Effect of Creatine and Guanidinoacetate Supplementation on Plasma Homocysteine in Metabolically Healthy Men and Women

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Dear Editor,

Hyperhomocysteinemia is an independent risk indicator for several cardiometabolic diseases [1]. A number of nutritional factors, including protein malnutrition and consumption of certain food compounds, can lead to variations in homocysteine levels [2], stressing the role of diet in the homeostasis of this non-proteinogenic α -amino acid. Creatine synthesis appears to be a critical metabolic determinant of homocysteine turnover [3], and dietary provision of creatine and guanidinoacetate (creatine precursor) might markedly affect circulating homocysteine. Interestingly, the net effect of pro- and anti-hyperhomocysteinemic dietary ingredients is rarely investigated, albeit their widespread occurrence in human nutrition. The present pilot trial prospectively tested the effects of medium-term coadministration of creatine and guanidinoacetate on plasma homocysteine levels among men and women without prior cardiometabolic disease.

Eight apparently healthy and hyperhomocysteinemia-free young adults (age 24.3 ± 2.3 years, 4 women) volunteered to take part in this uncontrolled interventional trial. The participants received guanidinoacetate-creatine mixture (2,000 mg/day of guanidinoacetate and 2,000

mg/day of creatine) for 28 days; the guanidinoacetate dose was designed as a hyperhomocysteinemia-provoking dosage in healthy individuals [4], and the creatine dose was advanced for homocysteine reduction [5] and was equal to the amount recommended from dietary intake for the general population [6]. The primary outcome (total plasma homocysteine) and secondary outcomes (patient-reported side effects, plasma levels of clinical enzymes, total albumin, creatinine, and blood urea nitrogen) were assessed at baseline (pre-intervention) and 28-day follow-up. The study design was approved by the local IRB at the University of Novi Sad (#46-06-01/2020-1e2), with the study systematized following the Declaration of Helsinki. This study was an extension preliminary trial of the primary study [7], assessing whether guanidinoacetate-creatine mixture has additional metabolic activity or effects.

All participants completed the study, and compliance with the interventional regimen was 100%, as calculated by the number of unused sachets. Guanidinoacetate-creatine induced a mild increase in total plasma homocysteine (from 9.3 ± 1.7 $\mu\text{mol/L}$ at baseline, to 11.6 ± 1.6 $\mu\text{mol/L}$ at 28-day follow-up; $p < 0.01$). The mixture insti-

gated no cases of hyperhomocysteinemia (e.g., total plasma homocysteine >15 $\mu\text{mol/L}$), with clinical enzymes and other safety biomarkers remaining within the normal ranges. The mean serum creatinine levels increased for 15.1% (95% confidence interval, from 3.7 to 26.5; $p = 0.02$), yet no participants experienced clinically significant creatinine elevation (>114.9 $\mu\text{mol/L}$ for men and >97.2 $\mu\text{mol/L}$ for women). The participants reported no side effects that precluded their participation in the study.

In this small-scale open-label preliminary trial, coadministration of creatine and guanidinoacetate elevated total plasma homocysteine for ~25% over a treatment duration of 28 days. There was no evidence of intervention-driven hyperhomocysteinemia, suggesting a small-to medium-scale potential of the guanidinoacetate-creatine mixture to markedly upregulate homocysteine homeostasis. It appears that guanidinoacetate-inducing hyperhomocysteinemia is largely preventable by creatine coadministration in metabolically healthy men and women; this perhaps happens since exogenous creatine may temper endogenous creatine biosynthesis sufficiently to lower homocysteine production [5]. Whether these beneficial effects of supplemental creatine remain in metabolically compromised individuals and following more prolonged exposure to other dietary homocysteine-raising compounds (e.g., phosphatidylethanolamine, niacin, and xenobiotics) remains to be elucidated. Given that diet is a major risk factor for hyperhomocysteinemia [8], increased creatine intake may be a newly recognized dietary factor in the prevalence of hyperhomocysteinemia and its related diseases.

References

- Piazzolla G, Candigliota M, Fanelli M, Castrovilli A, Berardi E, Antonica G, et al. Hyperhomocysteinemia is an independent risk factor of atherosclerosis in patients with metabolic syndrome. *Diabetol Metab Syndr*. 2019;11:87.
- Ingenbleek Y, Hardillier E, Jung L. Subclinical protein malnutrition is a determinant of hyperhomocysteinemia. *Nutrition*. 2002;18(1):40–6.
- Stead LM, Jacobs RL, Brosnan ME, Brosnan JT. Methylation demand and homocysteine metabolism. *Adv Enzyme Regul*. 2004;44:321–33.
- Ostojic SM, Niess B, Stojanovic M, Obrenovic M. Co-administration of methyl donors along with guanidinoacetic acid reduces the incidence of hyperhomocysteinaemia compared with guanidinoacetic acid administration alone. *Br J Nutr*. 2013;110(5):865–70.
- Korzun WJ. Oral creatine supplements lower plasma homocysteine concentrations in humans. *Clin Lab Sci*. 2004;17(2):102–6.
- Brosnan JT, Brosnan ME. Creatine: endogenous metabolite, dietary, and therapeutic supplement. *Annu Rev Nutr*. 2007;27:241–61.
- Semeredi S, Stajer V, Ostojic J, Vranes M, Ostojic SM. Guanidinoacetic acid with creatine compared with creatine alone for tissue creatine content, hyperhomocysteinemia, and exercise performance: a randomized, double-blind superiority trial. *Nutrition*. 2019;57:162–6.
- Zhou SS, Zhou YM, Li D, Lun YZ. Dietary methyl-consuming compounds and metabolic syndrome. *Hypertens Res*. 2011;34(12):1239–45.

Conflict of Interest Statement

S.M.O. serves as a member of the Scientific Advisory Board on creatine in health and medicine (AlzChem LLC). S.M.O. owns patent “Sports Supplements Based on Liquid Creatine” at European Patent Office (WO2019150323 A1) and active patent application “Synergistic Creatine” at the UK Intellectual Property Office (GB2012773.4). S.M.O. has served as a speaker at Abbott Nutrition, a consultant of Allied Beverages Adriatic and IMLEK, and an advisory board member for the University of Novi Sad School of Medicine, and has received research funding related to creatine from the Serbian Ministry of Education, Science, and Technological Development; Provincial Secretariat for Higher Education and Scientific Research; AlzChem GmbH; KW Pfannenschmidt GmbH; ThermoLife International LLC; and Monster Energy Company. S.M.O. is an employee of the University of Novi Sad and does not own stocks and shares in any organization. N.T. and V.S. declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Funding Sources

This research received no external funding.

Author Contributions

S.M.O. designed research (project conception, development of overall research plan, and study oversight), analyzed data and performed statistical analysis, wrote paper draft, and had primary responsibility for final content. N.T. conducted research, analyzed data and performed statistical analysis, wrote paper draft, and revised the manuscript. V.S. conducted research, analyzed data and performed statistical analysis, and revised the manuscript. All authors read and approved the final manuscript.