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Zinc Supplements Taken with Food Increase Essential Fatty Acid Desaturation Indices in Adult Men Compared with Zinc Taken in the Fasted State

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ABSTRACT

Background: Zinc intake is associated with reduced risk of metabolic disease in adults, possibly due in part to zinc's role in essential fatty acid (EFA) desaturation. Although plasma zinc is the accepted indicator of zinc status, product-to-precursor activity indices of fatty acid desaturase (FADS) 1 and 2 have also been proposed as response indicators for changes in zinc intake.

Objectives: To examine zinc supplement effects on plasma zinc concentration (PZC) and estimated FADS 1 and 2 activities, when zinc supplements are taken with food compared with fasted.

Methods: Apparently healthy adult men were randomly allocated to take 25 mg zinc as zinc gluconate either in the fasted state 30 min before breakfast [zinc before breakfast (ZBB)] or with breakfast [zinc with breakfast (ZWB)] daily for 13 d. Fasting PZC was measured by inductively coupled plasma optical emission spectrometry. Selected EFAs for FADS activity indices were measured by LC-MS/MS at study baseline and end.

Results: A total of 35 men completed the study (ZBB, $n = 18$; ZWB, $n = 17$). Mean ± SEM PZC was 86.2 ± 1.64 μg/dL at baseline. After 2 wk of zinc supplementation, the PZCs were 18% higher in the ZBB compared with the ZWB groups (105 ± 5.88 compared with 88.7 ± 2.36 μg/dL, $P = < 0.05$). However, the geometric mean (95% CI) FADS1 activity indices were 15% higher in the ZWB than the ZBB participants, 6.45 (5.84, 7.13) compared with 5.57 (5.05, 6.14), $P < 0.05$.

Conclusions: These data demonstrate a lack of congruence between the effects of zinc supplements on PZC and EFA metabolism in response to whether a zinc supplement is taken with or without food. Additional research is needed to determine how absorbed zinc may be directed differently toward metabolic processes, when coabsorbed with food. This trial was registered at clinicaltrials.gov as NCT03619421. *J Nutr* 2021;151:2583–2589.

Keywords: zinc, supplemental zinc, plasma zinc, essential fatty acid metabolism, fatty acid desaturase, activity index

Introduction

Zinc is an essential micronutrient that contributes to the structure and/or function of approximately one-tenth of the human proteome, or about one-tenth of the molecular machinery behind metabolic function (1). Current understanding of the link between lipid metabolism and zinc nutrition is based on observations that the signs of zinc deficiency and essential fatty acid (EFA) deficiency are similar across species (2). In acrodermatitis enteropathica, a hereditary disorder of zinc absorption, deficiencies in metabolites of linoleic acid (LA) returned to normal with zinc supplementation, likely due to the zinc dependence of LA desaturation, a process taking place primarily in the liver (3, 4). Recent studies suggest that EFA metabolism, specifically the pathways of desaturation and elongation of LA via fatty acid desaturases (FADS) 1 and 2 and elongase 5 (ELOVL5), may be sensitive to small fluctuations in zinc intake. Product-to-precursor ratios (activity indices) that provide indirect estimates of desaturase and elongase activities have been proposed as an indicator of zinc status (5–7).

Plasma zinc concentration (PZC), the recommended indicator of zinc status in populations, is maintained over a wide range of zinc intakes (8, 9). The PZC response to zinc intake appears to be the greatest when supplemental zinc is taken in the fasted state. For example, when supplemental zinc was taken daily after an overnight fast, PZC increased by nearly 15%, peaking after 5 d (10). Similar marked increases in PZCs do not occur if zinc is provided as a fortificant in bread (11).

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Food consumption affects zinc metabolism within the body. Lowe et al. (12) demonstrated that zinc is directed out of plasma and into tissues, such as into the liver, postprandially. It is reasonable that zinc absorbed with a meal is similarly directed to the liver via the portal circulation and that zinc taken in the fasted state is more readily directed to peripheral blood plasma. Because a large portion of lipid metabolism occurs hepatically, the postprandial direction of zinc into the liver may contribute to the effects of zinc on EFA metabolism. Correspondingly, the metabolic effects of increased zinc intake do not always manifest with concurrent increases in plasma zinc (13). A direct comparison of the effects of supplemental zinc on PZC and fatty acid desaturation, using the same form of zinc in the fasted and nonfasted states, has not been conducted previously.

Our objective was to compare the effects of the same form and amounts of zinc taken in the fasted and nonfasted states on PZC and proposed metabolic indicators of zinc status: FADS1 and FADS2 activity indices. We hypothesized that *1*) taking a zinc supplement in the fasted state compared with food increases PZC, and *2*) the effects on FADS1 and FADS2 activity indices are greater when zinc is taken with food compared with in the fasted state.

Methods

Participants

The single-blind, randomized clinical trial was conducted at the UCSF Benioff Children's Hospital in Oakland, California. The study was approved by the institutional review board at UCSF Benioff Children's Hospital Oakland, and all procedures were conducted in accordance with ethical standards.

Apparently healthy adult men, aged 18–50 y, with a BMI (kg/m^2) of 18–30, who reported breakfast intake as part of their normal daily routine were recruited for the study. Women were excluded as zinc status varies with the menstrual cycle, which would make it difficult to link the supplement intake to PZC measurements in a small sample (14). Exclusion criteria included any acute or chronic illness; use of tobacco, nicotine, or cannabis products; alcohol abuse; illicit drug use; regular use of prescription or over-the-counter medication; and intake of any nutritional supplements for the 4 wk prior to enrolling in the study.

Study design

The sample size was based on results from a previous zinc supplementation trial in men in which a baseline mean ± SD PZC of 79 ± 1.8 μg/dL was observed (10). Based on a 5% two-tailed type I error rate and 80% power, it was estimated that a sample of 16 participants per group would allow detection of a 15% difference in PZC. To allow for attrition, a recruitment target of 20 participants per group was set.

The participants were asked to fast (i.e., to abstain from any food or drink except water) for at least 8 h before the first blood sample. On the morning of study day 1, body weight and height were measured. Venous blood was collected using a 21-gauge butterfly needle and a 6-mL zinc-free trace element grade vacuum collection tube with potassium EDTA (Becton Dickinson) according to procedures recommended by IZiNCG (15). Within 30 min of collection, tubes were centrifuged at 1500 × *g* for 15 min at 4°C. One-milliliter aliquots of plasma were stored at –80°C until analysis.

Participants were then given a 2-wk supply of compressed pills containing 25 mg zinc as a zinc-gluconate (Best Naturals). Each participant was randomly assigned to 1 of 2 groups: zinc before breakfast (ZBB) or zinc with breakfast (ZWB). Participants were instructed to fast a minimum of 8 h from the evening until they woke up and to take their zinc supplement without food 30 min before breakfast (ZBB) or with their breakfast (ZWB) from days 2 to 14. All participants logged their breakfasts and the times they ate breakfast and took their zinc supplement. A second fasted blood sample was collected on the morning of study day 15.

Compliance with taking supplemental zinc was monitored by texting the participants once a week, reviewing logs, and counting remaining pills in the pill bottles at the end of the study. The clinical coordinator and study participants were not masked to their group assignment. Personnel involved in the laboratory and data analysis were masked until the laboratory analyses and data tabulation were completed.

Laboratory analysis

Prior to analysis, all plasma samples were visually checked for hemolysis, and plasticware was screened for zinc contamination. Pipette accuracy was verified by repeat weighing of water on a balance with precision of 0.1 mg (AE100; Mettler Toledo). An internal plasma pool and Seronorm Trace Elements Serum levels 1 and 2 reference serum samples (Sero AS) were analyzed along with the samples. Plasma samples and controls were vortexed using a Vortex Genie (Scientific Industries), and 100 μL was pipetted in triplicate into 15-mL polypropylene conical tubes (Perfector Scientific) using 200-μL polypropylene filter pipette tips (VWR International). Then, 250 μL of 67–70% Omnitrace trace element grade nitric acid (Millipore Sigma) was added to each conical tube, capped and vortexed, and digested at 60°C for 15 h. After heating, 2.8 mL Omnitrace Ultra water (Millipore Sigma) was added to each tube to achieve a final volume of 3.2 mL.

The PZCs were measured using an Agilent 5100 SVDV ICP-OES (Agilent Technologies). Calibration standards were made using SRM 3168a zinc in nitric acid (National Institute of Standards and Technology). Zinc analysis was performed in triplicate for all samples. All replicates from both time points for a given participant were analyzed together.

Total plasma 18:2n–6 linoleic acid (LA), 18:3n–6 γ-linolenic acid (GLA), 20:3n–6 dihomo-γ-linolenic acid (DGLA), and 20:4n–6 arachidonic acid (ARA) were quantified simultaneously by LC-MS/MS using a method adapted from Serafim et al. (16). Briefly, after adding labeled internal standards, plasma samples were subjected to alkaline hydrolysis using 0.3 M potassium hydroxide in 80% methanol, with butylated hydroxytoluene as a preservative. After neutralization using formic acid, total fatty acids were extracted in hexane, dried under nitrogen, and reconstituted in 80% methanol for analysis.

Samples were analyzed using a 1290 Infinity Quaternary liquid chromatography system in tandem with a 6490 Triple Quadrupole mass spectrometer (Agilent Technologies). Activity indices of FADS2, ELOVL5, and FADS1 toward desaturation and elongation of LA to ARA were determined by the ratios of product to precursor at each enzymatic step (**Figure 1**).

Data analysis

Statistical analyses were performed using SPSS Software (version 26; SPSS, Inc.). Prior to any comparison, data were checked for outliers and normal distribution. Normally distributed data included weight, height, BMI, PZC, and ARA. Data that were log-transformed to

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YNM and AGH contributed equally to the development of this manuscript.
Address correspondence to AGH (e-mails: aghall@berkeley.edu; aghall@ucdavis.edu).
Abbreviations used: ARA, arachidonic acid; DGLA, dihomo-γ-linolenic acid; EFA, essential fatty acid; FADS, fatty acid desaturase; GLA, γ-linolenic acid; ICP-OES, inductively coupled plasma optical emission spectrometry; LA, linoleic acid; PZC, plasma zinc concentration; ZBB; zinc before breakfast; ZWB, zinc with breakfast.

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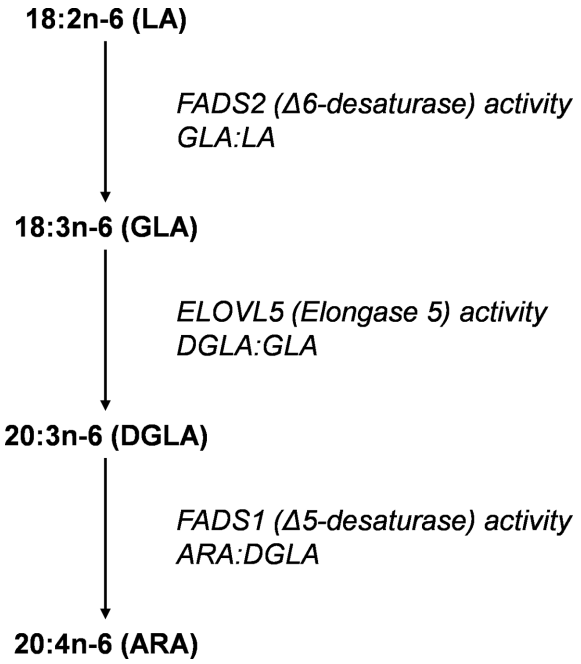

FIGURE 1 n–6 Fatty acid desaturation and elongation. The desaturation and elongation of linoleic acid (LA) to arachidonic acid (ARA) follows a 3-step pathway. Activities of each enzymatic step are estimated by the ratios of product to precursor.

a normal distribution included plasma LA, GLA, DGLA; GLA/LA, DGLA/GLA, ARA/DGLA, and DGLA/LA ratios. Descriptive statistics were calculated for all dependent variables. Independent samples *t* test was used for comparison between groups at baseline. Differences in age between groups were evaluated using the nonparametric independent samples Mann–Whitney *U* test. ANCOVA was used for the primary comparisons, as well as posttreatment differences between groups in PZC and plasma fatty acids, controlling for baseline values. Paired samples *t* test was used for comparison of PZC values within the same treatment group. Pearson correlations were calculated for each FA with PZC. Statistical significance for all tests was determined at a *P* value of < 0.05.

Results

Forty apparently healthy men were screened for the study (Figure 2). One was excluded based on the use of prescription medication, and another declined the invitation to participate. Thus, 38 adult men consented and were enrolled in the study. Nineteen were randomly assigned to each treatment group. Of the 38 men enrolled, 33 completed the study.

Age, height, weight, and BMI did not differ between the 2 groups (Table 1). At baseline, there was no difference in PZC, LA, GLA, DGLA, or ARA between those randomly allocated to ZWB compared with ZBB (Table 2). Three participants had PZCs <74 μg/dL, a population cutoff for zinc deficiency (15), 1 ZBB (73.1 μg/dL) and 2 ZWB (71.2 μg/dL and 69.3 μg/dL). Two participants were below the same cutoff after zinc supplementation, 1 ZBB (71.7 μg/dL) and 1 ZWB (70.0 μg/dL). The proportion below the cutoff was typical for the PZC distribution in a healthy population (10). The mean ± SD change in PZC due to zinc supplementation was 10.16 ± 3.39 μg/dL ($P = 0.005$). With supplementation, PZC was 18.4% higher among the ZBB compared with ZWB participants ($P = 0.026$).

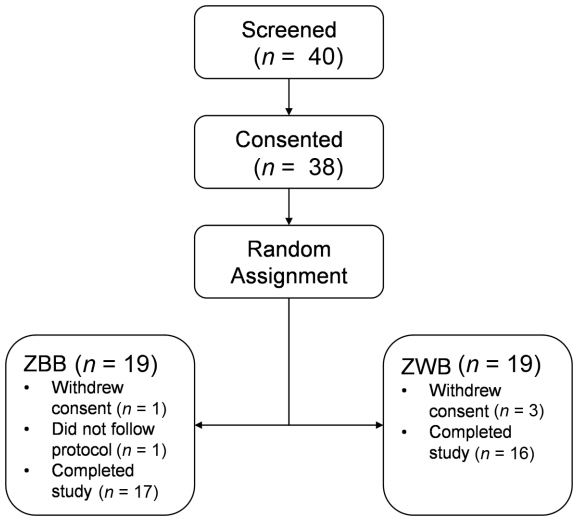

FIGURE 2 Enrollment flow diagram. The flow of participant enrollment from screening (top) through study completion (bottom) is shown. One in the zinc before breakfast (ZBB) group and 2 in the zinc with breakfast (ZWB) group withdrew from the study before the first sample; a second ZBB participant did not follow the protocol for the supplement, and 2 more ZWB participants withdrew from the study during the supplementation period.

Plasma LA, GLA, DGLA, and ARA did not differ between the 2 groups at baseline (Table 2). Controlling for baseline values, the plasma ARA concentrations were 13.7% higher with supplementation in the ZWB participants compared with ZBB ($P = 0.042$). No significant correlations between plasma zinc and LA, DGLA, or ARA were observed. However, the GLA was negatively correlated with PZC at baseline ($r = -0.37$, $P = 0.036$). None of the plasma fatty acids correlated significantly with PZC after zinc supplementation.

Plasma zinc concentrations and the activity indices of FADS2, ELOVL5, and FADS1 were determined before and after zinc supplementation in the ZBB and ZWB groups (Figure 3). When controlling for baseline values, FADS2 activity index with supplementation did not differ between the 2 groups ($P = 0.21$). The ELOVL5 activity index approached significance, tending to be higher in the ZBB group ($P = 0.074$). Consuming the zinc supplement with breakfast led to a significantly different FADS1 activity index compared with consuming the supplement without food ($P = 0.044$). While the FADS1 activity index was higher among those taking zinc with breakfast, PZC was higher among those taking zinc in the fasted state.

Previously, the desaturation by FADS2 and subsequent elongation have been combined into 1 step and estimated as the DGLA/LA molar ratio (or the inverse) for correlation with plasma zinc (7, 17). In the current study, the DGLA/LA molar ratio was 0.109 (0.095, 0.126) in ZBB compared with 0.111 (0.098, 0.126) in ZWB at baseline ($P = 0.90$), as well as 0.119 (0.107, 0.134) in ZBB compared with 0.113 (0.100, 0.127) in ZWB after zinc supplementation ($P = 0.48$).

Discussion

These results show that taking a zinc supplement with a meal obviates the increase in PZC normally observed when supplemental zinc is taken in the fasting state. In contrast, the effects of zinc supplementation on fatty acid desaturation

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TABLE 1 Participant characteristics at baseline[1]

Characteristic	ZBB	ZWB	Overall
n	18	17	35
Age, y	23.8 ± 1.71	25.6 ± 2.16	24.7 ± 1.36
Height, cm	174 ± 2.20	177 ± 1.71	175 ± 1.40
Weight, kg	71.8 ± 3.08	73.5 ± 2.80	72.6 ± 2.06
BMI, kg/m^2	23.7 ± 0.795	23.5 ± 0.793	23.6 ± 0.553

[1]Age, height, weight, and BMI are expressed as mean ± SEM. Data are missing for 1 ZBB and 2 ZWB participants who withdrew consent before the first visit. ZBB; zinc before breakfast; ZWB, zinc with breakfast.

are only seen when supplemental zinc is taken with food. Others have examined the short-term effects of zinc given with food compared with fasted, using differing forms of zinc (11). However, to our knowledge, the current study is the first to assess the effects on PZC when the same chemical form and amount of supplemental zinc are taken either in a fasted state or with a meal. We found that a marked increase in PZC occurred only when supplemental zinc was taken without food. Thus, the divergent plasma zinc response to supplemental zinc appears to be due to the presence or absence of food. Also, taking supplemental zinc with a meal increased the ARA/DGLA molar ratio, whereas that did not occur when supplemental zinc was taken before the meal. Thus, the effects of supplemental zinc on PZC and EFA metabolism are incongruent and depend on whether the supplement is taken before or with the meal.

The effects of food intake on PZC and zinc absorption have been studied previously (11, 16). In general, food intake causes a decline in PZC (18). In a short-term zinc kinetics study, women were given a stable zinc isotope intravenously either fasting or with food, and their PZC was measured over the following 2 h. The sharp decline in PZC following a meal was explained by an increase in the exchange of zinc with extravascular pools (i.e., the postprandial decline in PZC may reflect a redistribution of zinc from the plasma into the liver and other tissues to facilitate postprandial metabolism) (12). Previous studies show that both enteral and intravenous feeding caused a decline in plasma zinc and that a postprandial fall occurs with isocaloric amounts of either glucose or fat (17). Also, in a study of young Peruvian and Ecuadorian children, PZCs were positively related to the number of hours since the previous meal (i.e., the longer the time since eating, the higher the PZC) (19). On average, PZCs increased about 1 μg/h after eating. Participants in the current study were instructed to fast at least 8 h and fasted on average for 10.8 ± 0.28 h (mean ± SEM) overnight (data not shown).

The response in plasma of an orally administered zinc tracer (relative to an intravenously administered tracer) is considered a good indicator of zinc absorption. PZC is typically used as an intermediate variable reflecting the effect of zinc on various metabolic or physiologic pathways (20). However, several studies show a lack of congruence of PZC with zinc intake even when zinc intake had demonstrable metabolic or health-related effects. A recent analysis of NHANES (2011–2014) found no correlation of serum zinc with dietary or supplemental zinc intakes, despite 8% of participants falling below the respective serum cutoffs for zinc deficiency (21). In children undergoing chemotherapy for leukemia, supplemental zinc increased body weight and reduced infections compared with a placebo, with no effect on PZC (22). In adult men undergoing experimental dietary zinc depletion, DNA strand breaks increased and then returned to baseline levels with repletion of dietary zinc, without any changes in PZC (23).

When zinc is consumed in a meal, plasma zinc is directed postprandially into extravascular pools to facilitate metabolism. Also, because the liver is a major site for postprandial fatty acid desaturation, we predicted that zinc mobilized postprandially would facilitate fatty acid metabolism (5).

TABLE 2 Effects on plasma essential fatty acids after zinc gluconate supplementation[1]

Total plasma fatty acids	ZBB ($n = 17$)	ZWB ($n = 16$)	Overall ($n = 33$)	Correlation with PZC, r (P value)
PZC, μg/dL				
Baseline	87.6 ± 2.31	84.8 ± 2.34	86.2 ± 1.64	—
2 wk	105 ± 5.88	88.7 ± 2.36*	97.0 ± 3.49	—
LA, mM				
Baseline	1.35 (1.26, 1.44)	1.28 (1.21, 1.36)	1.31 (1.26, 1.37)	–0.22 (0.23)
2 wk	1.23 (1.13, 1.33)	1.31 (1.21, 1.42)	1.27 (1.20, 1.34)	0.18 (0.32)
GLA, nM				
Baseline	31.7 (25.7, 39.0)	30.2 (25.4, 35.9)	31.0 (27.2, 35.2)	–0.37 (0.04)*
2 wk	29.6 (25.1, 35.0)	36.8 (31.0, 43.7)	32.9 (28.8, 37.6)	0.04 (0.83)
DGLA, mM				
Baseline	0.147 (0.128, 0.169)	0.142 (0.128, 0.157)	0.145 (0.133, 0.157)	–0.19 (0.28)
2 wk	0.146 (0.128, 0.166)	0.149 (0.130, 0.170)	0.147 (0.133, 0.163)	0.12 (0.50)
ARA, mM				
Baseline	0.829 (0.760, 0.897)	0.825 (0.753, 0.896)	0.827 (0.780, 0.873)	–0.22 (0.22)
2 wk	0.752 (0.683, 0.821)	0.855 (0.784, 0.926)*	0.802 (0.745, 0.859)	0.03 (0.88)

[1]PZCs are reported as mean ± SEM. LA, GLA, DGLA, and ARA are geometric mean (95% CI). Significant differences between ZWB and ZBB groups at baseline and after supplementation are indicated by an asterisk. Values after supplementation are controlled for baseline (ANCOVA). Pearson correlation with PZC overall at baseline and after supplementation is indicated for each fatty acid, and significant correlation indicated by an asterisk. ARA, arachidonic acid; DGLA, dihomo-γ-linolenic acid; GLA, γ-linolenic acid; LA, linoleic acid; PZC, plasma zinc concentration; ZBB; zinc before breakfast; ZWB, zinc with breakfast.

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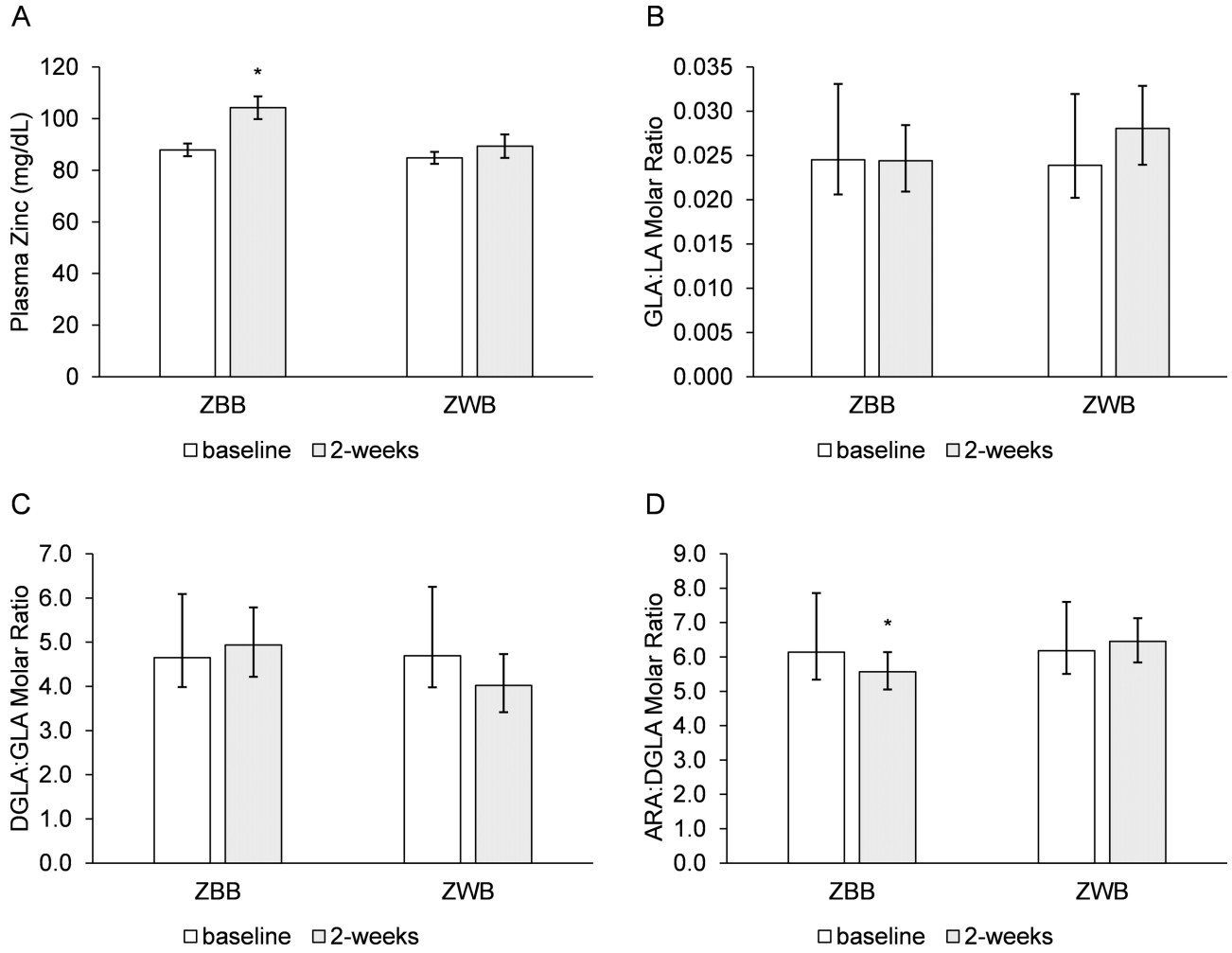

FIGURE 3 Effects on plasma zinc, and desaturation and elongation activity indices. ZBB ($n = 17$) and ZWB ($n = 16$). An asterisk signifies a statistically significant difference between treatment groups after zinc supplementation ($P < 0.05$) when controlling for baseline values (ANCOVA). (A) Data are expressed as mean ± SEM. (B–D) Fatty acid molar ratios for FADS2, ELOVL5, and FADS1 activity indices, respectively, are displayed as geometric mean, with error bars representing the 95% CI. *Different from ZWB ($P < 0.05$). ELOVL5, elongase 5; FADS, fatty acid desaturase; ZBB, zinc before breakfast; ZWB, zinc with breakfast.

Because the portal circulation is directed primarily to the liver, zinc-dependent hepatic processes may have a more direct access to zinc coabsorbed with food rather than that transferred postprandially from the peripheral blood plasma. An isotopic tracer study that includes compartmental modeling of oral and intravenous zinc tracers with mechanistic studies of tissue-specific metabolism could clarify the metabolic effects of food consumption on zinc metabolism.

FADS2 catalyzes the conversion of LA to GLA, whereas FADS1, coming later in the pathway of n–6 FA desaturation, catalyzes the conversion of DGLA to ARA. In a previous study, we found that limiting zinc intakes to 6 mg/d for 2 wk in healthy men reduced the activity indices of both FADS1 and FADS2 in the fasting state, which returned to normal when 25 mg supplemental zinc was provided daily (unpublished data). Others have similarly proposed the LA/DGLA ratio, which is dependent on FADS2 and ELOVL5, as a biomarker of zinc status in humans (7, 17).

The sensitivity of FADS1 compared with FADS2 activity indices to changes in zinc nutriture likely depends on a variety of factors, including characteristics of the participants, the study design, and sample collections. Hernandez et al. (6) measured the fatty acid composition of erythrocyte membranes of adult patients with type 2 diabetes receiving a 30-mg/d zinc supplement for 24 mo. Although changes in FADS1 and FADS2 activity indices were not observed in the erythrocyte membranes, changes in FADS1 mRNA were observed in leukocytes. The effects of zinc on FADS1 activity may therefore be partly regulated by gene expression. We propose that changes in n–6 FA desaturation, such as examined in the present study, reflect metabolism largely mediated hepatically, in which zinc may more immediately influence desaturase expression.

A strength of this study is that it is the first study, to our knowledge, to compare the metabolic effects of the same amount and form of supplemental zinc when it is given in a fasted state or with food. Possibly, the metabolic response varies with the form of supplemental zinc as observed by Aaron et al. (11). In that study, zinc oxide was provided as a fortificant of bread, whereas zinc sulfate dissolved in aqueous solution was provided for comparison. Because zinc oxide is not as well absorbed due to its lower solubility (24, 25), lack of a detectable effect on PZC may have been in part due to the form of zinc taken with food. Using same form and amount of zinc as a supplement before or with breakfast eliminated that ambiguity.

The study has several limitations. The participants were not masked to the intervention, and their diets were not controlled.

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The FA content of a meal may affect the concentration of FAs in circulation (6, 26). Also, this study does not identify a potential mechanism for the effects of supplemental zinc given before or with a meal on fatty acid desaturation. Both LA and ARA are precursors to the formation of oxylipins, which are involved in the regulation of inflammation (27, 28). Studying this metabolic pathway and its downstream effects on inflammation and cardiovascular health would be valuable. Such a study would require a larger sample and a longer study period. More research is also needed to determine whether consuming a smaller amount of food zinc over a longer period, typical of food fortification, would produce similar metabolic changes.

It is estimated that ~25% of the global population consumes low-zinc diets (29). However, PZCs, the most common biomarker of zinc status, are frequently normal (24). That led us to further assess the sensitivity of FADS activities as an indicator of zinc status. The divergent response of PZC and n–6 FA desaturation when a supplement is taken fasting or with food highlights the limitation of PZCs as a predictor of zinc-dependent metabolic effects. Furthermore, noncommunicable diseases, including cardiovascular disease and type 2 diabetes, are leading cause of mortality worldwide (30). Zinc interventions reduce risk factors for both (31). It is notable that those 2 chronic diseases are characterized, in part, by dyslipidemia and reduced essential fatty acid desaturation (27, 32), which both require zinc.

In summary, the results of this study show that taking supplemental zinc in a fasted state increases the PZC, whereas taking the same amount of zinc with food has no effect on PZCs. When food is present, the proportion of zinc absorbed is likely reduced. But, enhanced metabolism of EFAs suggests that tissue zinc uptake may be enhanced to better facilitate metabolism. Because the metabolic effects of zinc may depend on whether it is taken fasted or with food, we recommend that future studies of zinc supplementation control the timing of food intake in relation to the supplement. Future research is needed to determine how absorbed zinc may be directed differently toward metabolic and structural roles depending on whether it is coabsorbed with food.

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The authors' contributions were as follows—JCK, AGH, and JS: designed research; AGH, YNM, and JS: analyzed the data; YNM and AGH: wrote the paper; and all authors: had primary responsibility for final content and read and approved the final version.

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