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Effect of Icosapent Ethyl on Gynoid Fat and Bone Mineral Health in the Metabolic Syndrome: A Pilot Report

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Abstract

Purpose—The metabolic syndrome (MetS) is a systemic disorder associated with reduced atheroprotective gynoid fat and bone mineral content (BMC). The present pilot study aimed to assess whether administration of icosapent ethyl (IPE), a purified formulation of eicosapentaenoic acid would maintain gynoid fat and BMC over a 9-month treatment period.

Methods—Patients with MetS aged 40 years and older were randomly assigned to receive 4 grams daily of IPE (2 grams twice daily with food) or placebo (paraffin oil 2 grams twice daily with food) for 9 months. Data were collected at baseline and 9 months later. They included anthropometric measures, biochemical analysis and whole body fat mass, including gynoid fat. Bone mineral density (BMD) and bone mineral content (BMC) were measured by dual-energy X-ray absorptiometry. A two-tailed $p < 0.05$ was considered statistically significant.

Findings—The study sample consisted of 13 patients with MetS (mean age, 61.6 years; age range, 44–77 years; 77% female and 23% male). Compared to IPE, the placebo group experienced statistically significant mean reductions in percent gynoid fat (pre/post: 46.8% to 43.5%; $P=0.02$), BMC (pre/post: 2461 grams to 2423 grams; $P=0.02$) and BMD: (pre/post: 1.24 grams/cm² to 1.22 grams/cm²; $P=0.05$) over the 9-month study period.

Implications—The results of this pilot study raise the possibility that IPE supplementation may preserve gynoid fat distribution and bone mineral health in patients with MetS. Larger, randomized

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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longitudinal studies will be necessary to determine the potential long-term metabolic benefits of IPE treatment.

Keywords

Metabolic syndrome; Triglycerides; Icosapent Ethyl; Ectopic fat; Bone mineral health; hypertriglyceridemia; gynoid fat

Introduction

Metabolic Syndrome (MetS) is defined by the presence of 3 or more of the following 5 cardiovascular risk factors (hypertension (>130 mmHg systolic or >85 mmHg diastolic), hyperglycemia (fasting blood glucose ≥ 100 mg/dL), central obesity (waist circumference: >40 inches in men, >35 inches in women), elevated triglycerides (TG ≥ 150 mg/dL) and low HDL-C (<40 mg/dL in men, <50 mg/dL in women) with central obesity associated insulin resistance promoting its development (1). Effective therapies are needed to ameliorate the heightened risk of incident Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and osteoporosis that are associated with MetS (1–3). For example, marine-derived omega-3 fatty acid supplementation with eicosapentaenoic acid (EPA) not only improves metabolic biomarkers by lowering TG (4), but the highly purified EPA compound, icosapent ethyl (IPE) was recently shown to reduce CVD in high risk patients (5). Because the natural history of MetS involves reduction of atheroprotective gynoid fat and bone mineral health (1,3–4) this pilot study was conducted to examine whether IPE may help to reduce progression of these processes (6,7). While other studies have investigated the effects of IPE supplementation on improving MetS associated factors, most notably triglycerides, this is the first study to assess IPE supplementation on gynoid fat and indices of bone mineral health.

Materials and Methods

This study was funded as a National Institutes of Health (NIH) R21 Exploratory Award. Sixteen adult men and women with MetS were randomly assigned to receive 4 grams daily of IPE (2 grams twice daily with food) or placebo (paraffin oil 2 grams twice daily with food) for 9 months. Participants were asked to maintain weight stability (within 5 pounds) over the course of the study by maintaining similar activity levels and dietary habits and were also asked to remain on the same medications for MetS (e.g., blood pressure lowering [amlodipine, hydrochlorothiazide, indapamide, losartan, lisinopril, triamterene] and cholesterol lowering [atorvastatin, pravastatin, simvastatin, ezetimibe]) throughout the study without adjustment in dosage.

A total of 13 participants (77% women and 23% African Americans) completed the study, 8 were in the IPE treatment group and 5 in the placebo group (Table 1). The 3 dropouts were related to adverse gastrointestinal side effects (e.g. bloating, diarrhea), relocation or for personal reasons. Biochemical analysis (e.g., lipid and lipoprotein analysis, renal and hepatic panel) were performed on each participant after a 12-hour fast at baseline and 9 months. Whole body (e.g., trunk, limbs) fat mass and percent android and gynoid fat and total body bone mineral density (BMD) and bone mineral content (BMC) were measured by

dual-energy X-ray absorptiometry (Lunar iDXA, GE Healthcare). Blood pressure, weight, waist circumference, and other anthropomorphic measures were gathered at each monthly study visit, during which time compliance was checked and participants received a supply of pills (placebo or IPE) for the coming month. For statistical methods, we used R (R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>) to produce the results reported herein. The within group comparisons of change (P value IEP and P value placebo) were obtained using a regression: change= intercept, a technique that is functionally equivalent to a paired Student's t-test. The between group comparison of change (P difference) was accomplished with a regression, change = group, functionally equivalent to a two-group Student's t-test. Spearman's correlation was also used to measure the association between MetS variables and body fat (android:gynoid) composition. This study was conducted in accordance with the provisions of Good Clinical Practice and to the guiding ethical principles that have their origin in the Declaration of Helsinki. The protocol was approved by the Institutional Review Boards of the University of Maryland School of Medicine and the Baltimore Veterans Affairs Medical Center and all subjects signed informed consent.

Results

Baseline and 9-month results for selected variables in the 2 groups are presented in Table 1. There were no statistically significant differences between the groups in their baseline characteristics. Treatment with IPE was associated with a 26% reduction in mean plasma TG between baseline and 9-month visit (179 ± 56 to 132 ± 38 mg/dL; $P = 0.09$) and increase in weight (89.7 ± 19.8 to 91.2 ± 19.7 kg; $P = 0.03$), with no statistically significant differences in the change of either TG (165 ± 74 to 135 ± 64 mg/dL, -18%) or body weight (85.5 ± 15.3 to 84.4 ± 17.4 kg, -1.3%) compared to placebo ($P = 0.82$, $P = 0.17$, NS; respectively). Likewise, there were no significant differences in changes in other lipoprotein lipids, hepatic or renal function (data not shown), or HbA1c between the groups (Table 1A). However, IPE treatment was associated with a mean 0.3% increase in percent gynoid fat in the IPE treatment group compared to a mean -3.3% decrease in the placebo group (pre/post: 46.8% to 43.5% ; $P = 0.02$) with differences between groups of borderline significance ($P = 0.07$). However, there were no significant differences in android fat mass or percent android fat by DXA in either placebo or IPE treatment groups ($P > 0.10$, respectively) or between groups. There were reductions in total body BMC (pre/post 2461 grams to 2423 grams; $P = 0.02$) and BMD (pre/post 1.24 grams/cm² to 1.22 grams/cm²; $P = 0.05$) over 9 months in placebo treated participants and small, non-significant increases within the IPE group (2.5% , 3.4%) that did not differ from the placebo group ($P = 0.27$, $P = 0.33$; respectively) (Table 1B). Finally, among MetS features that underscore insulin resistance, the android:gynoid ratio was most correlated with body weight ($r_s = 0.46$), waist circumference ($r_s = 0.37$) and triglycerides ($r_s = 0.25$). This is consistent with a phenotype characterized by obesity and to a lesser extent, hypertriglyceridemic waist (8).

Discussion

In this small preliminary trial of 13 participants with MetS, treatment with 4 grams IPE daily was associated with no significant change in percent gynoid fat, BMC and BMD.

In contrast, these metabolic biomarkers decreased in the placebo group over the 9-month period. A reduction in percent gynoid fat coincides with the natural history of MetS and is associated with an increased risk of T2DM and CVD, that in part may reflect the upregulation of proinflammatory signaling pathways and insulin resistance (9–10). The purported mechanisms for the cardiometabolic benefits of gynoid fat relates to its negative association with insulin resistance and includes reduced expression of proinflammatory cytokines (e.g., interleukin-6) compared with android fat (11). The direct association of gynoid fat with enhanced bone formation and osteoblastic activity also appears to be related to its association with reduced levels of inflammatory proteins (12–13). Gynoid fat is also directly related to bone health through the preservation of BMD (14). This is believed to reflect estrogen mediated upregulation of Special adipose tissue (AT)-rich sequence binding protein 2 (SATB2), a key protein in osteogenic differentiation of bone stem cells and maintenance of bone integrity (15). The preservation of gynoid fat and BMC by IPE could prevent some of cardiovascular and bone-mineral complications associated with aging.

With respect to the mechanistic basis as it relates to MetS and gynoid fat, a negative correlation exists between gynoid fat mass and insulin resistance, including reduced expression of proinflammatory cytokines (e.g., interleukin-6) compared with android fat (10). The mechanism linking MetS and bone health includes suppression of osteoblastic differentiation with the subsequent reduction in bone formation coupled with increases in osteoclastic activity and enhanced bone resorptive capacity due to chronic inflammation (11–12). Gynoid fat is also directly related to bone health through preservation of BMD (13). This is believed to reflect estrogen mediated upregulation of the Special AT-rich sequence binding protein 2 (SATB2), a key protein in the osteogenic differentiation of bone stem cells and maintenance of bone integrity (14).

While MetS may also be associated with an enhanced predilection to osteoporosis (3), recent studies suggest that dietary intake of long-chain omega-3 fatty acids preserves BMD in osteopenic women (16,17). Notwithstanding the study's primary limitation of small sample size, the reduction in TG following IPE treatment is commensurate to that of the reducing effect in the cardiovascular events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), where TG lowering accounted for only a small proportion of the clinical benefit observed on CVD risk (5,18). Although other studies have investigated the effects of IPE supplementation on improving MetS associated factors (19) this is the first study to our knowledge to assess IPE supplementation on gynoid fat and indices of bone mineral health.

Collectively, these findings raise the possibility that in addition to recently proposed cardioprotective mechanisms (20), IPE may be associated with other health benefits, including preservation of bone health and a gynoid fat distribution that is associated with reduced atherogenicity. Further studies examining the effects of IPE on these and other metabolic processes (e.g., inflammation, regional adipocyte lipolysis, osteoclastic activity) over a longer period may provide further mechanistic insights and therapeutic potential for IPE to preserve bone health beyond the CVD benefits observed in the REDUCE-IT trial.

Conclusion

The results of this preliminary study raise the possibility that IPE supplementation may preserve gynoid fat and BMD in patients with MetS.

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Table 1A:

Selected MetS characteristics at baseline and after 9-month treatment with IPE or placebo

	IPE (n=8)		* <i>P</i> value	Placebo (n=5)	
	<i>Baseline</i>	<i>9-month</i>		<i>Baseline</i>	<i>9-month</i>
Age	63 (9)			59 (10)	
Weight (kg)	89.7 (19.8)	91.2 (19.7)	0.03	85.5 (15.3)	84.4 (17.4)
BMI (kg/m ²)	30.4 (3.1)	30.9 (3.2)		32.9 (4.6)	32.6 (5.2)
Waist (cm)	105 (9.4)	106 (10.4)		103 (11.9)	104 (11.3)
Waist:Hip ratio	0.94 (0.05)	0.94 (0.07)		0.90 (0.06)	0.92 (0.07)
Glucose (mg/dL)	88 (15)	74 (23)		81 (11)	72 (17)
TC (mg/dL)	229 (41)	221 (48)		219 (21)	203 (48)
HDL-C (mg/dL)	56 (11)	55 (12)		54 (18)	49 (16)
LDL-C (mg/dL)	137 (35)	140 (47)		132 (26)	128 (49)
non-HDL-C	172 (39)	166 (47)		165 (31)	155 (56)
TG (mg/dL)	179 (56)	132 (38)	0.09	165 (74)	135 (64)
A1c (%)	5.7 (0.4)	5.8 (0.4)		5.7 (0.3)	6.0 (0.4)

Values represent mean (sd)

* *P* value denotes within group change following IPE treatment.

Table 1B:

Body composition characteristics at baseline and after 9-month treatment with IPE or placebo

	IPE (n=8)		Placebo (n=5)		* <i>P value</i>	** <i>P value</i>
	<i>Baseline</i>	<i>9-month</i>	<i>Baseline</i>	<i>9-month</i>		
DXA ABD Fat Mass (g) Android	3268 (923)	3291(1045)	3012 (762)	2606(1168)		
DXA GLT Fat Mass (g) Gynoid	5659(1652)	5657(1589)	6245(1411)	5705(1208)	0.06	
Total Android Fat Mass (g)	7292(1859)	7360(1977)	6702(1448)	6407(1804)		
Total Gynoid Fat Mass (g)	13557(3492)	13573(3668)	13295(2138)	13164(2168)		
Android/Gynoid ratio	1.09 (0.19)	1.08 (0.17)	0.96 (0.06)	0.90 (0.16)		
Percent Android Fat	44.69(3.5)	44.39(3.4)	44.8(4.8)	39.6(10.4)		
Percent Gynoid Fat	41.86(7.8)	41.89(5.6)	46.78(6.7)	43.48(6.4)	0.02	
DXA Total BMC (g)	2641(801)	2708(815)	2461(384)	2423(375)	0.02	0.07
DXA Total BMD (g/cm ²)	1.16(0.18)	1.20(0.2)	1.24(0.16)	1.22(0.15)	0.05	

Values represent mean (sd)

* *P value* denotes within group change in placebo group over the 9-month treatment period.** *P value* denotes between group differences (IPE and placebo) over 9-months treatment.