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Marginal Zinc Deficiency Alters Essential Fatty Acid Metabolism in Healthy Men

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ABSTRACT

Background: Rice biofortification with Zinc (Zn) can improve the Zn status of rice-consuming populations. However, the metabolic impact in humans consuming Zn-biofortified rice is unknown.

Objectives: To determine the effects of Zn-biofortified rice on lipid metabolism in normolipidemic men.

Methods: The men consumed a rice-based diet containing 6 mg Zn/d and 1.5 g phytate (phytate/Zn ratio = 44) for 2 wk followed by a 10-mg Zn/d diet without phytate for 4 wk. An ad libitum diet supplemented with 25 mg Zn/d was then fed for 3 wk. Fasting blood samples were taken at baseline and at the end of each metabolic period for measuring plasma zinc, glucose, insulin, triglyceride (TG), LDL and HDL cholesterol, fatty acids, oxylipins, and fatty acid desaturase activities. Statistical differences were assessed by linear mixed model.

Results: Fatty acid desaturase (FADS) 1 activity decreased by 29.1% ($P = 0.007$) when the 6-mg Zn/d diet was consumed for 2 wk. This change was associated with significant decreases in HDL and LDL cholesterol. The alterations in FADS1, HDL cholesterol, and TG remained unchanged when Zn intakes were increased to 10 mg/d for 4 wk. Supplementation with 25 mg Zn/d for 3 wk normalized these metabolic changes and significantly increased LDL cholesterol at the end of this metabolic period compared with baseline. FADS1 activity was inversely correlated with FADS2 ($r_{mcorr} = -0.52$; $P = 0.001$) and TG ($r_{mcorr} = -0.55$; $P = 0.001$) at all time points.

Conclusions: A low-zinc, high-phytate rice-based diet reduced plasma HDL cholesterol concentrations and altered fatty acid profiles in healthy men within 2 wk. Consuming 10 mg Zn/d without phytate for 4 wk did not improve the lipid profiles, but a 25-mg Zn/d supplement corrects these alterations in lipid metabolism within 3 wk. *J Nutr* 2022;152:671–679.

Keywords: zinc, zinc biofortification, phytate, lipids, fatty acid metabolism, HDL cholesterol, LDL cholesterol, oxylipins, fatty acid desaturase

Introduction

Dietary zinc (Zn) deficiency is prevalent among populations subsisting on rice-based diets (1). In many low-income Asian populations, rice may contribute 80% of the daily energy intake, but it lacks sufficient amounts of several essential micronutrients, including Zn. Thus, biofortifying rice with Zn is an ideal approach for preventing Zn deficiency in regions where rice is a staple crop (1, 2). Zn-biofortified rice that has a 50% increase in the Zn concentration could increase dietary Zn as much as 4 mg/d. Although this biofortification strategy is promising, assessing the impact of Zn biofortification on the Zn status in vulnerable populations is challenging primarily because plasma/serum Zn concentrations are insensitive to modest changes in dietary Zn (3–5). Improved child growth or reductions in infections, such as diarrhea, may reflect dietary Zn changes, but those studies require longitudinal data and are influenced by many confounding factors. Thus, novel, sensitive biomarkers of changes in dietary Zn are urgently needed.

Zn is present in >3000 different proteins and participates in every aspect of the metabolic processes that occur in all cell types (6). Because of Zn's dynamic role in multiple cell types and diverse biochemical pathways, shifts in cellular functions sensitive to low dietary Zn have not been well defined. Studies in yeast and rodents have shown a close relation between Zn and lipid metabolism (7–9). Although specific mechanisms have not been elucidated, dietary Zn modulated

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Abbreviations used: AA, arachidonic acid; Apo-A1, apolipoprotein A1; DGLA, dihomo-γ-linolenic acid; FADS, fatty acid desaturase; GLA, γ-linolenic acid; LA, linoleic acid; LpL, lipoprotein lipase; MP, metabolic period; PPAR, peroxisome proliferator activated receptor; R_{mcorr}, repeated-measures correlation; SCD1, stearoyl-CoA desaturase 1; SREBP, sterol-responsive element binding protein; TG, triglyceride; Zn, zinc; 11(12)-EpETrE, 11,12-epoxyeicosatrienoic acid; 14(15)-EpETE, 14(15)-epoxy-eicosatetraenoic acid.

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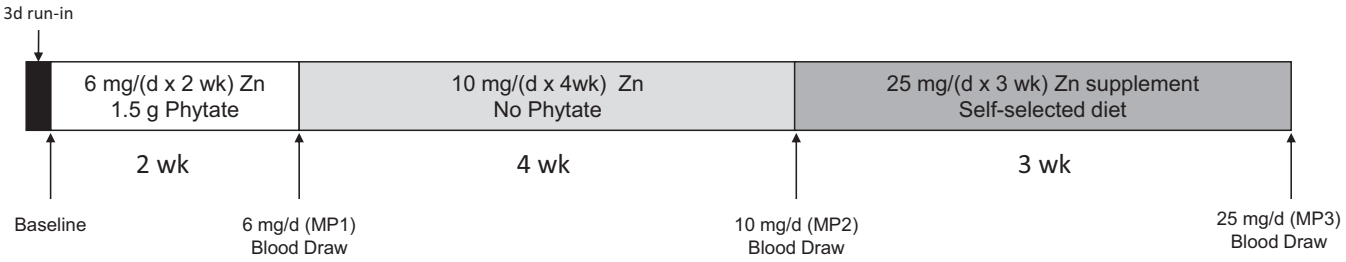

FIGURE 1 Study design. Eighteen healthy men aged 19–45 y with BMI 18–30 kg/m^2 participated in the study. The study consisted of a 3-d run-in period to acclimate the participants to the control diet, after which baseline blood samples were collected. The men then consumed a controlled diet providing 6 mg zinc (Zn)/d for 2 wk that was fortified with 1.5 g sodium phytate/d to induce a marginal Zn depletion (MP1). Between weeks 2 and 6, dietary Zn was increased to 10 mg Zn/d for 4 wk by adding 4 mg exogenous Zn sulfate to rice consumed daily. No exogenous phytate was provided during this period (MP2). During weeks 7 through 9, participants consumed an ad libitum diet with 25 mg/d supplemental Zn citrate for 3 wk. Blood samples were taken at the end of each MP. One participant missed a time point at the end of MP1, and another missed at the end of MP2. All participants completed the study. MP, metabolic period.

the lipid-sensing role of sterol-responsive element binding proteins (SREBPs) and mediated posttranslational regulation of enzymes that are responsible for lipid synthesis (10). In acrodermatitis enteropathica, a genetic condition caused by a rare mutation in the ZIP4 protein, Zn deficiency is associated with a marked reduction in omega-6 fatty acid incorporation into triglycerides, which is reversed with Zn supplementation (11). Recent research has also shown an association between Zn intake and linoleic acid (LA) (12, 13) and arachidonic acid (AA) metabolism (14). Although these studies illustrate a close mechanistic link between Zn and lipid metabolism, the sensitivity of lipid metabolic biomarkers to modest variations in Zn intake has not been comprehensively studied in human participants.

Previously, we conducted a randomized controlled diet intervention study to determine the effects of a modest reduction in dietary Zn on Zn absorption, exchangeable Zn pool sizes, leukocyte Zn concentration, DNA oxidation, and the plasma proteome (15). DNA oxidation and circulating concentrations of apolipoprotein A1 (Apo-A1) were both sensitive to reductions in dietary Zn to 6 or 10 mg/d. However, the metabolic impact in humans consuming Zn-biofortified rice is unknown.

Methods

Study design

The primary study that provided the samples for these analyses has been published previously (15). To determine the effects of modest increases in dietary Zn on measures of metabolic functions, a 6-wk feeding study was done in men who consumed a food-based diet with controlled amounts of Zn (**Figure 1**). During the initial 2-wk depletion period, the diet provided 6 mg Zn/d for 2 wk plus 1.5 mg sodium phytate/d that was followed by a controlled diet providing 10 mg Zn/d without added phytate for 4 wk. During the first and second metabolic periods (MPs), Zn intakes were adjusted by adding exogenous Zn sulfate to cooked rice. During the third metabolic period (MP3), participants consumed their typical diet ad libitum along with 25 mg supplemental Zn/d as Zn citrate.

Participants

Eighteen healthy men aged 19–45 y with a BMI (in kg/m^2) between 18 and 30 participated in the study between March 2012 and July 2013. After a 3-d run-in period to familiarize the participants to the controlled diet, fasting baseline blood samples were collected. The men then consumed a controlled diet providing 6 mg Zn/d that was fortified with 1.5 g sodium phytate/d to reduce Zn absorption for 2 wk (MP1). During MP2, weeks 2–6, dietary Zn was increased to 10 mg/d by adding 4 mg Zn/d to the diet rice to mimic the additional Zn content of Zn-biofortified rice without any dietary phytate. All 18 participants completed this study, but 1 participant did not have sample at post-MP1 and another participant did not have sample at post-MP2. In MP3 (weeks 7–9), the participants consumed an ad libitum diet with 25 mg supplemental Zn/d (Figure 1). Fasting blood samples were taken at baseline and at the end of each metabolic period, that is, the end of weeks 2, 6, and 9 (Figure 1).

Ethics

The study design and protocol were reviewed and approved by the Children's Hospital Oakland Research Institute Institutional Review Board. Written, informed consent was obtained from all participants.

Inclusion and exclusion criteria

Men aged 19–50 y with BMIs between 18 and 30 were eligible for the study. They needed to be willing to discontinue any dietary supplements for at least 4 wk prior to the study initiation and to report a usual Zn intake > 9.5 mg/d, as estimated from a 24-h dietary recall. They also needed to have a fasting plasma Zn concentration ≥ 60 μg/dL. Potential participants reporting any chronic or acute disease that required medications or substance/alcohol abuse were excluded. Participant height was measured at first clinical visit, and body weight was monitored twice weekly throughout the study period.

Study diets

A detailed description of the study diet menu and nutrient composition were reported previously (15). Briefly, the study diet consisted of a 4-d cycle menu with carbohydrate, protein, and fat contributing 80%, 10%, and 10%, respectively, of total energy. Participants could use salt and pepper freely with the meals, and water intake was not restricted. Alcohol or sugar-containing beverage consumption was prohibited. Compliance to the study diet was monitored through self-reports and the food containers that were returned biweekly. Any uneaten food was self-reported. To maintain a steady body weight, each participant's caloric intake was adjusted based on their resting metabolic rate, as estimated by a BOD POD whole-body, air-displacement plethysmography device (COSMED USA) and self-reported physical activity. Additional Zn-free beverages with the same macronutrient distribution as the study diet were provided to maintain body weight. Total energy intakes of the men ranged from 2500 to 3000 kcal/d.

Blood sampling and processing

Fasting blood samples were obtained between 07:00 and 09:00 on the clinical visit days. Trace element–free certified K_2EDTA tubes were used for the Zn measurements and plasma metabolite analyses. The blood tubes were centrifuged at 800 × *g* for 15 min at 4°C. The plasma

TABLE 1 Plasma Zn concentrations and clinical parameters of dyslipidemia and insulin resistance in 18 men at baseline and at end of each metabolic phases[1]

Characteristic	Baseline ($n = 18$)	6 mg Zn/d for 2 wk (MP1, $n = 17$)	10 mg Zn/d for 4 wk (MP2, $n = 17$)	25 mg Zn/d for 2 wk (MP3, $n = 18$)	*P* value for MP
Plasma Zn, μg/dL	75.0 ± 2.8^{c}	74.0 ± 3.0^{cd}	79.4 ± 3.0^{bc}	89.5 ± 3.0^{a}	<0.0001
Fasting blood glucose, mg/d	86.4 ± 1.7	84.1 ± 1.7	87.6 ± 1.7	89.0 ± 1.7	0.08
Insulin, mU/L	3.38 ± 0.42	3.95 ± 0.41	3.66 ± 0.41	3.73 ± 0.40	0.57
HOMA-IR	0.75 ± 0.10	0.83 ± 0.10	0.81 ± 0.10	0.84 ± 0.10	0.80
HDL cholesterol, mg/dL	43.3 ± 2.87^{b}	35.7 ± 2.14^{c}	38.5 ± 2.14^{cd}	50.4 ± 2.10^{a}	<0.0001
LDL cholesterol, mg/dL	83.3 ± 4.74^{bc}	73.9 ± 4.11^{cd}	81.4 ± 4.11^{c}	93.1 ± 4.03^{a}	0.0002
TG, mg/dL	95.2 ± 30.5^{bc}	110 ± 47.8^{b}	122 ± 47.5^{ab}	79.3 ± 21.2^{cd}	0.001

[1] Values are mean ± SEM. Means without common letter differ, $P < 0.05$. MP, metabolic period; TG, triglyceride; Zn, zinc.

fraction was collected and further centrifuged at 3000 × *g* for 10 min at 4°C.

Laboratory analysis

Plasma Zn concentrations were determined by inductively coupled plasma–optimal emission spectrometry as described previously (15).

Total plasma lipids were extracted and subaliquots were used to measure esterified and free fatty acids and oxylipins using internal standard methodology and mass spectrometry (16). Fatty acids were transesterified to produce fatty acid methyl esters and then analyzed by GC mass spectrometry using an Agilent 6890 GC system coupled to 5973 mass spectral detector.

Activity estimates for fatty acid desaturase (FADS1) 1, FADS2, and stearoyl-CoA desaturase enzymes were calculated based on the ratios of dihomo-γ-linolenic acid (DGLA)/AA (FADS1), γ-linolenic acid (GLA)/LA (FADS2), and the sum of palmitoleic and oleic acid/sum of palmitic and stearic acid [stearoyl-CoA desaturase 1 (SCD1)]. Validity of the use of these fatty acid ratios as activity estimates is supported by the strength of associations between these ratios and desaturase genetic polymorphisms and dietary intake as previously examined (17–21).

For oxylipins, deuterated oxylipin internal standards were added to subaliquots and samples were esterified in 0.1 N NaOH at 60°C for 1 h and then hydrolyzed to produce free fatty acids. Oxylipin free acids were extracted using 96-well Oasis HLB solid phase extraction plates (Waters Corp). Extracts were stored at –20°C until analysis by Waters Acquity ultrahigh pressure liquid chromatography coupled to API 4000 QTrap (AB Sciex) system (17, 18), and analytes were detected by negative mode electrospray ionization using the multiple-reaction monitoring method. Ratios of endogenous to spiked in stable isotope internal standards were used for quantification. Data quality assurance measures including surrogate recoveries and replicate analyses indicated acceptable performance, with comparable performance among batches.

Plasma triglycerides (TGs), total and HDL cholesterol, and glucose were measured by enzymatic endpoint analysis on a clinical chemistry analyzer (LIASYS 330) using methodology described previously (22). LDL cholesterol was calculated using the Friedewald equation (23). Fasting insulin was measured by ELISA, with 2 in-house quality control standards. HOMA-IR was calculated as [glucose (mg/dL) * insulin (mU/L)]/405.

Statistical analysis

Descriptive statistics of continuous variables were performed to calculate the mean, median, range, and standard deviations using the statistical program R version 3.5.1 (R Core Team) and the various packages indicated below. Combined fatty acid and oxylipin analysis yield a total of 101 lipid features. Features that were missing in > 80% of the cases were removed, resulting in a total of 93 features in the analysis. Following this filter, 2 and 8 instances of missing prostaglandin $F_{2\alpha}$ and 14,15-epoxy eicosatetraenoic acid [14-(15)-EpETE] data were identified, respectively. Cluster analysis of missing data was performed to determine if these occurred in random fashion by using the Naniar package. All instances of missing data involved single missing data points in different participants distributed across different time points, and no apparent clustering of missing information was detected. Missing values were omitted in pairwise manner. Repeated-measures differences between baseline and the end of each metabolic phase were determined using linear mixed models with dietary Zn intake at each metabolic phase (treatment) as the fixed effect and participants as the random effect using the procedures available in the lmerTest package. Multiple comparisons between time points were performed by the Tukey test using the multcomp package, and *P* values were adjusted for multiple comparisons using the single-step approach. Summary data statistics of these analyses were prepared using the Broom mixed package. Compound symmetry was used for modeling. Validity of these assumptions was made based on results obtained from the Shapiro–Wilk method for normality or the Bartlett test of homogeneity of variance available in the stats package version 3.6 in R.

For oxylipin analysis, a volcano plot was created by first $\log_2$ transforming data, and then differences between MP1 compared with baseline and MP2 compared with MP1 were calculated and plotted against –log *P* value using Prism v9 (GraphPad Software). *P* values were obtained using a mixed-effect linear model with metabolic phases as fixed effect and participants as random effect. Multiple comparisons of the groups were performed using the Tukey test available in the multicom package. Single-step method was used to adjust for multiple comparisons.

Repeated-measures correlation analysis (r_{mcorr}) was performed using the r_{mcorr} R statistical package based on previously described methods (24). Rmcorr calculates within-participant correlations for paired repeated measures that are made at different time points. Rmcorr provides best linear fit for each participant using parallel regression lines. In contrast to Pearson correlation, this analysis aims to determine overall intraindividual association between 2 measures. In this analysis, interindividual variability is accounted by ANCOVA analysis. For clarity, the intraindividual trends were plotted in facetted plots to show consistencies in paired observations made at multiple time points within each participant. Overall aggregate associations were assessed from the Rmcorr fitted model. For analysis, *P* values < 0.05 were used as the cutoff for statistical significance. Graphs were created using Prism version 8.4.2 or R version 3.5.1.

Results

Plasma Zn concentrations did not change during MP1 or MP2 when 6 mg Zn/d (2 wk) plus phytate or 10 mg Zn/d (4 wk) without phytate was fed. However, a 25-mg Zn/d (3-wk) supplement taken without food in the morning increased plasma Zn concentrations by 12.5% ($P < 0.005$) (**Table 1**). Fasting blood glucose and insulin concentrations and HOMA-IR did not change with the shifts in dietary Zn during the study.

Following MP1 when dietary Zn was 6 mg/d and phytate content were high, fasting HDL cholesterol and LDL cholesterol concentrations declined by –17.5% ($P = 0.001$) and

TABLE 2 Fasting plasma fatty acid concentrations at the end of sequential metabolic phases with varying Zn intakes[1]

Characteristic	Baseline ($n = 18$)	6 mg/d Zn for 2 wk (MP1, $n = 17$)	10 mg/d Zn for 4 wk (MP2, $n = 17$)	25 mg/d Zn for 2 wk (MP3, $n = 18$)	Synthetic enzyme	*P* value for MP effects
Palmitic C16:0	3050 ± 319^{c}	3352 ± 327^{bc}	3910 ± 327^{ab}	2910 ± 319^{cd}	—	0.05
Palmitoleic C16:1n–7	304 ± 69.9^{c}	456 ± 71.6^{bc}	574.3 ± 71.6^{ab}	204 ± 69.9^{cd}	SCD1	0.01
Stearic C18:0	517 ± 36.4	550 ± 37.7	637 ± 37.7	651 ± 36.8	EVOL6	0.25
Oleic C18:1n–9	2760 ± 266^{bc}	3210 ± 273^{b}	3610 ± 273^{a}	2540 ± 267^{c}	SCD1	0.01
n–6: fatty acids						
Linoleic C18:2n–6	3740 ± 264^{bc}	3030 ± 270^{cd}	3210 ± 270^{c}	4431 ± 264^{a}	—	<0.001
γ-Linolenic C18:3n–6	35.7 ± 6.68^{ba}	43.4 ± 6.86^{b}	57.9 ± 6.86^{ab}	32.4 ± 6.68^{ba}	FADS2	0.03
Dihomo-γ-linoleni C20:3n–6	118 ± 20.0^{ba}	158 ± 20.4^{b}	189 ± 20.5 ^{ab}	121.3 ± 20.0^{ba}	EVOL2	0.006
Arachidonic C20:4n–6	507 ± 37.2^{b}	438 ± 37.9^{c}	453 ± 37.9^{bc}	525 ± 37.2^{a}	FADS1	0.008
n–3: fatty acids						
α-Linolenic C18:3n–3	38.4 ± 3.73	39.3 ± 3.84	43.3 ± 3.83	36.7 ± 3.74	—	0.25
Eicosatrienoic C20:3n–3	5.84 ± 0.54	5.92 ± 0.55	5.46 ± 0.55	7.17 ± 0.54	EVOL2	0.17
Eicosatetraenoic C20:4n–3	5.55 ± 1.13^{cd}	8.21 ± 1.16^{b}	10.3 ± 1.16^{a}	7.96 ± 1.13 ^{bc}	FADS2	0.04
Eicosapentaenoic C20:5n–3	18.1 ± 4.78^{b}	18.0 ± 4.91^{c}	22.9 ± 4.91^{bc}	35.3 ± 4.78^{ab}	FADS1	0.03
Docosapentaenoic C22:5n–3	14.6 ± 1.19^{cd}	16.2 ± 1.23^{c}	17.9 ± 1.23^{a}	16.6 ± 1.20^{bc}	EVOL2/EVOL5	0.01
Docosahexaenoic C22:6n–3	49.8 ± 4.65	45.3 ± 4.77	49.2 ± 4.78	45.8 ± 4.65	—	0.25

[1]Values are mean ± SEM and units are μmol/L for all observations. Means without common letter differ, $P < 0.05$. EVOL2, fatty acid elongase 2; EVOL5, fatty acid elongase 5; EVOL6, fatty acid elongase 6; FADS1, fatty acid desaturase 1; FADS2, fatty acid desaturase 2; MP, metabolic period; SCD1, stearoyl-CoA desaturase.

–10.8% ($P = 0.03$), respectively. Following consumption of diet containing 10 mg Zn/d without phytate for 4 wk, HDL cholesterol remained significantly decreased by 12.0% relative to baseline ($P = 0.02$). However, post-MP2, LDL cholesterol concentrations were similar to the baseline concentration. Following supplementation with 25 mg Zn/d during the last 3 wk of the study, HDL cholesterol and LDL cholesterol increased by 30.9% ($P = 0.001$) and 14.8% ($P = 0.0006$) relative to concentrations at the end of MP2 (Table 1).

In comparison to baseline concentrations, fasting plasma TG concentrations tended to be 17.9% higher after MP1 ($P = 0.09$) and were 24.0% higher at the end of MP2 ($P = 0.02$). Supplementation with 25 mg Zn/d for 4 wk significantly decreased plasma TG concentrations by 33.6% relative to

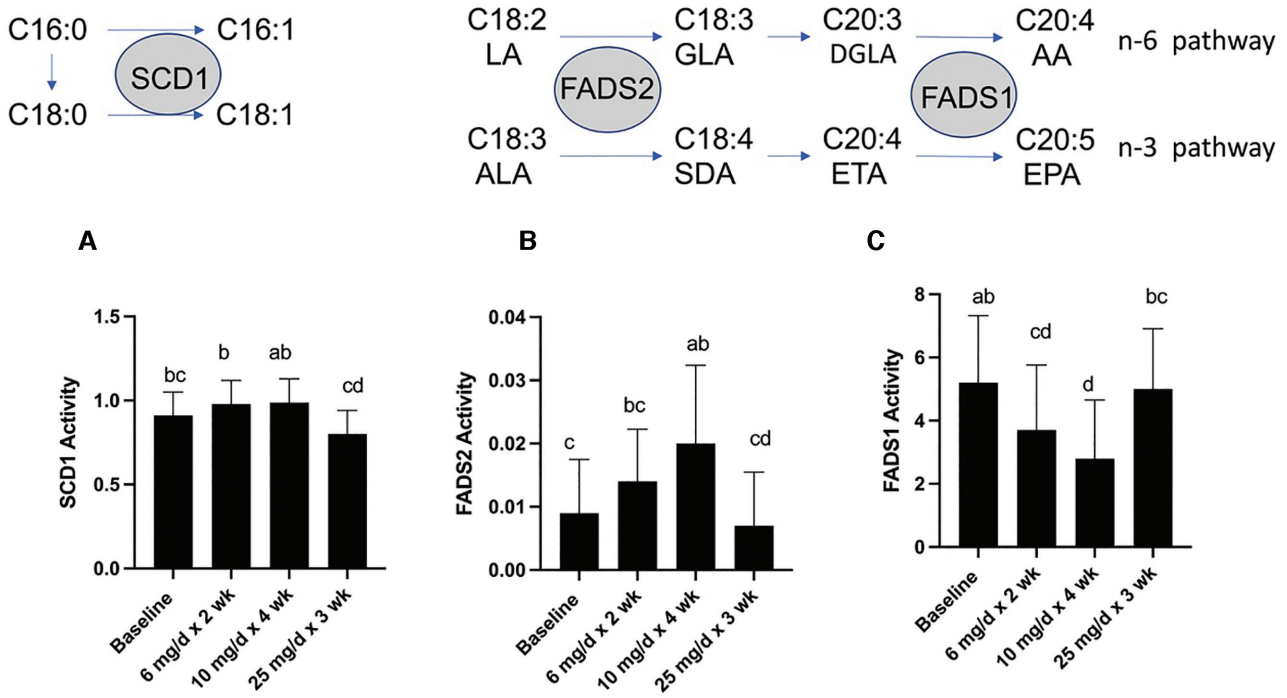

FIGURE 2 Modest changes in dietary zinc (Zn) intake alter fatty acid desaturase activities in 18 men at baseline and at the end of each metabolic phases with varying dietary Zn. Stearoyl-CoA desaturase 1 (SCD1) and fatty acid desaturase 1 and 2 (FADS1 and FADS2) activities were estimated from total plasma fatty acids at the end of each metabolic period. (A, B) SCD1 and FADS2 activities trended higher during the first 2 metabolic phases. (C) FADS1 activity significantly decreased following the 6-mg/d Zn intake period. Changes in FADS1 and FADS2 activities normalized to baseline following supplementation with 25 mg/d Zn citrate. Values are mean ± SEM. Sample sizes were $n = 18$, $n = 17$, $n = 17$, and $n = 18$ for baseline, MP1, MP2, and MP3 time points, respectively. Missing data were omitted from analysis. Means without common letter differ, $P < 0.05$. MP, metabolic period.

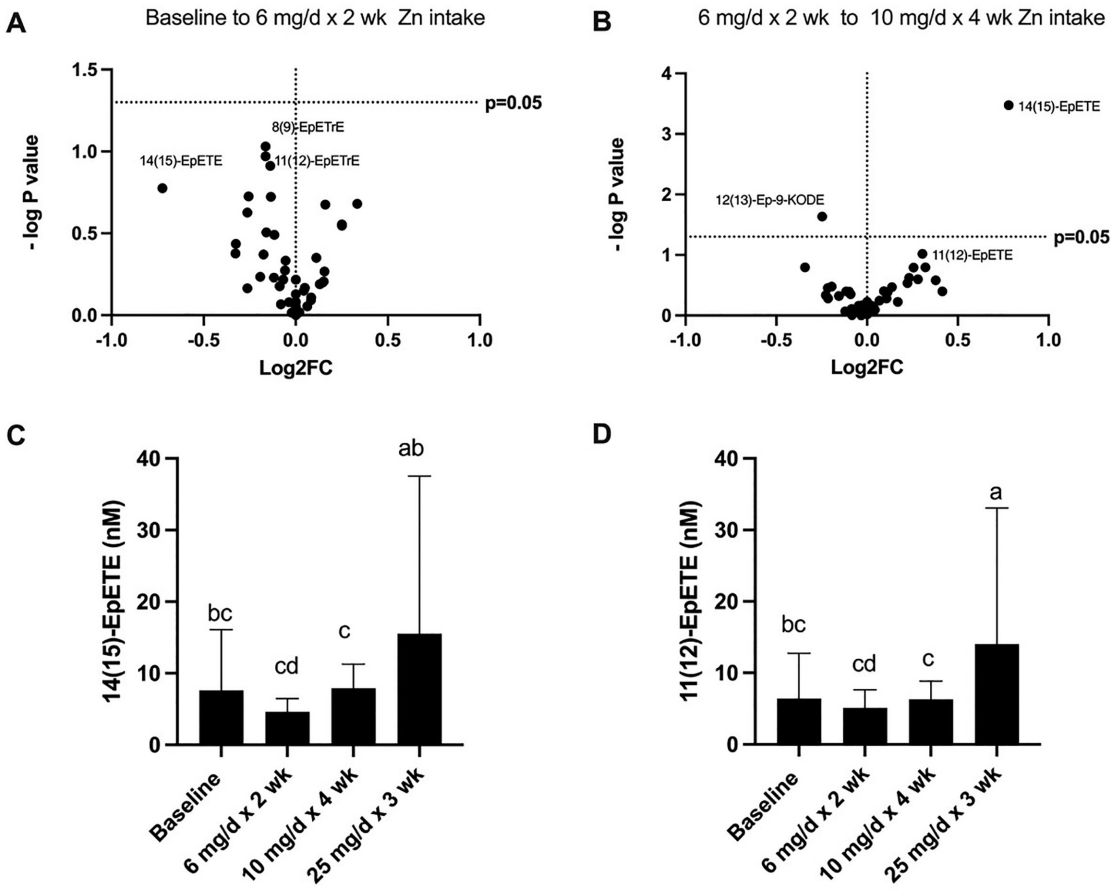

FIGURE 3 Oxylipin changes in 18 men at baseline and at the end of each metabolic phase with varying dietary zinc (Zn). (A) Volcano plot of $\log_2$ fold change (Log2FC) in 49 oxylipins detected at the end of 6 mg Zn/d for 2-wk intake period. (B) Volcano plot of oxylipin change due to increasing Zn intake from 6 mg Zn/d for 2 wk to 10 mg Zn/d for 4 wk. Results show that 14(15)-epoxy-eicosatetraenoic acid [14(15)-EpETE] trended lower with reduced Zn intake (panel A; $P < 0.1$). 8,9-Epoxyeicosatrienoic acid [8(9)-EpETrE] and 11,12-epoxyeicosatrienoic acid [11(12)-EpETrE], which are products of arachidonic acid oxidation by P450 pathways, also trended lower (panel A; $P < 0.1$). A modest increase in dietary Zn intake from 6 mg Zn/d for 2 wk to 10 mg Zn/d for 4 wk significantly elevated plasma 14(15)-EpETE (panel B). (C, D) The effects of dietary Zn modulation on plasma concentrations of EPA-derived 14(15)-EpETE and 11(12)-EpETE. Results show significant dose-dependent increases in these compounds with a higher Zn intake. Values are mean ± SEM and units are nmol/L. Means without common letter differ, $P < 0.05$.

concentrations at the end of MP2 ($P = 0.001$) to a concentration that did not differ from baseline.

The effects of modest dietary Zn modulation on plasma total fatty acid concentrations were determined to assess the shifts in desaturase activity index at each time point (**Table 2**). Lipids are ordered sequentially to reflect substrate–product relations with notations for the synthesis enzyme involved in the desaturase steps.

SCD1 desaturates palmitic acid and stearic acid to form palmitoleic acid and oleic acid, respectively. Palmitic and stearic acids (substrates for SCD1) were unaffected by MP1 diet. However, the concentrations of palmitic and stearic acid rose by 26% ($P = 0.03$) and 23% ($P = 0.01$), respectively, by the end of MP2, that is, both palmitoleic and oleic acids increased significantly by 88% ($P = 0.01$) and 31% ($P = 0.01$) (Table 2). SCD1 activity estimates based on ratios of the sum of these fatty acids trended higher by 8% ($P = 0.06$) at the at end of the MP2 period (**Figure 2**A). Switching to an ad libitum diet plus 25 mg supplemental Zn/d in MP3 caused palmitoleic and oleic acids (Table 2) and SCD1 activity to decrease significantly relative to post-MP1 and post-MP2 concentrations (Figure 2A).

FADS2 desaturates LA to GLA (Table 2). A transient but significant 19.0% ($P = 0.03$) decrease in plasma LA occurred during MP1. But following MP2, the LA concentrations were no longer different from baseline concentrations. However, a significant 62.4% ($P = 0.01$) increase in GLA was observed in MP2 when 10 mg Zn/d was fed. FADS2 activity trended higher by 56% ($P = 0.07$) at the end of MP1, and it was increased by 126% ($P = 0.0001$) following MP2. Supplementation with 25 mg Zn/d in MP3 decreased the FADS2 activity back to baseline concentrations (Figure 2).

FADS1 is required for de novo synthesis of AA and EPA. FADS1 activity, estimated from the ratio of AA/DGLA ratios, increased by 33.8% ($P = 0.07$) in MP1. During MP2, the DGLA increased further by 160% ($P = 0.002$). When participants took the 25 mg Zn/d supplement, DGLA concentrations returned to baseline. Plasma AA were similar throughout the study. FADS1 activity increased significantly, 28.9% ($P = 0.007$) and 45.6% ($P = 0.00005$) following MP1 and MP2 phases, respectively; the activity levels returned to baseline following the 25-mg Zn/d supplementation period.

FADS1 and FADS2 activities may modulate systemic inflammation by generating oxylipins from PUFAs. To evaluate these activities, 49 oxylipin species derived from LA, α-linolenic acid, AA, and EPA were analyzed by mass spectrometry. As shown in **Figure 3**A, 14(15)-EpETE), 8,9-epoxyeicosatrienoic acid, and 11,12-epoxyeicosatrienoic acid [11(12)-EpETrE] trended ($P < 0.1$) lower following MP1. When participants increased

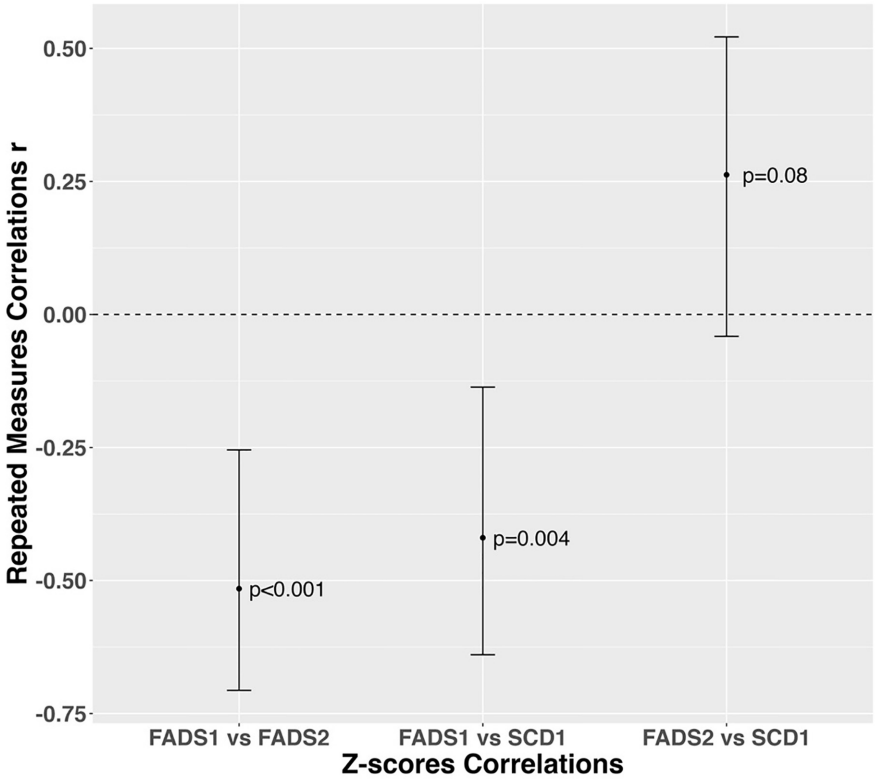

FIGURE 4 Repeated-measures correlations between stearoyl-CoA desaturase 1 (SCD1), fatty acid desaturase 1 (FADS1), and fatty acid desaturase 2 (FADS2) activities measured in 18 men at baseline and at the end of each metabolic phases with varying dietary zinc (Zn). Repeated-measures correlations between FADS1, FADS2, and SCD1 activity *z* scores at baseline and at the end of each metabolic phases were assessed using repeated-measures correlation analysis (R_{mcorr}). Common regression slope, which is association shared among individuals, and the 95% CI of these estimates are plotted. MP, metabolic period.

Zn intake from 6 to 10 mg/d during MP2, 14(15)-EpETE increased significantly (Figure 3C). 11(12)-EpETE, which is an EPA-derived oxylipin, also showed significant ~50% increases following MP2 (Figure 3D). Both 14(15)-EpETE and 11(12)-EpETE are P450-dependent EPA oxidation products, and these results suggest that cytochrome P450-dependent EPA oxidation is sensitive to dietary Zn variations.

Intraindividual correlations between activities of the different desaturase enzymes measured at multiple time points were analyzed by using repeated-measures correlation analysis (**Figure 4**). Using this approach, the significance of intraindividual correlations between paired observation desaturases was determined using *z*-transformed data. Results show highly correlated inverse association between FADS1 and FADS2 activities in almost all 18 participants. Composite r_{mcorr} of all participants were estimated to be –0.52 ($P = 0.0001$). Similar significant inverse correlations with $r_{mcorr} = –0.4$ ($P < 0.005$) were observed with FADS1 and SCD1 activities. Conserved correlations between the desaturases across multiple time points in different individuals suggest that desaturase enzymes are coregulated and sensitive to changes in Zn intake.

Correlations of TGs or HDL cholesterol with SCD1, FADS1, and FADS2 were examined by repeated-measures correlation analysis of *z*-transformed values (**Figure 5**). For TGs, FADS2 was the most significantly correlated ($r = 0.5$; $P = 0.001$), followed by FADS1 and SCD1. HDL cholesterol was most strongly associated with changes in SCD1 activity ($r = –0.64$; $P < 0.001$), followed by FADS1 and FADS2. These highly significant correlations suggest that modulations in dietary Zn alter plasma TG or HDL cholesterol ratios through desaturase-dependent mechanisms.

Discussion

Marginal Zn intakes are risk factors for inflammation, oxidative stress, and the metabolic syndrome, but detecting a suboptimal Zn intake is challenging because serum/plasma Zn concentrations are insensitive to small variations in dietary Zn (3–5, 24). In this study, the effects of modest adjustments in Zn intake on lipid and glucose metabolism were measured in healthy men. As reported previously (2, 6), modest adjustments in dietary Zn failed to alter plasma Zn concentrations. Despite lack of change in plasma Zn, sensitive alterations in lipid metabolism were detected. Our results showed that FADS1 activity was most sensitive to the effects of consuming 6 mg Zn/d for 2 wk; it decreased (–29%; $P = 0.007$). This change was associated with decreases in HDL cholesterol (–17.1%; $P = 0.001$) and LDL cholesterol (–10.8%; $P = 0.03$). Unexpectedly, increasing dietary Zn intake to 10 mg Zn/d for 4 wk failed to correct this response. Furthermore, many of the lipid differences that were trending at the end of MP1 were significantly altered at the end of the MP2 period. These changes returned to baseline when a 25-mg Zn/d supplement was given daily for 3 wk, suggesting that normalization of the effects of a marginal Zn intake (6 mg/d) may require either longer intervention with 10 mg Zn/d or higher dietary Zn intake. Although the changes in P450-dependent EPA-derived oxylipins were modest, clustering of the

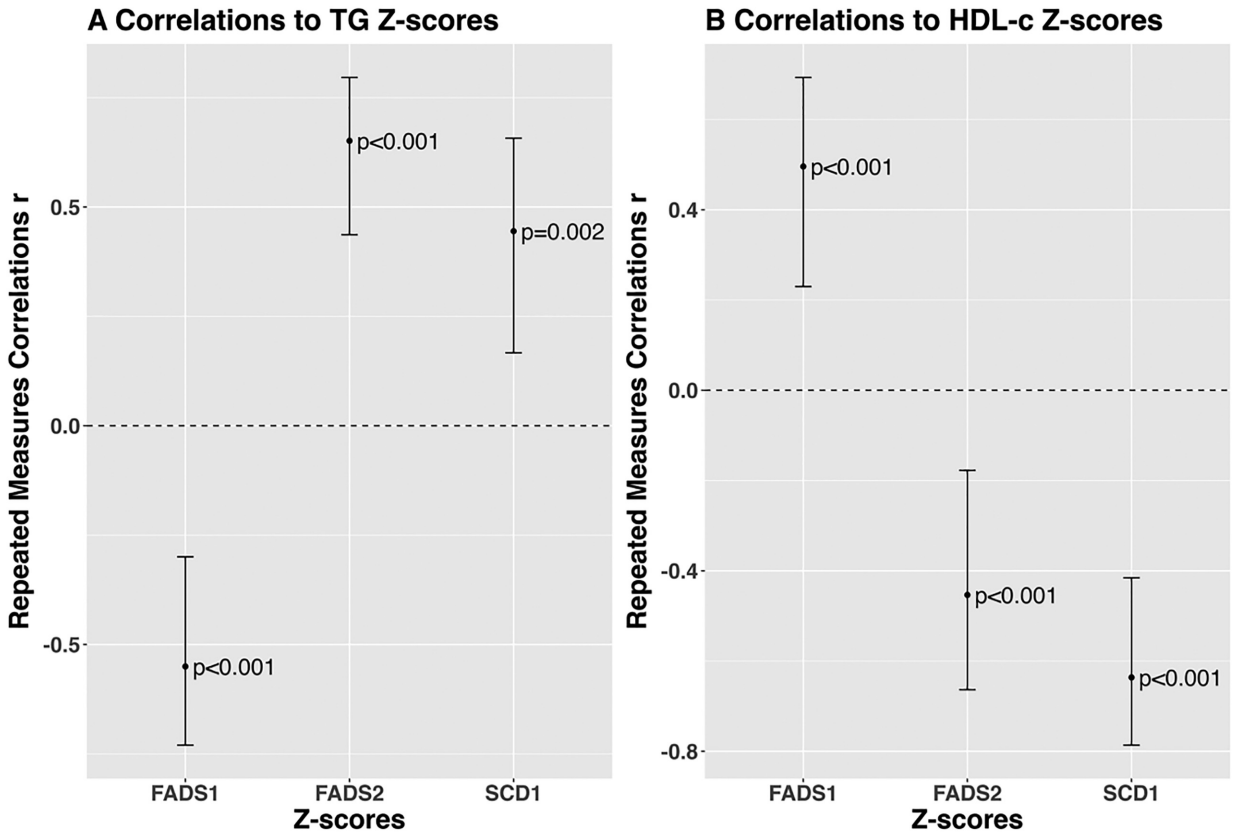

FIGURE 5 Repeated-measures correlations between enzyme activity, triglyceride (TG), and HDL cholesterol *z* scores calculated at baseline and at the end of each metabolic phases in 18 men. Repeated-measures correlation analysis was performed to determine the common within-individual associations between fatty acid desaturase 1 (FADS1), fatty acid desaturase 2 (FADS2), and stearoyl-CoA desaturase 1 (SCD1) activity *z* scores and fasting TG and HDL cholesterol *z* scores in 18 participants. Estimation of the common regression slope and 95% CI, with *P* values shown.

changes at the end of the MP1 and MP2 periods, which were directionally opposite to one another, suggests that Zn status can directly modulate anti-inflammatory oxylipin production.

Among our healthy male participants, HDL cholesterol concentrations was more sensitive to a modest reduction in dietary Zn than were concentrations of blood glucose. However, we previously reported that plasma Apo-A1 concentrations were among the proteins most likely to increase following the switch from a 6- to 10-mg/d Zn diet (15). This contrasting effect of supplemental Zn on HDL cholesterol and Apo-A1 may reflect the fact that the plasma mass concentration ratios of HDL cholesterol to Apo-A1 are approximately 0.35 for small nascent particles (25). That would make it easier to detect a rise in Apo-A1 that may occur prior to HDL cholesterol change. Thus, plasma Apo-A1 appears to be a good indicator of the acute metabolic changes associated with shifts in Zn intakes.

Apo-A1 is the main HDL cholesterol protein synthesized mostly in the intestine and liver (26). Low dietary Zn decreases while Zn supplementation raises circulating Apo-A1 concentrations (27, 28). Evidence of increased mRNA and protein Apo-A1 suggests that these effects are mediated in part through Zn-dependent transcriptional reprogramming of lipid metabolism. It is notable that in growing piglets, Apo-A1 was among the top 4 proteins that were responsive to changes in dietary Zn (28). This effect may explain previously observed positive associations between Zn supplementation and HDL cholesterol in nonhealthy individuals who may have higher dietary need for Zn due to chronic inflammation (29). Also, human Zn supplementation data are extremely noisy due to the wide ranges of supplement doses used and the lack of control for baseline diet variations. The strength of our study is that we were able to observe subtle but significant effects of modest Zn depletion and repletion on plasma HDL cholesterol when the diet was controlled.

In addition to HDL cholesterol response, we also observed significant Zn-dependent variations in plasma TG. Plasma TG concentrations increased during the low-Zn/d, high-phytate/d diet, reaching a 30% increase by the end of the 10-mg Zn/d 4-wk period. However, the highest TG concentration reached in an individual, 150 mg/dL, remained within the normal range for plasma TGs. Supplementation with 25 mg/d Zn reversed plasma TG to baseline, suggesting that higher Zn intake or a longer intervention period is required to lower TG in Zn-deficient individuals. A major route of TG clearance is through activation of lipoprotein lipase (LpL) and the subsequent release and oxidation of fatty acids through β-oxidation pathways (as reviewed in 29, 30). Zn is required for optimal regulation of peroxisome proliferator activated receptors (PPARs) (31, 32) that serve as critical transcriptional regulators of LpL and β-oxidation gene expression. Further studies are needed to validate the relative sensitivity of PPARs to modest changes in dietary Zn.

The rise in LDL cholesterol between MP1 and MP3 was an unexpected finding. The underlying reason for this change is unknown, but it may be related to the ad libitum dietary intake

during MP3. Alternatively, studies show that correcting Zn deficiencies in patients can relieve steatosis and other metabolic abnormalities that are reported with Zn deficiency (33). This may involve upregulating the secretion of a VLDL that is a precursor to LDL (34). This may explain why the metabolic benefits of Zn supplementation also lead to a seemingly paradoxical rise in LDL cholesterol.

Repeated-measures correlations between different desaturases and plasma TG and HDL cholesterol concentrations measured at 4 different time points showed highly significant and conserved variations in FADS1, FADS2, and SCD1 enzyme activities. Desaturation of fatty acids is a critical mediator of TG homeostasis (35, 36). FADS1–3 genes are located in chromosome 11. The transcription initiation site of FADS1 genes is encoded close to that of FADS2, and both genes share a common promoter binding region that is located in between both genes (37). It is thought that this "head-to-head" orientation with common promoter binding regions allows FADS1 and FADS2 genes to be inversely regulated by transcription factors that regulate their expression. PUFAs synthesized by FADS1 and FADS2 are potent inhibitors of SCD1 transcription (38). SCD1 activity strongly influences TG synthesis (39, 40). Coordinated regulation of these desaturases suggests that Zn has a common regulatory influence on the expression of these lipid-metabolizing enzymes. Also, the proteolytic activation of SREBP-1 by a site 2 protease is a Zn-dependent process (41). Thus, the influence of dietary Zn on SREBP-1 activity in humans needs further study.

Zn deficiency or supplementation modulates inflammation through generation of pro- or anti-inflammatory oxylipins synthesized from AA and EPA (42–44). Our comprehensive panel of oxylipins included products of cyclooxygenase, lipoxygenase, and P450 pathways (45). Results from this analysis identified that the EPA oxidation product, 14(15)-EpETE, was responsive to variations in dietary Zn. P450-derived epoxyeicosatrienoic and epoxyeicosatetraenoic acids act as potent anti-inflammatory agents (46–49). Although further studies are needed to validate our findings, the ability of Zn to specifically modulate P450-dependent oxylipins may contribute to the anti-inflammatory effects of Zn supplementation.

In sum, our results show that lipid metabolic pathways are modulated by dietary Zn. However, generalization of our findings is limited by the *1*) relatively small sample size of our study; *2*) the fact that all of our participants were healthy, normolipidemic, and insulin-sensitive men; and *3*) the high (80%) dietary carbohydrate content. Despite these limitations, the observed tight, coregulated changes in TGs, HDL cholesterol, fatty acid desaturases, and P450-derived oxylipins with modest reductions in dietary Zn provide the basis for mechanistic studies of the relation between dietary Zn and cardiometabolic disorders. An enhanced understanding of these mechanisms may lead to the identification of novel biomarkers of dietary Zn status in the general population.

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