

Fish Oil Supplementation Ameliorates Fructose-Induced Hypertriglyceridemia and Insulin Resistance in Adult Male Rhesus Macaques^{1,2}

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Abstract

Fish oil (FO) is a commonly used supplemental source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), 2 n-3 (ω -3) polyunsaturated fatty acids (PUFAs) that have been shown to have a variety of health benefits considered to be protective against cardiometabolic diseases. Although the effects of EPA and DHA on lipid metabolism have been extensively studied, not all of the metabolic effects of FO-derived n-3 PUFAs have been characterized. Our laboratory recently showed that a high-fructose diet in rhesus monkeys induces the features of metabolic syndrome (MetS) similar to those observed in humans. Thus, we specifically wanted to evaluate the effects of FO in rhesus monkeys fed a high-fructose diet and hypothesized that FO supplementation would mitigate the development of fructose-induced insulin resistance, dyslipidemia, and other cardiometabolic risk factors. In this study, adult monkeys (aged 12–20 y) received either a standard unpurified diet plus 75 g fructose/d (control group; $n = 9$) or a standard unpurified diet, 75 g fructose/d, and 4 g FO (16% EPA + 11% DHA)/d (treatment group; $n = 10$) for 6 mo. Importantly, our results showed that daily FO supplementation in the monkeys prevented fructose-induced hypertriglyceridemia and insulin resistance as assessed by intravenous-glucose-tolerance testing ($P \leq 0.05$). Moreover, FO administration in the monkeys prevented fructose-induced increases in plasma apolipoprotein (Apo)C3, ApoE, and leptin concentrations and attenuated decreases in circulating adropin concentrations ($P \leq 0.05$). No differences between the control and FO-treated monkeys were observed in body weight, lean mass, fat mass, or fasting glucose, insulin, and adiponectin concentrations. In conclusion, FO administration in a nonhuman primate model of diet-induced MetS ameliorates many of the adverse changes in lipid and glucose metabolism induced by chronic fructose consumption. *J. Nutr.* 144: 5–11, 2014.

Introduction

The incidence and prevalence of insulin resistance and metabolic syndrome (MetS)⁷ in the United States and worldwide have increased dramatically over the past decade (1–3). We and others have proposed that this increase may in part be attributable to increased consumption of fructose derived from dietary sucrose and high-fructose corn syrup (1–4). Individuals with MetS have a higher likelihood of developing atherosclerotic cardiovascular

disease (ASCVD) and type 2 diabetes mellitus (T2DM) (1,3,5–8); thus, safe interventions to prevent or mitigate the conditions associated with MetS (including central adiposity, hypertension, hypertriglyceridemia, and impaired glucose tolerance) are needed.

To date, there are no U.S. Food and Drug Administration–approved pharmaceutical agents to treat or prevent MetS. As such, consumers often resort to over-the-counter nutraceutical therapies, many of which have little data to demonstrate their efficacy. One such agent is fish oil (FO). FO is a commonly used supplemental source of EPA (20:5n-3) and DHA (22:6n-3), 2 marine-derived n-3 PUFAs that have been shown to have a variety of protective effects against cardiometabolic diseases (9–11). The n-3 PUFAs are most widely known for their TG-lowering effects (12,13), which are considered to be primarily mediated via peroxisome proliferator-activated receptor (PPAR)–dependent mechanisms (14). However, their potential ability to alleviate inflammation and increase insulin sensitivity has become an area of interest as well (11,15).

Although the effects of EPA and DHA on lipid metabolism have been extensively studied (16), not all of the metabolic

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⁷ Abbreviations used: ASCVD, atherosclerotic cardiovascular disease; FO, fish oil; IVGTT, intravenous-glucose-tolerance test; MetS, metabolic syndrome; PPAR, peroxisome proliferator-activated receptor; T2DM, type 2 diabetes mellitus.

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effects of FO-derived n-3 PUFAs have been characterized. Whereas EPA and DHA have been shown to prevent and reverse insulin resistance in obese rodents fed a high-fat (17–19) or high-sucrose (20) diet, they have not consistently shown insulin-sensitizing effects in obese humans and those with T2DM (21–23). Despite lowering circulating lipid concentrations, supplementation with EPA or FO for 11 mo also did not delay the onset of diabetes in University of California Davis–T2DM rats (24), a well-characterized rodent model of T2DM that exhibits polygenic adult-onset obesity and insulin resistance with inadequate β -cell compensation (25). However, other data suggest that FO-derived n-3 PUFAs may delay the development of MetS or its progression to T2DM (26).

Our laboratory recently demonstrated that a high-fructose diet in rhesus monkeys induces the features of MetS in humans, including obesity, dyslipidemia (particularly hypertriglyceridemia), and insulin resistance (27). Thus, we specifically designed a study to evaluate the effects of FO in rhesus monkeys fed a high-fructose diet and hypothesized that treating rhesus monkeys with a high-fructose diet combined with FO supplementation would mitigate the development of dyslipidemia, insulin resistance, and other associated cardiometabolic risk factors in this model. Herein, we report our findings demonstrating that FO prevents fructose-induced insulin resistance and hypertriglyceridemia in rhesus monkeys.

Materials and Methods

Animals. The rhesus monkeys used for this study were provided by and maintained at the California National Primate Research Center at the University of California, Davis. Protocols for all the animal studies were approved by the University of California, Davis, Institutional Animal Care and Use Committee and were conducted in accordance with the USDA Animal Welfare Act and the NIH's Guide for the Care and Use of Laboratory Animals. A total of 19 adult male rhesus monkeys, aged 12–20 y (body weight: 15.6 ± 0.4 kg), were studied. At baseline, all monkeys had fasting plasma glucose concentrations <100 mg/dL, fasting insulin concentrations <100 μ U/mL, fasting plasma TG concentrations <100 mg/dL, and percentage body fat $>20\%$.

Diet and energy intake measurements. A commercial monkey unpurified diet (Advanced Protocol Old World Primate, LabDiet 5047) was provided ad libitum to all of the monkeys. This is a grain-based standard primate diet that provides 30% of energy as protein, 11% of energy as fat (n-3 FAs, 0.14% of unpurified diet; n-6 FAs, 1.68% of unpurified diet; total FAs, 1.83% of unpurified diet), and 59% of energy as carbohydrate. In addition, following baseline measurements, all monkeys were provided with 500 mL/d of a fruit-flavored (Kool-Aid; Kraft Foods), 15% fructose-sweetened beverage (75 g of fructose). Ten monkeys (treatment group) also received 4 g of FO supplementation/d. The FO (16% EPA/11% DHA; 32.1% n-3 FAs; 2.4% n-6 FAs; 77.3% total FAs; Jedwards International, validated by Covance) was mixed into a treat such as ice cream, yogurt, jelly, applesauce, or pudding; and 1% by weight of egg powder was added to make an emulsion. Then, 44 g of the mixture containing 4 g of FO was provided to the monkeys each day. The control monkeys received the same mixture with 4 g of safflower oil [0.05% FFAs; 6.54% palmitic acid (16:0); 2.62% stearic acid (18:0); 14.97% oleic acid (18:1); 73.47% linoleic acid (18:2); 0.05% linolenic acid (18:3); 0.15% behenic acid (22:0); Jedwards International] instead of FO. Beverage intake was recorded daily, and food intake was recorded for 1 wk at baseline, and then for another 1-wk period at 6 mo. The monkeys were randomly assigned by age equally to the FO-treated and control groups.

Body weight and body adiposity. Body weights of the monkeys were determined monthly. At baseline and at 6 mo, percentage and total body fat were determined by DXA, a sensitive technique for

measuring body fat (28) that has been previously validated for the determination of body composition in monkeys (29).

Intravenous-glucose-tolerance tests. At baseline and at 6 mo, intravenous-glucose-tolerance tests (IVGTTs) were performed and the AUC for glucose and insulin calculated by using the trapezoidal method; glucose tolerance was estimated by the area above baseline under the glucose curve from 0 to 60 min, and an index of insulin sensitivity was calculated as described previously (27,30).

Glucose, insulin, and HOMA-IR. Plasma insulin concentrations were measured by using an RIA (Millipore), and plasma glucose concentrations were measured with a YSI Glucose Analyzer (YSI Life Sciences). HOMA-IR was calculated by using the following equation: ([fasting glucose (mmol/L) \times fasting insulin (μ U/mL)]/22.5) (31).

Lipid and lipoproteins. Plasma total cholesterol, HDL cholesterol, LDL cholesterol, TG, apoA1, apoB, apoC3, and apoE concentrations were determined by using a Polychem Chemistry Analyzer (PolyMedCo).

Adipocyte and hepatic hormones. Plasma adiponectin and leptin concentrations were measured by RIA (Millipore). Plasma adropin concentrations were measured by using a commercially available ELISA (Peninsula Laboratories, Bachem) (32). Before the analyses, all of the antibodies were tested to ensure their ability to measure the target hormone in samples from rhesus monkeys (27). The AUC for adropin during the 6-mo study was calculated by using the trapezoidal method.

TABLE 1 Effects of FO on fasting plasma lipid and lipoprotein concentrations in rhesus monkeys fed a high-fructose diet¹

	Control (n = 9)		FO (n = 10)	
	Result	Δ	Result	Δ
	mg/dL		mg/dL	
Cholesterol				
Baseline	142 \pm 8	—	137 \pm 9	—
6 mo	146 \pm 8	+5 \pm 4	125 \pm 10	-12 \pm 6
LDL-C				
Baseline	70 \pm 6	—	66 \pm 7	—
6 mo	64 \pm 5	-6 \pm 4	62 \pm 7	-5 \pm 5
HDL-C				
Baseline	55 \pm 3	—	54 \pm 4	—
6 mo	55 \pm 4	0 \pm 3	49 \pm 5	-5 \pm 2*
TGs				
Baseline	83 \pm 8	—	81 \pm 10	—
6 mo	136 \pm 22	+53 \pm 21*	74 \pm 8	-7 \pm 7 [‡]
ApoA1				
Baseline	143 \pm 6	—	144 \pm 4	—
6 mo	147 \pm 8	+4 \pm 4	132 \pm 6	-11 \pm 3 [†]
ApoB				
Baseline	55 \pm 4	—	51 \pm 5	—
6 mo	56 \pm 4	+1 \pm 3	50 \pm 6	-1 \pm 3
ApoC3				
Baseline	2.28 \pm 0.19	—	2.28 \pm 0.19	—
6 mo	2.85 \pm 0.19	+0.57 \pm 0.13**	2.11 \pm 0.21	-0.17 \pm 0.18 [‡]
ApoE				
Baseline	2.12 \pm 0.15	—	1.92 \pm 0.13	—
6 mo	2.74 \pm 0.14	+0.62 \pm 0.14*	2.09 \pm 0.14	+0.18 \pm 0.11 [†]

¹ Values are means \pm SEMs. Differences in means from baseline: * $P \leq 0.05$, ** $P \leq 0.01$. Differences in means from baseline to 6 mo between control and FO groups: [†] $P \leq 0.05$, [‡] $P \leq 0.01$. FO, fish oil; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol.

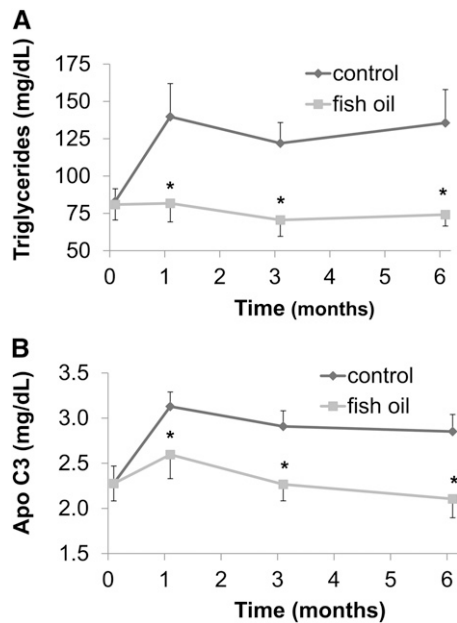


FIGURE 1 The effect of fish oil on fasting plasma TG (A) and apoC3 (B) concentrations in rhesus monkeys fed a high-fructose diet for 6 mo. Values are means \pm SEMs; $n = 9$ (control) or 10 (fish oil). *Different from control, $P \leq 0.05$.

Statistical analysis. Descriptive statistics are provided for each of the outcomes as means \pm SEMs. Within a given treatment group, Wilcoxon's Signed Rank tests were used to compare baseline data for each outcome with the 6-mo measurements. Linear mixed models were used to assess the longitudinal trend of each outcome and to compare the changes in the FO treatment group compared with the control group. Unless otherwise noted, the P values reported represent the results of the linear mixed-model analyses. Each linear mixed model regressed a single outcome postbaseline on time (categorical for 1, 3, and 6 mo), group, group by time interaction, and the baseline value of the respective outcome. Random intercepts were included to account for repeated

measures. Estimated mean differences between groups were calculated at 1, 3, and 6 mo, adjusting for baseline values. Before the analyses, the distributions of each outcome variable were also assessed for normality; for those outcome variables with skewed distributions, log transformations were applied to meet the normality assumptions of the linear mixed model. For each outcome requiring a transformation, the estimated differences between time points were back transformed to represent ratios of geometric means with corresponding 95% CIs and P values. One-tailed t tests were also performed to evaluate the AUC for the glucose and insulin excursions during the IVGTTs at baseline and 6 mo and the AUC for the adipon concentration changes from baseline to 6 mo. Statistical analyses with P values ≤ 0.05 were considered significant.

Results

Body weight and body composition. In the control monkeys ($n = 9$), body weight increased from 15.8 ± 0.6 kg at baseline to 17.8 ± 0.8 kg at 6 mo (+13%; $P = 0.004$), whereas in the FO-treated monkeys ($n = 10$), body weight increased from 15.5 ± 0.5 kg at baseline to 16.9 ± 0.6 kg at 6 mo (+9%; $P = 0.002$). Although the increase in body weight from baseline to 6 mo was significant for each group, the mean difference in weight gain between the control monkeys and the FO-treated monkeys was not significant after adjusting for baseline values. Furthermore, there were no significant differences between the 2 groups with respect to lean body mass and fat mass.

Fasting lipid and lipoprotein concentrations. As shown in **Table 1**, fasting TG and apoC3 concentrations were significantly higher in the control group versus the FO treatment group at the completion of the 6-mo study ($P = 0.005$). Specifically, in the control monkeys, both fasting TG (+71 \pm 25%; **Fig. 1A**) and fasting apoC3 (+28 \pm 8%; **Fig. 1B**) concentrations increased. In contrast, both fasting TG concentrations ($-3 \pm 7\%$; **Fig. 1A**) and fasting apoC3 concentrations ($-5 \pm 9\%$; **Fig. 1B**) were unchanged in the monkeys that received the daily FO supplementation. ApoA1 concentrations decreased modestly in the FO-treated monkeys ($-8 \pm 2\%$; $P = 0.018$). ApoE concentrations

TABLE 2 Effects of FO on fasting plasma glucose and insulin concentrations, glucose tolerance, and insulin sensitivity in rhesus monkeys fed a high-fructose diet¹

	Control ($n = 9$)		FO ($n = 10$)	
	Result	Δ	Result	Δ
Glucose, mg/dL				
Baseline	68 \pm 4	—	87 \pm 5	—
6 mo	69 \pm 2	+1 \pm 3	81 \pm 7	-6 \pm 7
Insulin, μ U/mL				
Baseline	55 \pm 13	—	61 \pm 15	—
6 mo	113 \pm 44	+57 \pm 32*	89 \pm 26	+28 \pm 27
AUC glucose, mg/dL \times 60 min				
Baseline	11,002 \pm 536	—	11,021 \pm 600	—
6 mo	11,841 \pm 392	+839 \pm 611	11,545 \pm 332	+524 \pm 365
AUC insulin, μ U/mL \times 60 min				
Baseline	15,327 \pm 2406	—	16,275 \pm 4407	—
6 mo	28,895 \pm 8697	+13,568 \pm 7594*	17,345 \pm 3509	+1070 \pm 4280
HOMA-IR				
Baseline	10.04 \pm 3.09	—	12.37 \pm 2.79	—
6 mo	19.46 \pm 7.99	+9.43 \pm 5.10	18.20 \pm 6.22	+5.48 \pm 6.71
Insulin sensitivity index				
Baseline	0.63 \pm 0.11	—	0.76 \pm 0.21	—
6 mo	0.47 \pm 0.11	-0.16 \pm 0.09	0.71 \pm 0.24	-0.06 \pm 0.07

¹ Values are means \pm SEMs. *Different from baseline, $P \leq 0.05$. FO, fish oil.

also increased in the control group ($+33 \pm 9\%$) more than in the FO-treated group ($+11 \pm 6\%$) ($P = 0.030$). Moreover, cholesterol concentrations increased slightly in the control group ($+4 \pm 3\%$), whereas they decreased modestly in the monkeys treated with FO ($-8 \pm 5\%$) ($P = 0.025$, Wilcoxon's rank-sum test).

Fasting glucose and insulin concentrations, glucose tolerance, and insulin sensitivity. During the course of the study, none of the monkeys developed frank diabetes (defined by a fasting blood glucose concentration >125 mg/dL), and the fasting blood glucose concentrations remained fairly stable in both the control and FO treatment groups (Table 2). Both groups exhibited increased fasting insulin concentrations, suggesting β -cell compensation for insulin resistance; however, the increase of fasting insulin concentrations in the FO-treated monkeys tended to be smaller ($+28 \pm 27$ mg/dL) than in the control monkeys ($+57 \pm 32$ mg/dL). Furthermore, although the glycemic excursions and the AUC for glucose concentrations during the IVGTTs in the control and FO treatment groups were similar at the end of the 6-mo study (Figs. 2A and 3A), the insulin excursions and AUC for insulin concentrations were different (Figs. 2B and 3B). Specifically, the AUC insulin for the control group increased by $81 \pm 39\%$, whereas the AUC insulin for the FO-treated monkeys increased only by $30 \pm 27\%$ ($P = 0.037$).

Adipocyte and hepatic hormones. Fasting total adiponectin concentrations decreased comparably in both the control ($-21 \pm$

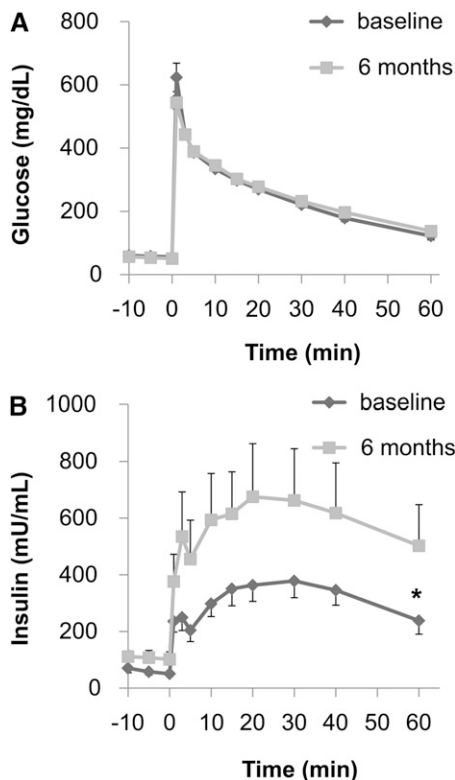


FIGURE 2 Plasma glucose and insulin responses during an intravenous-glucose-tolerance test (IVGTT) in control monkeys at baseline and after 6 mo. The plasma glucose response (A) did not differ between the 2 time points. However, the plasma insulin response (B) during the IVGTT was significantly increased after 6 mo consuming fructose. Values are means \pm SEMs; $n = 9$. *Different AUC from baseline, $P \leq 0.05$.

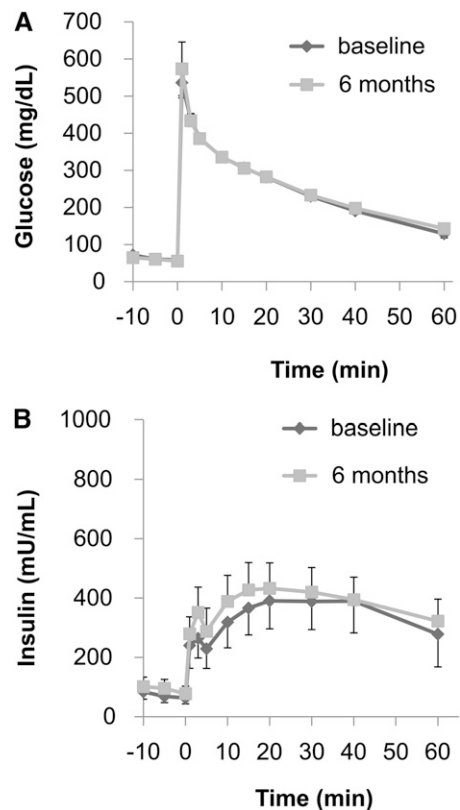


FIGURE 3 Plasma glucose and insulin responses during an intravenous-glucose-tolerance test in the FO-treated monkeys at baseline and after 6 mo. The plasma glucose response (A) did not differ between the 2 time points. Unlike in the control monkeys, the plasma insulin response (B) also did not differ between the 2 time points, demonstrating the insulin-sensitizing effects of FO. Values are means \pm SEMs; $n = 10$. FO, fish oil.

8%) and the FO treatment ($-27 \pm 8\%$) groups at the completion of the study (Table 3). In contrast, the increase in fasting leptin concentrations was significantly greater in the control monkeys ($+32 \pm 8\%$) than in the monkeys treated with FO ($+9 \pm 5\%$) ($P = 0.033$). In addition, circulating adiponin concentrations increased in the FO-treated group ($+25 \pm 18\%$), whereas they decreased in the control group ($-12 \pm 6\%$) ($P = 0.042$), a difference demonstrated by the AUC for plasma adiponin concentrations over the course of the study (Fig. 4).

Discussion

In this study, we demonstrated that daily FO supplementation in rhesus monkeys prevents fructose-induced hypertriglyceridemia and insulin resistance. Moreover, we report that FO administration in nonhuman primates prevents fructose-induced increases in apoC3 and apoE concentrations and attenuates the increase in leptin and the decrease in adiponin concentrations.

Previous studies suggest that FO, particularly the long-chain $n-3$ PUFAs DHA and EPA, reduce plasma TG concentrations primarily from the decline in hepatic VLDL-TG production, and secondarily from an increase in VLDL-TG clearance (33). Specifically, FO counteracts intracellular lipolysis in adipocytes by suppressing adipose tissue inflammation, resulting in a decrease in the activity of hormone sensitive lipase, thereby decreasing the availability of nonesterified fatty acids for hepatic TG production (33). In addition, FO increases extracellular

TABLE 3 Effects of FO on fasting plasma adipocyte and hepatic hormones in rhesus monkeys fed a high-fructose diet¹

	Control (n = 9)		FO (n = 10)	
	Result	Δ	Result	Δ
Adiponectin, μg/mL				
Baseline	5.87 ± 1.01	—	6.55 ± 0.71	—
6 mo	4.63 ± 0.88	-1.24 ± 0.45*	4.71 ± 0.67	-1.85 ± 0.68*
Leptin, μg/L				
Baseline	19.01 ± 1.46	—	21.49 ± 2.12	—
6 mo	24.63 ± 1.76	+5.62 ± 1.18**	22.88 ± 1.81	+1.38 ± 0.83†
Adropin, μg/L				
Baseline	1.92 ± 0.18	—	1.65 ± 0.34	—
6 mo	1.66 ± 0.15	-0.27 ± 0.11	1.83 ± 0.24	+0.16 ± 0.29

¹ Values are means ± SEMs. Differences in means from baseline: * $P \leq 0.05$, ** $P \leq 0.01$. Difference in means from baseline to 6 mo between control and FO groups: † $P \leq 0.05$. FO, fish oil.

lipolysis by lipoprotein lipase, which is inhibited by apoC3. Thus, agents that lower apoC3 concentrations would be expected to also lower TG concentrations. Although a previous study reported that the TG-lowering effect of an ethyl ester preparation of FO in humans normalized elevated plasma TG concentrations independent of its effect on apoC3 (34), our data suggest that the FO-induced lowering of apoC3 may be a contributing factor to the effects of FO to prevent the increase in TG concentrations in response to dietary fructose.

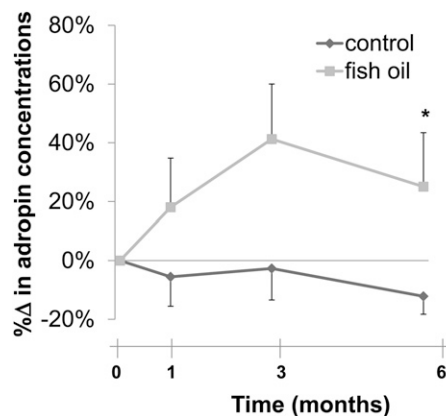
In this study, we also demonstrate that FO supplementation prevents fructose-induced insulin resistance as demonstrated by the AUC insulin data during the IVGTTs, supporting an insulin-sensitizing action of n-3 PUFAs. Moreover, although others have reported that n-3 PUFAs lower increases in leptin expression in animal models of diet-induced obesity (35), we found that FO attenuates fructose-induced increases in leptin concentrations in a weight-independent manner, an interesting result that requires further investigation. Agonists of PPAR- γ have been demonstrated to increase the expression and secretion of adiponectin (36–38) and reduce the expression and secretion of leptin (39–41). Therefore, if FO supplementation were to elicit significant PPAR- γ activation in our rhesus monkey model, we would expect it to also prevent or attenuate the decrease in adiponectin observed during fructose feeding. However, the decreases in adiponectin concentrations were similar in the control and FO-treated monkeys. Although the results of studies investigating the effects of dietary n-3 PUFAs on circulating adiponectin concentrations in humans have been conflicting, we have reported that consumption of a diet high in n-3 PUFAs did not increase either total or high-molecular-weight adiponectin in humans over a 14-wk period (42). We also found that FO attenuates fructose-induced decreases in circulating adropin concentrations. Adropin is a peptide hormone produced by the liver that appears to have a role in metabolic and glucose homeostasis (43). Adropin deficiency is associated with increased adiposity and insulin resistance (44), and adropin concentrations increase with weight loss (32). Interestingly, our findings suggest that FO increases circulating adropin concentrations relative to controls and independent of changes in body weight/adiposity, another intriguing result that requires further investigation.

In addition, FO supplementation modestly decreased plasma apoA1 concentrations, a finding observed in previous studies evaluating the effect of the n-3 PUFAs on apo1 expression and

concentrations (45,46). In our study, FO supplementation also prevented fructose-induced increases in apoE concentrations, a positive finding with regard to cardiometabolic risk given that high plasma apoE concentrations strongly associate with cardiovascular mortality independent of APOE genotype and plasma lipids (47). In summary, because the ratio of n-6:n-3 PUFAs affects cardiovascular disease risk (48) and individuals with a low n-3 index (erythrocyte EPA+DHA as a percentage of total FAs) (49,50) have a higher risk of cardiovascular events (51), the results of the present study indicating that FO ameliorates multiple lipid and metabolic variables in our fructose-fed rhesus monkey model (27) are consistent with FO's positive clinical attributes.

Importantly, the current study reinforces the use of rhesus monkeys as an animal model relevant to human metabolic diseases that allows for strict control of dietary variables and physical activity as well as the assurance of near 100% compliance with an intervention. As we have demonstrated previously and in this study (27), nutritional intervention studies conducted in rhesus monkeys can also be performed over an extended period of time (e.g., months to years), which is not practical nor feasible with human subjects. Moreover, this study is, to our knowledge, the first to assess circulating adropin concentrations in nonhuman primates and to demonstrate the prevention of fructose-induced hypertriglyceridemia by FO in a nonhuman primate model.

In conclusion, given the increasing incidence and prevalence of MetS, and the lack of approved pharmaceutical agents for its prevention, many individuals resort to the use of nutraceutical therapies for the prevention of the syndrome or at least its many components. FO is one of the most commonly used nutraceuticals and is well known as a rich source of n-3 PUFAs. Given the many health benefits of n-3 PUFAs, mainly EPA and DHA, interest in their biological mechanism(s) of action continues to grow. Because we previously demonstrated that, like in humans (52), consumption of a high-fructose diet in rhesus monkeys produces many of components of MetS within a relatively short (6-mo) period of time, we used this model to study the effects of FO on the development of diet-induced metabolic disease. In this study, we report the novel findings that FO prevents fructose-induced hypertriglyceridemia and insulin resistance in fructose-fed rhesus monkeys. We therefore demonstrate that the rhesus monkey model of fructose-induced MetS is directly translatable

**FIGURE 4** Effect of fish oil on percentage changes of fasting plasma adropin concentrations in rhesus monkeys fed a high-fructose diet. Values are means ± SEMs; $n = 9$ (control) or 10 (fish oil). *Different AUC from control at 6 mo, $P \leq 0.05$.

to the study of diet-induced MetS in humans and can be efficiently and effectively used to investigate the metabolic effects of pharmaceutical and nutraceutical agents and interventions for the prevention and treatment of diet-induced dyslipidemia and insulin resistance. New studies investigating the biochemical and molecular mechanisms underlying these metabolic effects of FO, DHA, and EPA are thus warranted.

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