

Applied nutritional investigation

The safety of oral use of L-glutamine in middle-aged and elderly individuals

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Abstract

Objective: To evaluate the safety of nutraceutical oral administration of L-glutamine (L-Gln) in middle-aged and elderly individuals.

Methods: In this randomized, crossover, double-blind clinical study, 30 residents of a long-term-care institution, selected according to a modified SENIEUR protocol (Working Party of the EURAGE Concerted Action Programme on Ageing of the European Community), were studied. Fourteen subjects received orally $0.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ of L-Gln and 16 received calcium caseinate for 14 d, followed by a 5-d washout. Supplements were switched for the second 14-d trial. Laboratory tests for hepatic and renal functions and ammonemia were performed and the estimated glomerular filtration rate (eGFR) was calculated.

Results: Of the 30 subjects, 16 were men, mean age was 69 ± 8.8 y, average weight was 61.8 ± 14.2 kg, and mean serum albumin was 4.0 ± 0.3 g/dL. Neither adverse clinical effects nor clinically significant laboratory changes were noted during L-Gln supplementation. There was no difference in ammonemia between the groups. There were statistically but not clinically significant increases in plasma urea nitrogen and creatinine concentrations. There was no significant decrease in eGFR during calcium caseinate supplementation (-2.9%). The eGFR decreased significantly after L-Gln supplementation (-13.3%) but well below the 25% limit for biologic significance.

Conclusion: Increases in serum urea nitrogen and creatinine and decrease in eGFR are probably due to difficulties by older kidneys in metabolizing the supplemented protein sources. Although not clinically significant, those alterations impose a rigorous control on the evaluation parameters of renal function during oral L-Gln supplementation, with doses of $0.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in middle-aged and elderly individuals. © 2010 Elsevier Inc. All rights reserved.

Keywords:

Glutamine; Elderly; Middle age; Safety

Introduction

Glutamine is the most abundant free amino acid in the human body, comprising about 20% of free amino acids in plasma and more than 50% of the amino acid pool in human skeletal muscle. It is not considered essential but a “conditionally essential” amino acid because its plasma concentration decreases by as much as 50% during stress, creating a deficiency condition [1–4]. In addition to multiple biochemical reactions, it participates in the maintenance

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and function of many organs and tissues such as the kidneys, liver, intestine, heart, muscle, neurons, lymphocytes, macrophages, neutrophils, pancreatic β -cells, and fat cells [1].

It is a link between the carbon metabolism of carbohydrates and proteins and an efficient precursor of glutathione, which works as an antioxidant in the enzymatic system composed of glutathione oxidase and reductase and in the non-enzymatic system [5–8].

The effect of glutamine supplementation in recovery from disease may come from its support to the intestinal mucosa or to the immune system, biosynthesis of glutathione, or a possible effect on the endogenous inflammatory response. These mechanisms are probably due to a decrease in the production of proinflammatory mediators and/or the regulation of inflammatory factors and glutamine's role in the release of insulin by the pancreas [1,9–11]. The benefits from glutamine supplementation in critically ill patients has been well established and described in the literature [3,12–14].

Sacks [4] in a review demonstrated good tolerance to glutamine without adverse effects except in specific patient groups such as those with renal disease and premature newborns. Questions remain, however, concerning the preferred route of administration, namely enteral, oral, or parenteral [3,4].

The oral/enteral use of glutamine in critically ill patients has not received much study because of the limitations of formulas in powder containing free L-glutamine (L-Gln), requiring reconstitution with water. Ready-to-use closed-system liquid enteral formulas are preferred and appear to be safer for use by severely ill patients. However, due to glutamine's instability to heat retorting, these latter diets do not contain free L-Gln [4,15,16]. The oral administration in healthy subjects has similarly been the object of only a few studies, but no adverse effects have been reported in young and middle-aged adults [8,9,17,18].

Aging is characterized by a decrease in the function of many systems and a reduction in the ability to adapt to stress and overloads [19]. In the elderly, in comparison with the young, there is a reduction in the therapeutic window and the probability of a therapeutic effect without side effects diminishes drastically [20].

Functional foods are defined as products that contain a biologically active substance, called a *nutraceutical*, that, when included in the routine diet, modulates metabolic or physiologic processes, reducing the risk of disease and maintaining health [21,22]. Nutraceutical doses are higher than the habitual nutritional intake, but there is still no consensus, to our knowledge, regarding the ideal dose for oral L-Gln supplementation or which groups would benefit the most from it [3,4].

There appears to be no information on the safety of glutamine administration at nutraceutical doses in the elderly. There are questions as to whether the resulting nitrogen overload would be adequately metabolized by the kidneys and the liver [17].

The objective of this study was to evaluate the safety of L-Gln administered orally to middle-aged and elderly subjects.

Materials and methods

A clinical, controlled, randomized, double-blind, crossover study was performed at Lar Torres de Melo, a long-term-care facility in Fortaleza, State of Ceará, Brazil. The project was approved by the research ethics committee of the Federal University of Ceará (reference no. 382/05, protocol COMEPE no. 164/05) and authorized by the institution's administration and technical staff. The study was conducted in conformity with Brazilian law (CNS-MS Resolution 196/96) and with the Declaration of Helsinki, including its subsequent revisions.

After evaluating 207 subjects, 32 volunteers who met the study's criteria were selected and signed an informed consent. The study used the theoretical basis of the SENIEUR protocol (Working Party of the EURAGE Concerted Action Programme on Ageing of the European Community) for establishing a known and validated parameter for sample selection [23]. The only deviation from this protocol was the inclusion of subjects with mild hypertension under drug treatment and individuals taking antidepressive, antipsychotic, and hypnotic drugs, but they had to be under control or in remission. Any patient could freely decide to withdraw from the study at any time.

Supplements used

Used in the study were calcium caseinate (CAS; Kerry do Brazil Ltda., Três Corações, Minas Gerais, Brazil), a milk protein powder treated with food-grade glyceryl monooleate, and L-Gln (Ajinomoto Interamericana Ind. Com. Ltda., São Paulo, São Paulo, Brazil) in the form of a white, crystalline powder. The problems that might occur with the use of L-Gln because of prolonged storage and limited solubility were avoided by fresh preparation at ambient temperature and immediate ingestion.

Oral supplementation

The participants received protein supplementation with powdered milk prepared with mineral water at ambient temperature and homogenized with a blender. A cross-study was performed by distributing the randomly selected participants into two groups. In group 1 individuals ($n = 14$) received 0.5 g of L-Gln per kilogram of body weight per day in a single daily dose, and in group 2 individuals ($n = 16$) received 0.5 g per kilogram of body weight per day of CAS, equally in a single dose, to keep the supplementation isocaloric and isoproteic in both groups for 14 d. This was followed by a 5-d washout period, after which the supplementation was inverted in that group 1 received CAS and group 2 received L-Gln in the same quantities and for the same 14 d as during the first round. The participants were checked daily on the occasion of supplementation, looking for the eventual

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