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Letter to editor

Dose-escalation study with supplemental creatine-guanidinoacetate in healthy adults

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Abstract. *Background and aim:* A co-administration of creatine and guanidinoacetate (GAA) emerges as a promising dietary intervention yet limited information is currently available regarding its safety for dose-escalating studies. In this open-label pilot study, we assessed the impact of escalating doses of supplemental creatine-GAA on total homocysteine levels (T-Hcy) in the plasma of healthy adults. *Methods:* Eight young, physically active volunteers (age 22.5 ± 2.2 years, weight 64.1 ± 10.8 kg, height 165.4 ± 7.1; six females) provided informed consent to receive three escalating doses of the mixture, each administered for four weeks. *Results:* One-way ANOVA analysis revealed no significant differences in mean T-Hcy levels across the study (P = 0.76). Moreover, no cases of hyperhomocysteinemia (T-Hcy > 15 μmol/L) were observed during the study period. *Conclusions*: These findings suggest that the mixture is generally well-tolerated when administered up to three grams each of creatine and GAA over a three-month dose-escalating protocol in healthy adults, with no significant increase in homocysteine levels.

Key words: creatine, guanidinoacetate, homocysteine, dose-escalating

To the Editor,

A co-administration of creatine and guanidinoacetate (GAA, a direct precursor of creatine) emerges as a promising dietary intervention for augmented tissue bioenergetics (1-4). However, limited information is currently available regarding its safety for dose-escalating studies. The pharmacovigilance of the mixture particularly relates to elevated blood homocysteine, a risk factor for cardiometabolic disorders (5-7), with GAA acting as a hyperhomocysteinemic agent while creatine is recognized as a homocysteine-lowering nutrient (8). In this open-label pilot study, we evaluated the effects of escalating doses of supplemental creatine-GAA on total homocysteine levels (T-Hcy) in plasma of healthy adults. A total of eight young physically active volunteers (age 22.5 ± 2.2 years, weight 64.1 ± 10.8 kg, height 165.4 ± 7.1; six females) provided informed consent to be allocated into three escalating doses of the mixture (CreGAAtine™, Carnomed, Novi Sad, Serbia), each administered for four weeks. The study began with supplementation of one gram of each component for the first four weeks, followed by two grams of each component for the next four weeks, and finally three grams of each component for the last four weeks. Plasma T-Hcy levels were evaluated at baseline (pre-administration), and at 4 weeks, 8 weeks, and 12 weeks using multiplex enzyme-linked immunosorbent assay. One-way ANOVA demonstrated no differences in mean T-Hcy levels across the study (F = 3.03, P = 0.76); changes in plasma T-Hcy levels are depicted in Figure 1. No cases of hyperhomocysteinemia

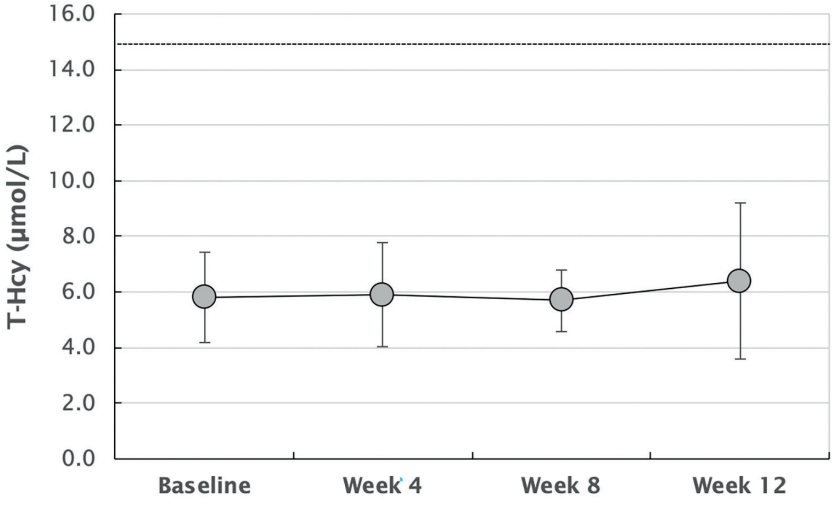

Figure 1. Alterations in plasma total homocysteine (T-Hcy) levels over the course of the study (n = 8). Error bars represent standard deviation, and dashed line indicates the hyperhomocysteinemia threshold.

(T-Hcy > 15 µmol/L) were observed during the study. In addition, no participant reported any adverse effects of each dosage regimen. After the intervention, all participants reported an improvement in well-being, a reduction in fatigue, and enhanced energy levels.

Our pilot study confirmed the absence of hyperhomocysteinemia risk in young, healthy adults who consumed up to three grams each of creatine and GAA in a 3-month dose-escalating interventional protocol. Additionally, baseline plasma T-Hcy levels remained essentially unchanged throughout the study, with alterations for all post-administration intervals averaging less than 15%. Our findings are consistent with preliminary studies demonstrating that the addition of creatine to GAA attenuates the increase in homocysteine levels (9,2). This phenomenon may be attributed to creatine potentially balancing homocysteine production induced by GAA (10-12), or to the provision of methyl group donors in the supplement which facilitate the remethylation of homocysteine to methionine (13-15). Further studies are necessary to assess the long-term safety of the creatine-GAA mixture utilizing various ratios between the components across diverse populations, as well as employing advanced biomarkers to evaluate homocysteine metabolism and methylation/remethylation indices. Specifically, a dosage of the mixture relative to body weight should be utilized to ensure equal exposure to both creatine and GAA. In the present study, the relative exposure to creatine and GAA varied substantially, ranging from 13 to 19 mg per kg body weight within the one-gram protocol. Consequently, some low-weight participants were administered dosages up to 46% higher compared to others.

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Conflict of Interest: SMO serves as a member of the Scientific Advisory Board on Creatine in Health and Medicine (AlzChem LLC). SMO co-owns patent "Supplements Based on Liquid Creatine" at the European Patent Office (WO2019150323 A1) and patent application "Composition Comprising Creatine for Use in Telomere Lengthening" at the U.S. Patent and Trademark Office (# 63/608,850). GF, ZB and VS declare that they have no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: Conceptualization: VS, SMO; funding: GB, ZB, VS, SMO; methodology: all authors; formal analysis: GF, ZB, VS, SMO; supervision: VS, SMO; writing - original draft: SMO; editing: all authors.

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