stress, limited dietary intake, or specific diseases. Those nutrients are often called conditionally essential or indispensable, and the US National Academy of Medicine recognizes several conditionally essential nutrients, such as choline or arginine (1). In this opinion article, we summarize arguments that creatine, a nonproteinogenic amino acid derivative, should be considered a conditionally essential nutrient for humans, and propose several questions that should be addressed in future research.

Creatine (*N*-carbamimidoyl-*N*-methylglycine) is produced endogenously in the human liver, kidney, and pancreas, and is naturally present in animal-based foods. It mainly serves as a critical metabolic intermediary of energy transfer by facilitating the recycling of ATP, the source of energy for use and storage at the cellular level. Consequently, creatine is abundant in organs with high energy turnover, with ∼95% of the human body's creatine stores found in the skeletal muscle and the remaining 5% in the brain, liver, kidney, and testes (2). The average amount of total creatine stored in the body is ∼120 g, and the rate of creatine

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Perspective articles allow authors to take a position on a topic of current major importance or controversy in the field of nutrition. As such, these articles could include statements based on author opinions or point of view. Opinions expressed in Perspective articles are those of the author and are not attributable to the funder(s) or the sponsor(s) or the publisher, Editor, or Editorial Board of *Advances in Nutrition*. Individuals with different positions on the topic of a Perspective are invited to submit their comments in the form of a Perspectives article or in a Letter to the Editor.

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loss is estimated to be ~1.7% of the total body pool per day (3). To compensate for a daily loss, an average person needs ~2 g of creatine per day, with about half of this daily need (1 g) synthesized internally and the remaining amount being consumed from the diet (4). A traditional dogma of creatine turnover contends that de novo synthesis can adapt to meet all creatine needed; nevertheless, several circumstances suggest otherwise.

Plants contain virtually no creatine (5). Therefore, the individuals who eat only plant-based foods must acquire essentially all of their creatine via internal synthesis. Previous studies confirm that vegans who obtain no dietary creatine encounter an augmented creatine synthesis, but the creatine concentrations in the circulation and skeletal muscle remain lower than expected [for a detailed review, see (6)]. To restore creatine concentrations in the body, vegans and vegetarians need exogenously administered creatine, resulting in greater concentrations of creatine postsupplementation despite lower baseline concentrations (7). This means that creatine ought to be supplied from external sources to normalize its homeostatic balance, being an essential nutrient in this population. The question remains, how much creatine of the total net requirements could be covered by the endogenous synthesis in the best-case scenario. A rough calculation from feeding studies in broilers (8) suggests that ~ 2/3 of the daily creatine needs can be met without dietary sources at best, whereas the remaining 1/3 (e.g., 0.67 g for an average man) must be provided by the diet. That being said, a plant-exclusive eating pattern has an imminent risk of creatine deficiency if not complemented by exogenous creatine.

Besides vegetarians, food creatine appears indispensable in several health conditions with compromised or restrained internal production of this organic compound. For instance, children with creatine deficiency syndromes, a group of inherited metabolic disorders with impaired creatine synthesis and transport, depend exclusively on supplemental creatine to revive creatine stores [for a detailed review, see (9)]. Creatine should also be considered an essential nutrient in kidney conditions. Dialysis-dependent chronic kidney disease appears to damp down endogenous production of creatine and provokes unopposed losses of creatine into the dialysate (10), leading to a negative creatine balance that needs to be offset by dietary creatine. In a recent comprehensive review, Muccini and co-workers (11) suggested that children born preterm might be under an increased risk of inadequate creatine supply due to immature creatine synthetic machinery, thus being more reliant on external sources of creatine during early postnatal life. Interestingly, Kreider and Stout (12) suggest in their comprehensive review on creatine in health and disease, that similar neuromuscular features of creatine deficiency characterize the above conditions, and all respond fairly well to dietary creatine in experimental and clinical trials. How much creatine needs to be supplied depends on the degree of internal synthesis obstruction in each case; some conditions may entail covering the total net requirements (100%) by dietary creatine.

Another set of evidence suggesting that creatine is an essential nutrient emerges from recent population-based studies. It appears that the low dietary intake of creatine is associated with various unfavorable health outcomes in the general public, including the higher risk of depression in adults (13), reduced cognitive performance in the elderly (14), and shorter stature in children and adolescents (15). Individuals of all ages who do not consume enough creatine from a regular diet are thus under an increased risk of creatine deficiency; the net amount of creatine (including the quantity that the body naturally synthesizes) might not be sufficient to meet needs in these circumstances. Creatine deficiency is still a speculative entity with perplexing characterization and diagnosis, yet the shortage of creatine likely entails clinical attributes of low levels of energy output due to its role in energy metabolism (16). Creatine status is not routinely measured in healthy people, and the concentration in serum ranges from 0.2 to 0.6 mg/dL in men, and from 0.6 to 1.0 mg/dL in women (17). According to 1 study, serum creatine concentrations decline below 66% of reference values in individuals who follow a diet limited in creatine (18); this could be put forward as a possible set point for assessing inadequate creatine intake and status. Since low creatine intake might affect as much as 42.8% of the general population (19), a supposed population-wide creatine deficiency might require extensive nutritional interventions to compensate for creatine shortfall.

Still, several important issues remain to be addressed before bringing forward creatine as an indispensable nutrient. Before anything else, insufficient data are available to establish intake recommendations for creatine, with individual needs apparently influenced by life stage, gender, the amount of creatine in the diet, or capacity to produce or transport creatine endogenously. For instance, creatine is synthesized from L-arginine and glycine in a 2-step reaction that also requires methionine, and the amount of these amino acids in a diet may markedly affect the amount of creatine that a person needs (3). Second, no standard reference information is available for creatine content across various foods, and no component search for creatine is accessible through FoodData Central, an integrated data system with nutrient profile data (20); this is accompanied by deficient bioavailability data on different forms of dietary creatine (2). In addition, the figures for creatine intake and status in the general population were scarce, with creatine consumption usually estimated via proxy approaches (13). Finally, only limited information is available on health risks from excessive creatine intake in the general population, along with clinically relevant interactions with medications.

In conclusion, creatine has begun to be recognized as a nutritionally important amino acid derivative for the general population, and several aspects qualify creatine as an essential nutrient in human nutrition (**Figure 1**). Studies across various populations have shown that endogenous synthesis of creatine is not sufficient for humans under many physiological and pathological conditions, while the

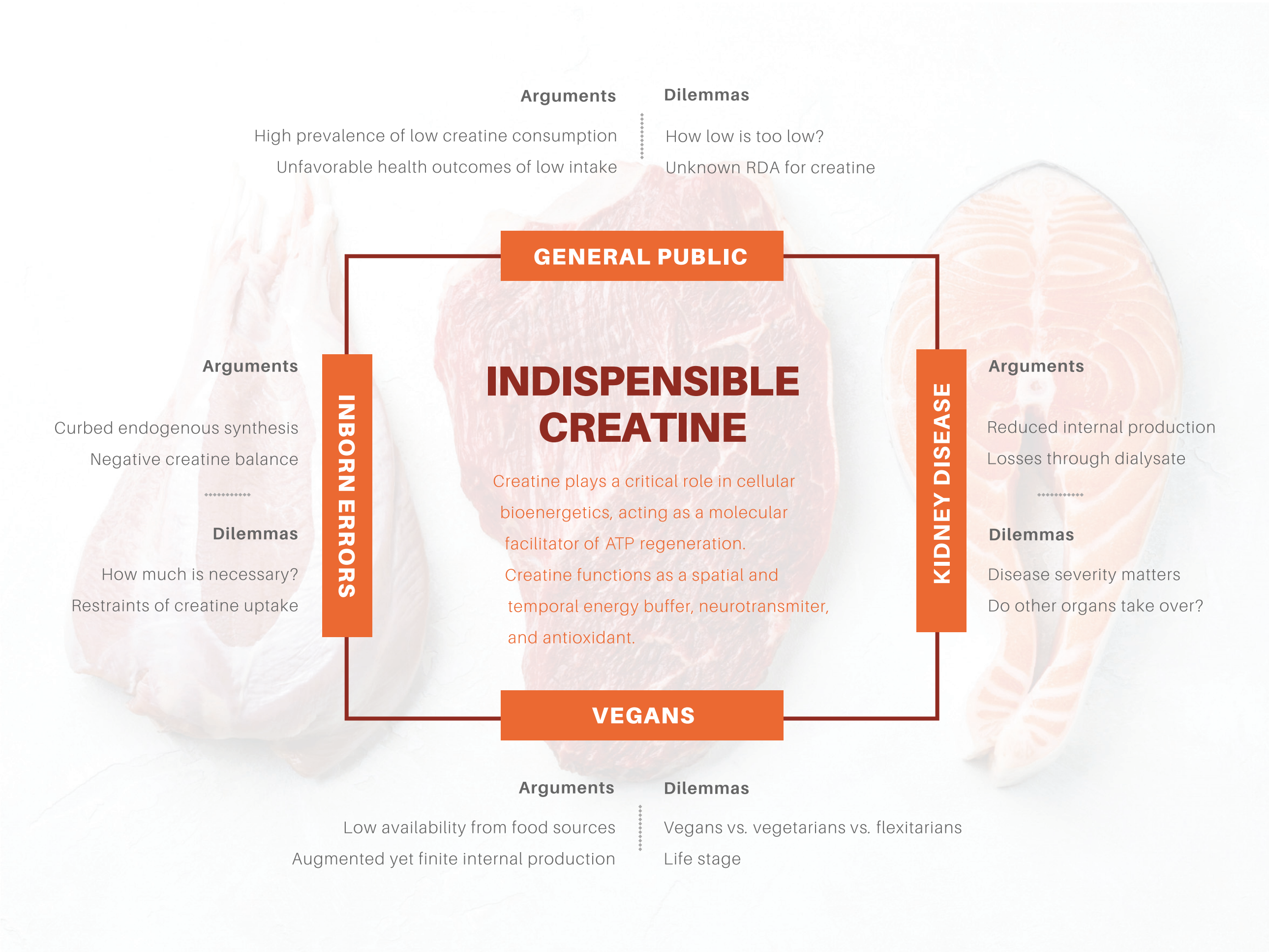

FIGURE 1 Creatine as an essential nutrient: arguments and dilemmas.

adequate provision of dietary creatine might be indispensable for maintaining optimal health and growth. To further build a case for creatine as an essential nutrient, the research community and public authorities should join forces to address open questions and set reference values for creatine intake for the general population.

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