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# Glycerophosphocholine enhances growth hormone secretion and fat oxidation in young adults

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ABSTRACT

*Objective:* α-Glycerophosphocholine (GPC) is a putative acetylcholine precursor that potentially increases growth hormone secretion through the action of acetylcholine-stimulated catecholamine. The aim of this study was to investigate acute physiologic responses to a single intake of GPC.
*Methods:* Eight healthy male subjects (25 ± 1 y old) ingested GPC 1000 mg or a placebo in a double-blind randomized crossover study. Fasting blood samples were obtained before the administration of GPC (baseline) and 60 and 120 min after administration. All subjects repeated the identical protocol using the placebo.
*Results:* Plasma free choline levels significantly increased at 60 and 120 min after GPC administration. Plasma growth hormone secretion was increased significantly 60 min after taking GPC, whereas no significant change was observed with the placebo. In addition, the serum free fatty acid was increased 120 min after GPC ingestion, but no changes were seen with the placebo. Moreover, serum acetoacetate and 3-hydroxybutyrate levels, which are indices of hepatic fat oxidation, were increased at 120 min after taking GPC, whereas the placebo had no effect.
*Conclusion:* These findings suggest that a single dose of GPC increases growth hormone secretion and hepatic fat oxidation, with concomitant increases in choline levels, in young adults.


## Introduction

Choline is crucial for normal cell function and plays several vital roles in the body [1]. It is an important dietary nutrient, which, in humans, is related to neurotransmission (acetylcholine), transmembrane signaling, methyl metabolism, synthesis of phospholipids in the cell membrane, and fat and cholesterol metabolism [2]. Several human studies have demonstrated that a choline-deficient diet induces the development of hepatic steatosis and tissue damage (e.g., in patients receiving total parenteral nutrition), but the effect resolves when a source of dietary choline is provided [3–5]. In healthy male subjects with normal folate and vitamin B12 levels, average plasma free choline levels were about 10 μmol/L, and a 3-wk diet deficient in choline lowered these levels to about 7 μmol/L, leading to incipient liver dysfunction [1]. Moreover, in rodents and humans, choline deficiency affects brain structure and function [6] and increases the risk of neural tube defects [7], coronary artery disease [8], and cancer [9]. Therefore, the Institute of Medicine of the National Academy of Sciences (USA) recognizes choline as an essential nutrient for humans and has made recommendations for the dietary choline intake [10].

α-Glycerophosphocholine (GPC) is synthesized from beans and is a natural choline compound that has been used in medicines and supplements. In clinical trials, choline supplementation has been found to improve dementia, memory, and cognitive impairments in patients with Alzheimer's disease [11,12]. Although it has been shown that GPC supplements may substitute for insufficient dietary choline and protect the liver [1], the effects of a single dose of GPC on hepatic fat metabolism in healthy subjects with sufficient dietary sources of choline are unclear.

Orally administered GPC is effectively absorbed in the intestine [13], and plasma total choline levels increase rapidly after the ingestion of GPC, with high circulating levels of choline

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maintained for over 24 h in animal models [13,14]. We hypothesized that GPC administration would increase the fat metabolism in healthy young adults, and that ingested GPC might play a role in the regulation of growth hormone (GH) secretion. We investigated eight young Japanese men to clarify whether acute ingestions of GPC increased resting GH secretion. To confirm the GPC effects on fat metabolism, we examined whether the GPC-induced changes in GH secretion concomitantly affected serum free fatty acid (FFA) and glycerol. Moreover, we measured acetoacetate and 3-hydroxybutyrate, which are indices of fat oxidation in the liver.

## Materials and methods

### Subjects

Eight healthy males participated in this study (mean ± standard error: age 25.4 ± 1.1 y old, height 171.3 ± 1.9 cm, body mass 66.0 ± 2.2 kg, fat mass 11.4 ± 1.1%). Subjects were informed about the experimental procedures and the potential risks involved, and written consent was obtained. The inclusion criteria were as follows: participants should not be habitual consumers of any fatty acid supplement or medication known to affect lipid metabolism, should have no symptoms of chronic disease, and should be non-smokers. The study was approved by the ethics review board of Ritsumeikan University.

### Experimental procedures

This was a double-blinded, randomized, placebo-controlled, crossover study. Subjects were instructed to fall sleep before 12:00 the night before the study and to avoid alcohol and any nutrients that might affect choline on the day before. After overnight fasting, the subjects arrived at the laboratory at 08:00 and rested for 30 min before the first blood collection. Venous blood samples were obtained from an indwelling cannula in the antecubital vein at 60 and 120 min after ingestion of 1000 mg of GPC. All subjects repeated an identical protocol, ingesting the placebo in place of GPC, 2 wk after the first experiment. All subjects were in the same state of rest during the two experiments. Blood samples for the measurement of hormones and metabolites were stored at −80°C until use. The room temperature was maintained at 24°C throughout the experiment.

### Glycerophosphocholine

Glycerophosphocholine was synthesized as follows. Lecithin extracted from soybeans at 85% purity was deacylated by hydrolysis. Thereafter, it was subjected to silica gel column chromatography to obtain a GPC solution, which was crystallized and lyophilized. The GPC purity was determined to be >99% by $^{31}$P-nuclear magnetic resonance. The GPC supplement was composed of a mixture of 33.3% GPC, 65.7% maltitol and 1.0% silica (w/w). The placebo was composed of a mixture of maltitol 99.67% and silica 0.33% (w/w). GPC was present at 1000 mg in a total dose of 3000 mg.

### Blood analyses

Plasma free choline (Alfresa Pharma Corporation, Osaka, Japan), serum FFA, ketone body (Eiken Chemical Co., Ltd, Tokyo, Japan; and Kainos Laboratories, Inc., Tokyo, Japan), serum glycerol (Cayman Chemical Company, Ann Arbor, MI, USA), and plasma glucose were measured by an enzymatic colorimetric method [15,16]. The coefficients of variation were 1.3% for free choline, 0.8% for FFA, 2.9% for ketone bodies, 5.0% for glycerol, and 2.3% for glucose.

The plasma GH concentration was analyzed using the Immulite 1000 Analyzer (Siemens Healthcare Diagnostics, Inc., Tokyo, Japan). The sensitivity of the assay for GH and the coefficient of variation were 0.05 ng/mL and 2.9%, respectively. All samples were assayed in duplicate.

### Statistical analysis

A paired Student's *t* test was used to evaluate the differences between the GPC and placebo groups, and two-way repeated-measure analysis of variance was used to evaluate differences among time points taken for the two groups. The values after the different treatments were compared by using deviations from fasting values to allow for any differences from baseline, and group and time course interactions were included in these models. All pairwise testing was adjusted for multiple comparisons by using a Bonferroni correction factor (StatView 5.0, SAS Institute, NC, USA). The area under the curve (AUC) was evaluated for parameters calculating the curve interpolating times at 0, 60, and 120 min. Values are expressed as mean ± standard deviation. $P < 0.05$ was considered statistically significant for the analysis of variance and *P* values for the post hoc test were corrected by a Bonferroni analysis.

## Results

### Free choline levels

No significant difference was observed in plasma free choline levels at baseline. The average basal plasma free choline concentrations were 8.1 ± 1.4 and 8.5 ± 1.6 μmol/L for the GPC and placebo groups, respectively. In response to ingesting GPC, free choline concentrations increased significantly within 60 min and were maintained for the entire experimental period in the GPC group (Fig. 1). In contrast, no significant changes in plasma free choline concentrations were observed in the placebo group. Plasma free choline levels at 60 and 120 min after GPC administration were significantly higher than those observed after the ingestion of the placebo (Tables 1 and 2). There were significant interactions of time course and group on free choline levels (Tables 1 and 2).

### FFA and glycerol levels

No significant differences in serum FFA and glycerol concentrations were observed between the two groups at baseline. Serum FFA levels were significantly increased at 60 and 120 min after GPC ingestion (Tables 1 and 2), whereas no changes were observed in the placebo group (Fig. 2A). In contrast, serum glycerol levels were not significantly affected in either group (Fig. 2B). However, there were significant interactions of time

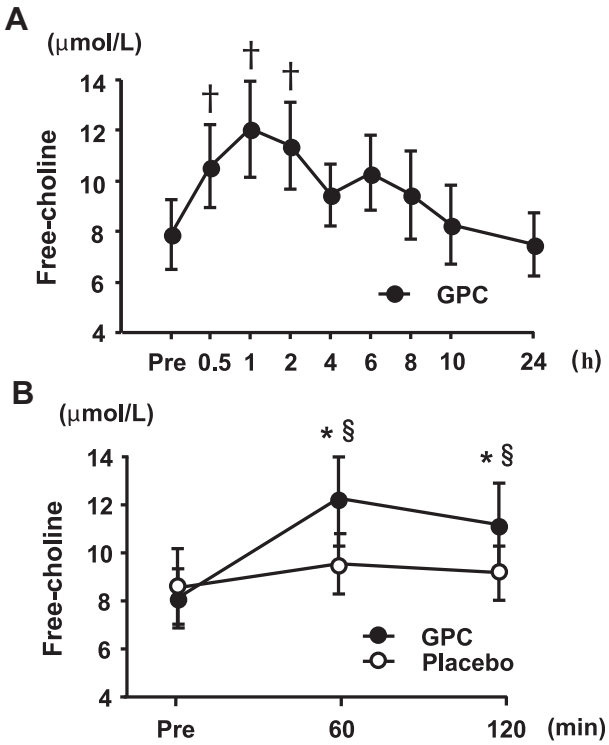


**Fig. 1.** Plasma free choline concentrations in the GPC and placebo groups from baseline (0 h) to 24 h (A) or from baseline to 120 min (B) after GPC or placebo administration. Data are expressed as mean ± SD. * $P < 0.0167$, † $P < 0.0014$ for GPC compared with baseline (Pre). § $P < 0.0167$ for GPC compared with placebo (B). GPC, α-glycerophosphocholine; Pre, before treatment.

**Table 1**
Absolute values in the GPC and placebo groups

| | GPC | | | Placebo | | | *P* | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | 60 min | 120 min | Pre | 60 min | 120 min | Group | Time | Group × Time |
| Free choline (μmol/L) | 8.1 ± 1.4 | 12.1 ± 1.9 | 11.4 ± 1.7 | 8.5 ± 1.6 | 9.6 ± 1.3 | 9.2 ± 1.1 | 0.0096 | 0.0002 | 0.0194 |
| Free fatty acid (μmol/L) | 336 ± 85 | 428 ± 137 | 694 ± 223 | 372 ± 127 | 282 ± 83 | 429 ± 96 | 0.0075 | 0.0004 | 0.0280 |
| Glycerol (mg/dL) | 5.3 ± 1.4 | 5.1 ± 0.8 | 6.5 ± 1.7 | 5.6 ± 1.1 | 5.7 ± 0.7 | 4.9 ± 0.7 | NS | NS | 0.0431 |
| Acetoacetate (μmol/L) | 21.7 ± 11.4 | 19.6 ± 9.6 | 66.8 ± 44.2 | 15.6 ± 4.3 | 10.8 ± 3.9 | 11.6 ± 4.9 | 0.0036 | 0.0251 | 0.0161 |
| 3-Hydroxybutyrate (μmol/L) | 38.7 ± 13.4 | 33.0 ± 13.3 | 138.0 ± 73.9 | 34.8 ± 12.3 | 20.2 ± 7.8 | 22.6 ± 9.0 | 0.0012 | 0.0027 | 0.0011 |
| Growth hormone (ng/mL) | 1.4 ± 1.6 | 4.5 ± 2.7 | 0.5 ± 0.4 | 0.2 ± 0.2 | 0.1 ± 0 | 1.2 ± 1.5 | 0.0360 | NS | 0.0120 |

GPC, α-glycerophosphocholine; Pre, before treatment
Values are presented as mean ± SD. *P* values are for significant effects using two-way repeated-measures analysis of variance ($P < 0.05$)

course and group on serum FFA and glycerol levels, respectively (Tables 1 and 2).

*Acetoacetate and 3-hydroxybutyrate levels*

There were no significant differences in basal acetoacetate and 3-hydroxybutyrate levels between the two groups; however, the two readings increased significantly 120 min after GPC, but not placebo, ingestion (Fig. 3). There were significant interactions of time course and group on the acetoacetate and 3-hydroxybutyrate levels, respectively (Tables 1 and 2).

*Glucose levels*

There were no significant differences in plasma glucose levels (millimoles per liter) between the two groups at baseline (GPC 5.20 ± 0.06 mmol/L, placebo 5.31 ± 0.19 mmol/L) or during the experimental period (60 min: GPC 5.23 ± 0.06, placebo 5.00 ± 0.18; 120 min: GPC 5.14 ± 0.04, placebo 5.00 ± 0.14).

*Hormone levels*

There were no significant differences in basal plasma GH levels between the groups. After GPC administration, plasma GH concentrations increased significantly after 60 min, whereas no significant changes were observed in the placebo group (Fig. 4A). There were significant interactions of time course and group on the GH level (Tables 1 and 2).

*AUC for each parameter*

The AUCs for free choline, FFA, 3-hydroxybutyrate, and GH levels were significantly higher in the GPC compared with the placebo group, whereas the AUCs for glycerol and acetoacetate were not significantly different between the two groups (Table 3).

## Discussion

In the present study, we observed that the oral ingestion of GPC acutely increased plasma free choline levels by 50% within 60 min and concomitantly increased GH concentrations in young adult male subjects. In addition, serum FFA, acetoacetate, and 3-hydroxybutyrate levels increased significantly, and serum glycerol was modestly increased 120 min after GPC ingestion. However, blood glucose levels were not affected. Thus, acute oral doses of GPC may increase GH secretion and hepatic fat oxidation, with concomitant increases in choline levels, in young adults.

The increased plasma free choline levels observed 60 min after the oral administration of GPC were maintained at 120 min and represented an increase of 38% to 51% over basal levels. In healthy subjects, average plasma free choline levels range from 9.6 to 10.9 μmol/L [17], and dietary choline deficiency lowers these values to about 7 μmol/L [1]. Although, in this study, the subjects' basal plasma free choline levels were within the normal range, their dietary choline intake may have been low. However, in support of our results, animal studies have shown that plasma total choline levels rapidly increase after GPC administration, and that high levels of circulating free choline are maintained for longer than 24 h [13,14]. In our preliminary data (see Fig. 1A) on GPC administration to humans, plasma free choline levels rapidly increased within 30 min of treatment and were maintained for 2 h. By 24 h after GPC ingestion, circulating free choline levels had returned to baseline. Thus, a single 1000-mg dose of GPC induced an acute increase of plasma choline levels in healthy young men.

Plasma GH levels were increased by about 290% at 60 min after the oral administration of GPC. In contrast, single sessions of moderate intensity aerobic exercise (e.g., 50% of peak oxygen uptake for 30 min) have been found to increase GH secretion by 210%, from 2.7 ± 1.7 ng/mL at rest to 5.7 ± 2.1 ng/mL after exercise [18]. Thus, the GPC-induced increases in GH levels observed in this study were of a comparable degree to the increase induced by moderate-intensity exercise. Furthermore, GH secretion increases the lipolysis from triacylglycerols to FFA

**Table 2**
Ratio of change in the GPC and placebo groups

| | GPC | | | Placebo | | | *P* | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | 60 min | 120 min | Pre | 60 min | 120 min | Group | Time | Group × Time |
| Free choline (%) | 0 | 54 ± 18 | 47 ± 32 | 0 | 13 ± 12 | 9 ± 15 | 0.0001 | 0.0001 | 0.0070 |
| Free fatty acid (%) | 0 | 35 ± 65 | 108 ± 41 | 0 | −18 ± 28 | 21 ± 22 | 0.0003 | 0.0001 | 0.0143 |
| Glycerol (%) | 0 | −0.3 ± 22.5 | 30.2 ± 33.0 | 0 | 4.7 ± 15.4 | −13.9 ± 19.2 | NS | NS | 0.0230 |
| Acetoacetate (%) | 0 | −12 ± 38 | 146 ± 129 | 0 | −33 ± 19 | −17 ± 29 | 0.0025 | 0.0017 | 0.0022 |
| 3-Hydroxybutyrate (%) | 0 | −24 ± 12 | 181 ± 166 | 0 | −42 ± 12 | −22 ± 31 | 0.0032 | 0.0013 | 0.0017 |
| Growth hormone (%) | 0 | 1807 ± 2644 | 105 ± 301 | 0 | −34 ± 44 | 255 ± 910 | NS | NS | 0.0452 |

GPC, α-glycerophosphocholine; Pre, before treatment
Values are presented mean ± SD. *P* values are for significant effects using two-way repeated-measures analysis of variance ($P < 0.05$)

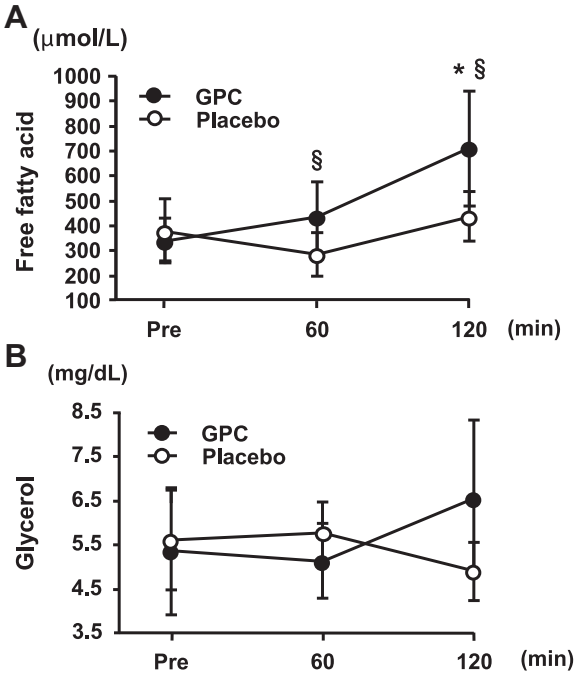


**Fig. 2.** Serum free fatty acid (A) and glycerol (B) concentrations after treatment with GPC or placebo. Data are expressed as mean ± SD. * $P < 0.0167$ and § $P < 0.0167$ for the GPC and placebo groups, respectively, compared with baseline (Pre). GPC, α-glycerophosphocholine; Pre, before treatment.

and glycerol, a function that may partly explain the increases observed in serum FFA levels.

Growth hormone production is stimulated by the GH-releasing hormone and is inhibited by the release of the hypothalamic somatotropin release-inhibiting factor (SRIF). Increased plasma choline concentrations lead to increased brain choline concentrations because of the kinetic characteristics of the blood–brain barrier transport system [19]. Because choline is converted into acetylcholine by choline acetyltransferase, the increased choline levels observed after GPC ingestion accelerate acetylcholine synthesis and release [17,20]. In a rabbit model system, α2-adrenergic blockade with yohimbine suppressed the release of the hypothalamic GH-releasing hormone and increased the release of endogenous SRIF, thereby suppressing GH secretion [21]. Based on these observations, it is considered that acetylcholine accelerates the catecholamine-induced stimulation of the α2-adrenergic receptor and thus inhibits the secretion of SRIF in the hypothalamus [21]. This would contribute to the underlying mechanism of GPC-stimulated GH secretion. In addition, in our study, GH returned to fasting levels by 120 min, whereas free choline levels remained significantly increased. The increase of GH is inhibited by SRIF and/or insulin-like growth factor-1 through a central regulatory point, e.g., the hypothalamus [22,23]. Therefore, the transient change observed in GH levels, which returned to baseline by 120 min, may be effected by a negative feedback of the central regulation mechanisms governing GH. However, we did not measure tissue levels of SRIF, GH-releasing hormone, and insulin-like growth factor-1. Further studies will be needed to understand the mechanisms regulating the GH increases after GPC ingestion.

Growth hormone induces the increase of lipolysis from triacylglycerols to FFA and glycerol, mainly in the adipose tissue. In turn, the released FFA is oxidized in the liver and skeletal muscles. In the present study, we noted that GPC ingestion increased GH secretion, increased serum FFA levels, and

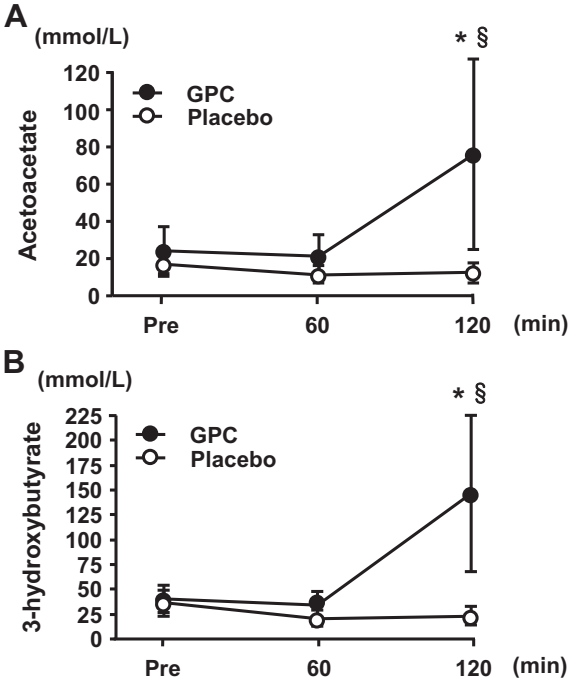


**Fig. 3.** Serum acetoacetate (A) and 3-hydroxybutyrate (B) concentrations after treatment with GPC or placebo. Data are expressed as mean ± SD. * $P < 0.0167$ and § $P < 0.0167$ for the GPC and placebo groups, respectively, compared with baseline (Pre). GPC, α-glycerophosphocholine; Pre, before treatment.

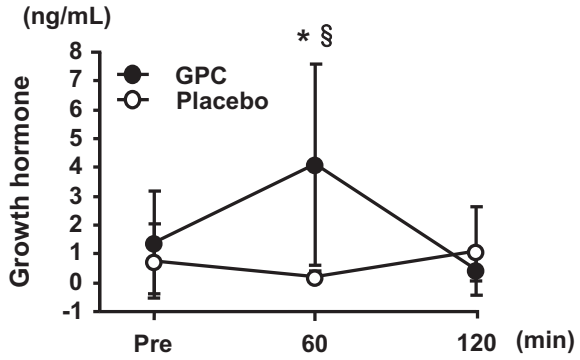


**Fig. 4.** Plasma growth hormone concentrations after treatment with GPC or placebo. Data are expressed as mean ± SD. * $P < 0.0167$ and § $P < 0.0167$ for the GPC and placebo groups, respectively, compared with baseline (Pre). GPC, α-glycerophosphocholine; Pre, before treatment.

**Table 3**
Area under the curve in the GPC and placebo groups

| | AUC | | *P* |
|---|---|---|---|
| | GPC | Placebo | |
| Free choline (μmol · $L^{-1}$ · $h^{-1}$) | 21.7 ± 2.7* | 18.5 ± 2.5 | 0.0419 |
| Free fatty acid (μmol · $L^{-1}$ · $h^{-1}$) | 944 ± 215* | 215 ± 167 | 0.0347 |
| Glycerol (mg · $dL^{-1}$ · $h^{-1}$) | 11.0 ± 1.7 | 10.9 ± 1.2 | 0.9301 |
| Acetoacetate (μmol · $L^{-1}$ · $h^{-1}$) | 61 ± 34 | 24 ± 8 | 0.0658 |
| 3-Hydroxybutyrate (μmol · $L^{-1}$ · $h^{-1}$) | 116 ± 48* | 49 ± 17 | 0.0159 |
| Growth hormone (ng · $mL^{-1}$ · $h^{-1}$) | 5.5 ± 3.1* | 0.8 ± 0.8 | 0.0083 |

AUC, area under the curve; GPC, α-glycerophosphocholine
Values are presented as mean ± SD
* $P < 0.05$ versus placebo.

modestly increased serum glycerol levels. Concomitantly, serum acetoacetate and 3-hydroxybutyrate levels, which are indices of the ketone body fraction, were increased after GPC administration. Increased ketone bodies in the resting state may have indicated a role for an increased hepatic fat oxidation rather than skeletal muscle fat oxidation, because the subjects avoided any movement and exercise during the experiment. Thus, these results suggested that GPC ingestion increased the serum FFA levels by increasing GH secretion, with concomitant increases in choline levels in young adults. Subsequently, the increased serum FFA levels led to increases in hepatic tissue FFA levels, which increased the oxidation of hepatic fat.

We focused on the acute effects of GPC intake on GH secretion and fat oxidation. However, the sample in the present study was small; therefore, further investigation is needed to confirm these results. There is a strong potential for GPC supplements to improve health; for example, choline supplementation may acutely decrease the risk of cardiovascular diseases [24,25] and increase learning and memory performance [26]. These findings bolster the need for an improved understanding of the mechanism of the action of GPC in healthy subjects.

## Conclusion

In response to a single oral dose of GPC, we observed an increase in plasma free choline levels, a concomitant increase in GH secretion, and increased FFA and ketone body levels. These findings suggested that a single dose of GPC may increase GH secretion and fat oxidation in young adults.

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