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## Increased human growth hormone following oral consumption of an amino acid supplement: results of a randomized, placebo-controlled, double-blind, crossover study in healthy subjects

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### Abstract

**Background:** Human growth hormone (hGH) is best known for influencing bone and muscle growth as well as body composition but use of recombinant hGH is controversial. Amino acids are a potentially safer alternative, however, preliminary investigations of the effects of oral amino acids on hGH release have been inconclusive. Therefore, we tested the effects of a novel blend of amino acids optimized to increase hGH release.

**Study Question:** Does an investigational amino acid supplement affect hGH release?

**Study Design:** This was a randomized, placebo-controlled, double-blind, crossover study that included 16 (12 males, 4 females; age 32 ±14 years; body mass index 26.4 ±5.0 kg/m<sup>2</sup>) healthy participants. All participants received both placebo and the amino acid supplement after an overnight fast and completed all study visits. Treatment order was randomized and each treatment was separated by a 1-week washout period.

**Measures and Outcomes:** The primary outcome were the percent change in hGH from baseline to 120 minutes and the area under the curve of hGH over baseline. Serum hGH was measured using enzyme-linked immunosorbent assay at baseline and 15, 30, 60, 90 and 120 minutes.

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**Author contributions:** WDJ, ALH, FLG participated in study design. JR, FLG collected data and/or ran samples. WDJ, JR, FLG took part in data analysis. All authors were involved in data interpretation and critically reviewed the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors have given final approval of the version to be published.

Conflicts of interest:

CST, WDJ, and JR have no conflict of interest. ALH provides consultant services for Sierra Research Group, LLC. and Basic Research, LLC. FLG is a consultant for Beachbody, Basic Research, LLC., Eisai, Inc., General Nutrition Corporation, Melior Discoveries, and Techenterprises, is on advisory boards for Baronova, Inc., Curves-Jenny Craig, Gelesis, Microbiome Therapeutics, Novo Nordisk, Novartis, Plensat, and Zafgen, holds stock or stock options in Microbiome Therapeutics, Plensat, and Zafgen, and holds patents in Neuroquest.

**Results:** At 120 minutes, hGH levels increased by 682% (8-fold) from baseline and were significantly higher than placebo ( $p=0.01$ ). In addition, a significantly higher mean AUC was observed for the amino acid supplement compared to placebo (20.4 [95% CI: 19.9-21.0 ng/ml] vs. 19.7 [95% CI: 18.7-20.6 ng/ml];  $p=0.04$ ).

**Conclusions:** These results show that a single dose of the oral amino acid supplement was sufficient to significantly increase hGH levels in healthy adult males and females.

## Abstract

[clinicaltrials.gov NCT01540773](https://clinicaltrials.gov/NCT01540773).

## Keywords

amino acid; growth hormone; pituitary

## INTRODUCTION

Human growth hormone (hGH) is a peptide hormone that is best known for influencing bone and muscle growth and body composition.<sup>1</sup> The primary source of circulating hGH is the pituitary gland. hGH is secreted from the pituitary in a pulsatile manner, with the majority being released at night.<sup>2</sup> The greatest predictor of hGH secretion is age; hGH secretion is highest during adolescence and decreases with aging.<sup>3,4</sup> However, hGH levels are also influenced by many other external factors. Exercise, stress, hypoglycemia, and some amino acids have been shown to stimulate hGH release, while elevated glucose, free fatty acids, and other amino acids have been shown to inhibit hGH release.<sup>2</sup>

It is well established that intravenous (IV) administration of some amino acids results in significantly increased hGH secretion. In females, intravenous infusion of 183mg of arginine/kg body weight increased hGH levels >20-fold<sup>14</sup> and 30g of arginine elevated serum hGH levels 8.6-fold in males.<sup>15</sup> Such studies prompted testing of oral amino acids supplements (primarily arginine, lysine and ornithine) to stimulate hGH secretion; however, these studies yielded mixed results.<sup>16-20</sup> A low-dose amino acid supplement (SeroVital®, Sanmedica International, LLC, Salt Lake City, UT) containing 2.9 g of supplemented L-lysine, L-arginine, oxo-proline, N-acetyl-L-cysteine, L-glutamine, and schizonepeta was developed based on the stimulatory effects of some amino acids on hGH release.

This was a crossover, placebo-controlled study designed to determine the acute effects of the oral amino acid supplement on secretion of hGH in healthy subjects with normal hGH.

## METHODS

### Study Design

This was a randomized, placebo-controlled, double-blind, crossover study conducted between October 2011 and March 2012. The study included 16 participants (12 males and 4 females) who were recruited from the Pennington Biomedical Research Center. Male and female participants between 18 and 70 years of age were eligible. Participants were excluded if they were pregnant or nursing or taking any chronic medication, including hormonal

contraception. All participants received both placebo and treatment article (amino acid supplement); participants were randomized to treatment order in a 1:1 ratio via computer-generated random sequence. Blinding was maintained by study investigators and participants throughout the study.

The institutional review boards at the study site approved the protocol prior to study initiation. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent approved by the Pennington Biomedical Research Center Institutional Review Board (IRB Number 10036). This trial is registered with [clinicaltrials.gov](https://clinicaltrials.gov): NCT01540773.

## Procedures

Each participant reported to the Inpatient Unit in the morning on 2 occasions 1 week apart after an overnight fast. Blood was drawn from an IV line at -30, -15, 0, 15, 30, 60, 90 and 120 minutes. Study treatment (amino acid supplement or matching placebo) was administered orally at time 0. Serum samples were frozen at -80°C until the end of study. Serum hGH (Recombinant 98/574) was measured using enzyme-linked immunosorbent assay (ELISA; Siemens Immulite 2000 Immunoassay System, Siemens Medical Solutions USA, Inc., Malvern, PA). The intra-assay coefficient of variability (CV) for the hGH assay was 3.72% and the inter-assay CV was 5.70%. The detection limit for growth hormone was 0.05 ng/ml.

## Outcomes

The primary outcome measures were the percent change in hGH from baseline (0 minutes) to 120 minutes and the area under the curve (AUC) of hGH (0 to 120 minutes) over baseline.

## Statistical Analysis

Based on early work showing the ability of amino acids to stimulate hGH secretion,<sup>17,19</sup> a very conservative estimate of the mean and standard deviation for the change in hGH was  $15.4 \pm 10$  ng/mL. A sample size of 16 was employed to provide 80% power to detect a minimum mean change in hGH of  $15.4 \pm 10$  ng/mL using the nominal  $p < 0.05$  significance level.

Study drug was administered at 0 minutes. Baseline hGH was calculated as the average of hGH measurements -30, -15 and 0 minutes. The change from baseline to 15, 30, 60, 90 and 120 minutes was calculated as differences (ng/ml) by subtracting the baseline hGH level from the corresponding level at each time point. The area under the change curve (AUC) was calculated for each treatment using the trapezoidal rule. To avoid negative AUC's and with invariant alterations in determining statistical significance of differential treatment effects, a constant of 20 was added to each calculated change in hGH level in the analytical sample. A mixed effects linear model was used that included terms for the effects on hGH of sequences, participants within sequence, sessions, sequence by session interaction (treatments) and residual error. Consistent with our a priori hypothesis that the study treatment would increase hGH levels, the decision was made to reject the null only if the data supported the one directional alternative consistent with a favorable response to the

supplement. Statistical significance was assumed for  $p < 0.05$ . All calculations were performed using the software package SAS® Version 9.3 and data are presented as mean (95% CI) or mean  $\pm$  SEM.

## RESULTS

A total of 16 healthy participants (12 males and 4 females) were included in the study, received both placebo and the amino acid supplement, and completed all study visits. Of these, 56% (9/16) were Caucasian and 38% (6/16) were African American. At baseline, participant characteristics were (mean  $\pm$  standard deviation [SD]): age  $23 \pm 14$  years (range: 18 to 62 years), weight  $79.9 \pm 18.9$  kg (range: 55.5 to 121.6 kg), and body mass index (BMI)  $26.4 \pm 5.0$  kg/m<sup>2</sup> (range: 19.1 to 36.8 kg/m<sup>2</sup>).

At baseline, the mean value for hGH was slightly higher during treatment with placebo than with the amino acid supplement, though the difference was not statistically significant ( $p > 0.05$ ; Table 1). There was an initial decrease in mean hGH from baseline after administration of placebo and the amino acid supplement (Figure 1). However, following treatment with the amino acid supplement, mean hGH was increased from baseline at both the 90- and 120-minute assessments while hGH remained unchanged after treatment with placebo. At  $t=120$  minutes, hGH was 1.33 ng/ml after administration of the amino acid supplement, compared with only 0.45 ng/ml after placebo. The increase in hGH 120 minutes following administration of the amino acid supplement represented a 682% or 8-fold increase from baseline (Table 1, Figure 1). The area under the curve for hGH from time 0 to 120 minutes (AUC<sub>0-120 min</sub>) was also significantly greater following treatment with the amino acid supplement compared to placebo (Table 1).

The adverse events reported during the study were nausea and lightheadedness that occurred in a participant treated with the amino acid supplement. Both events were deemed unlikely related to treatment (they were attributed to study procedures, eg, blood draw) by the investigator.

## DISCUSSION

In this placebo-controlled, crossover design study, we report 682% or 8-fold increase in mean hGH from baseline following oral administration of an amino acid supplement in healthy fasted volunteers. In contrast, mean hGH remained similar to baseline after oral administration of placebo. Similarly, the AUC of hGH during the 120 minutes after treatment was significantly increased after administration of the amino acid supplement compared to placebo.

Prior to this study, only intravenous administration of amino acids was shown to reliably increase endogenous hGH<sup>14, 15</sup> while studies of the effects of oral administration of amino acids on hGH release yielded conflicting results.<sup>16-20</sup> Potential reasons for these variable outcomes may be the dose and composition of amino acids used, fasting vs fed conditions,<sup>21</sup> controlling for timing and study procedures (eg, venipuncture),<sup>22,23</sup> or small sample size.<sup>18,24</sup> In addition, growth hormone binding proteins may interfere with available hGH.<sup>25</sup> Moreover, multiple limitations with current methodologies for measuring hGH can result in

inter-assay variability of as much as 2- to 3-fold.<sup>24,26</sup> For example, assays may employ different antibodies to target specific hGH epitopes (monoclonal or polyclonal).<sup>24</sup> Thus, each assay is associated with variability that limits quantitative comparisons across assays; the magnitude of the change within a single assay (ie, change from baseline) is the most appropriate comparison.

A notable strength of the current study is the randomized, placebo-controlled, double-blind, crossover design in which each participant received the treatment article (amino acid supplement) and matching placebo in a randomized order and both investigators and participants were blinded to the treatment. Thus, each participant served as their own control, reducing the need for a large number of participants by minimizing the influence of confounding variables. This study design is appropriate for assessing the effects of acute treatment with a test article. Additionally, the study was powered to detect changes in hGH based on estimates obtained from previous studies.<sup>17,19</sup> Finally, the inclusion of male and female participants across a broad range of ages and BMIs strengthens the external validity of the results.

In conclusion, these results demonstrate that a single dose of the amino acid supplement is sufficient to produce a statistically significant increase in hGH without evidence of a waning effect during the testing period. Our findings strengthen the evidence that oral administration of a specifically formulated combination of amino acids can increase serum hGH levels.

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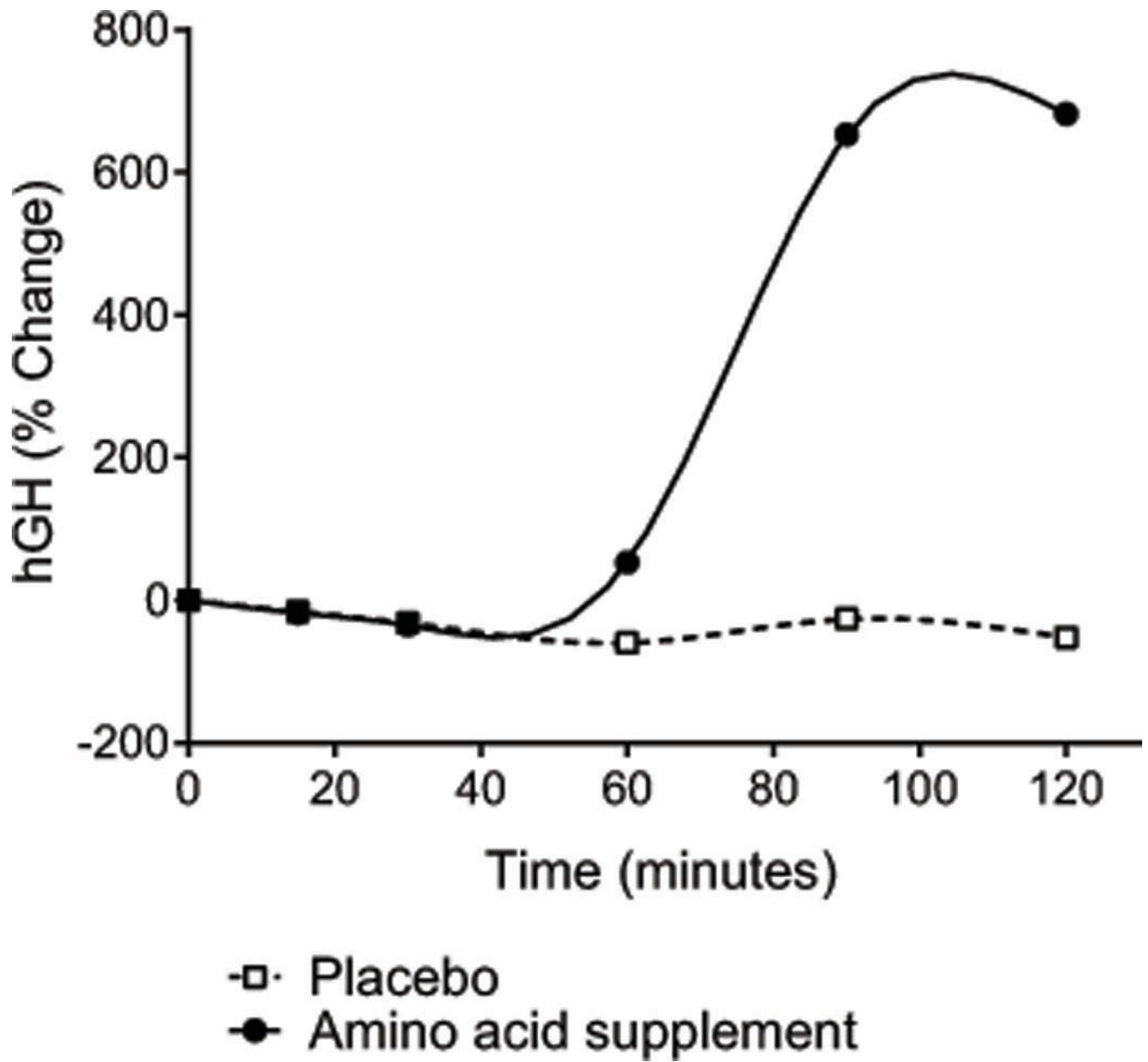
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**Figure 1. Percent change in serum hGH concentrations over 120 minutes.**  
 Data are the % change from baseline in serum hGH levels following ingestion of SeroVital® or matching placebo (N=16). After an overnight fast, baseline blood samples were collected at -30, -15, and 0 minutes. Treatment was administered at 0 minutes and blood was collected at 15, 30, 60, 90, and 120 minutes.



**Table 1.**

Change in human growth hormone (hGH)

	<b>Placebo</b>	<b>Amino Acid Supplement</b>
Baseline hGH (ng/ml)	0.93	0.17
hGH at t=120 minutes <sup>I</sup> (ng/ml)	0.45	1.33
Change in hGH <sup>I</sup> (ng/ml)	-0.48	1.15
95% Confidence interval	-1.47, 0.50	0.17, 2.14
p-value vs placebo		0.01
AUC <sub>0-120 min</sub>	19.67	20.43
95% Confidence interval	18.74, 20.59	19.90, 20.95
p-value vs placebo		0.04

<sup>I</sup>Change from baseline (t=0) to t=120 minutes.

AUC<sub>0-120 min</sub> = area under the curve from 0 to 120 minutes.

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