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Metabolic and Endocrine Effects of Long Chain vs. Essential Omega-3 Polyunsaturated Fatty Acids in Polycystic Ovary Syndrome

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Abstract

Objective—To compare the effects of essential vs. long chain omega (n)-3 polyunsaturated fatty acids (PUFA) in polycystic ovary syndrome (PCOS).

Materials/Methods—In this 6-week, prospective, double-blinded, placebo (soybean oil) controlled study, 51 completers received 3.5 g n-3 PUFA/day (essential from flaxseed oil or long chain from fish oil). Anthropometric variables, cardiovascular risk factors and androgens were measured; oral glucose tolerance test (OGTT) and frequently sampled intravenous GTT (FSIVGTT) were conducted at the baseline and 6 wks.

Results—Between group comparisons showed significant differences in serum triglyceride response ($p = 0.0368$), while the changes in disposition index (DI) also tended to differ ($p = 0.0621$). When within group changes (after vs. before intervention) were considered, fish oil and flaxseed oil lowered serum triglyceride ($p = 0.0154$ and $p = 0.0176$, respectively). Fish oil increased glucose at 120 min of OGTT ($p = 0.0355$); decreased Matsuda index ($p = 0.0378$); and tended to decrease early insulin response during IVGTT (AIRg; $p = 0.0871$). Soybean oil increased glucose at 30 min ($p = 0.0030$) and 60 min ($p = 0.0121$) and AUC for glucose ($p = 0.0122$) during OGTT; tended to decrease AIRg during IVGTT ($p = 0.0848$); reduced testosterone ($p = 0.0216$) and tended to reduce SHBG ($p = 0.0858$). Fasting glucose, insulin, adiponectin, leptin or hs-CRP did not change with any intervention.

Conclusions—Long chain vs. essential n-3 PUFA rich oils have distinct metabolic and endocrine effects in PCOS, and therefore they should not be used interchangeably.

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Conflict of interest: None.

Institutional approval: The study was approved by the Human Subjects Committee of the UC Davis and all subjects signed the approved informed consent.

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Keywords

Omega-3 fatty acids; polycystic ovary syndrome; insulin resistance

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disease of women in reproductive age. Depending on the ethnic background, one out of ten to sixteen women has PCOS. Disorders related to PCOS can be divided into two categories: reproductive and metabolic. The former includes anovulation, oligomenorrhea/amenorrhea, infertility; and androgen excess manifesting as hirsutism. The latter consists of insulin resistance, dyslipidemia and obesity ¹. Although inflammation is increased, this seems to relate to obesity, but not directly to PCOS ². Insulin resistance leads to compensatory increase in circulating insulin (hyperinsulinemia) which in turn stimulates androgen production and contributes to ovarian dysfunction ³. As a testament to the importance of insulin resistance in ovarian dysfunction, treatment of insulin resistance and obesity increases ovulation and improves fertility in PCOS ⁴.

Omega-3 polyunsaturated fatty acids (n-3 PUFA) improve several disorders associated with PCOS. Experimental and clinical research have indicated that n-3 PUFA increase insulin sensitivity, reduce hyperinsulinemia, lower plasma triglyceride and liver fat, decrease inflammation and possibly obesity ^{5–7}. Therefore, PCOS patients are frequently advised to increase n-3 PUFA intake. However, there is an important knowledge gap in this field. Differences between the effects of essential n-3 PUFA (alpha linolenic acid, ALA) vs. long chain n-3 PUFA (eicosapentanoic acid, EPA, and docosahexanoic acid DHA) have not been distinguished. Thus patients and health care providers often use flaxseed oil (a rich source of the essential n-3 PUFA ALA) and fish oil (a rich source of the long chain n-3 PUFA EPA and DHA) inter-changeably. This may not be appropriate because *in vivo* conversion of the essential to the long chain n-3 PUFA is very inefficient in humans ⁸. In addition, essential and long chain n-3 PUFA act on different metabolic steps: ALA competes with the essential n-6 PUFA linoleic acid (LA;18:2 n-6) at the $\Delta 6$ desaturase enzyme—the rate limiting step for production of long chain PUFA, and inhibits conversion of LA to arachidonic acid (AA; 22:4 n-6) ⁹. On the other hand, the long chain n-3 PUFA (EPA and DHA) compete directly with AA on the lipoxygenase and cyclooxygenase enzymes that regulate production of leukotrienes and prostaglandins, respectively ⁹.

This study compared the effects of equal amounts of the essential n-3 PUFA (ALA) from flaxseed oil vs. the long chain n-3 PUFA (EPA plus DHA) from the fish oil on anthropometric measures, glucose homeostasis, cardiovascular risk factors and androgen levels in women with PCOS. Soybean oil which is rich in n-6 PUFA linoleic acid was used as the control oil.

RESEARCH DESIGN AND METHODS

Subjects

The study was approved by the Institutional Review Board of University of California, Davis and registered with the NIH. The investigators did not have any conflict of interest.

Women between the ages 20–45 y and with a body mass index (BMI) of 25–45 kg/m² who fulfilled the NIH criteria for PCOS ¹⁰ by having ovarian dysfunction, as evidenced by amenorrhea (no periods for >6 mo) or oligomenorrhea (<6 periods/y), clinical (hirsutism) or laboratory evidence for hyperandrogenemia (total testosterone >54 ng/dl or free testosterone

>9.2 pg/ml), along with the absence of any confounding clinical pathology (i.e. Cushing's disease, 21 hydroxylase deficiency or prolactinoma) were recruited. Patients were excluded if they used oral contraceptives, anti-androgenic medications, insulin sensitizers, d-chiro inositol, or any other medications or supplements that affect weight or insulin sensitivity during the preceding two months; had diabetes mellitus, untreated hypothyroidism or thyroid disease, and any other systemic illness such as renal, hepatic, and gastrointestinal disease; smoke; or drink > 2 alcoholic drinks per week.

Consort statement

Two hundred and twenty-six PCOS patients were assessed for eligibility; 159 subjects either failed to meet the inclusion/exclusion criteria (n=96), refused to participate (n=41) and had other reasons that prevented participation (n=22). Remaining 67 patients were allocated to randomization. Five subjects left after the baseline studies, before receiving the interventions; the remaining patients received either fish oil (n = 21), soybean oil (n=18) or flaxseed oil (n=23). Fifty-one patients (17 in each intervention) completed the 6-week study. The ethnic distribution of the completers was: 35 White, 5 African American, 5 Hispanic, 4 Asian, 1 American Indian and 1 Other.

Study design

Fatty acid compositions of the supplements are shown in Table 1. The goal was to supplement approximately 3.5 g of total n-3 PUFA daily. This was accomplished by providing six capsules of each supplement. Each capsule of flaxseed oil contained 545 mg ALA (Barleans Organic Oils, Ferndale, WA) and each capsule of fish oil contained 358 mg EPA plus 242 mg DHA (Nordic Naturals, Watsonville, CA). Soybean oil (Nordic Naturals, Watsonville, CA) was selected as placebo based on the recommendations of the Product Quality Working Group (PQWG) of the National Center for Complementary and Alternative Medicine. Each capsule of soybean oil contained 200 mg of oleic acid, 429 mg of LA acid 57 mg ALA and very small amounts of palmitic and stearic acids. Based on the nutrition intake data obtained in our previous PCOS study ¹¹, flaxseed supplementation was expected to increase ALA intake by approximately 3-folds and fish oil supplementation was expected to increase EPA plus DHA intake by 20 folds. Six weeks of study duration was elected because this length of time is adequate to observe the effects of dietary fatty acids on plasma lipids and glucose homeostasis ¹².

Data collection

Data were obtained at the beginning and at the end of the study at the Clinical and Translational Science Center Clinical Research Center of the University of California, Davis (CCRC). Menstruating women were tested during the follicular phase of the cycle. The OGTT and FS-IVGTT were performed one week apart.

Nutrition data

7-day food records were obtained at the beginning and at the end of the study and were analyzed by the CCRC dietitian using the Food Processor software (esha Research, Salem, OR).

Anthropometric data

Weight was measured in light clothing using the Tanita BWB800-P Digital Medical Scale. Body composition was determined using bioelectrical impedance ¹³.

OGTT

After an overnight fast, baseline samples were obtained; participants drank 75 g of glucose (Glucola™) and additional blood samples were obtained every 30 min for 2 hours.

FS-IVGTT

Participants were tested between 0600 and 0900, after an overnight fast. An intravenous catheter was placed in their forearm and kept open with normal saline. Heating pads were used in order to maximize blood flow. Three blood samples were obtained at times -15, -10 and -5 minutes. Glucose (0.3u/kg as 25% dextrose) was given intravenously at time 0 min. Intravenous insulin 0.03 u/kg (Humulin Regular: Eli Lilly) was given at time 20 min after the glucose administration. Blood samples were obtained at times 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160 and 180 min. Acute insulin response to glucose (AIR_{Glucose}: an index of insulin secretion), β -cell function, sensitivity index (SI) and disposition index (DI) were calculated using MiniMod Millennium software (Dr. Bergman, Los Angeles, CA).

Biochemical measurements

Glucose was measured using YSI 2300 STAT Plus Glucose & Lactate Analyzer (YSI Life Sciences, Yellow Springs, OH), with a coefficient of variation (CV) of 1%. Insulin was measured by RIA (Millipore, St. Charles, MO) with a CV of 8.2%. Triglyceride, cholesterol and HDL-cholesterol were measured using Poly-Chem System Analyzer (Cortlandt Manor, NY) with CVs of 3.5%, 4% and 3.6%, respectively. Leptin and adiponectin were measured using RIA (Millipore, St. Charles, MO) with CVs of 4.3% and 6.5%. hs-CRP was measured using a highly sensitive (hs) latex-enhanced immunonephelometric assay with a CV <5%. Total testosterone, sex hormone binding globulin (SHBG) and DHEAS were measured by RIA (Diagnostic Systems Laboratories, Webster, TX) with CVs of 8.3%, 4.4% and 9.6%, respectively.

Calculations

Peripheral insulin resistance was assessed by calculating Matsuda's sensitivity $\times$ fasting insulin $\times$ (mean glucose $\times$ index (ISI_{Matsuda}: 10,000/square root of [(fasting glucose mean insulin during OGTT)]) and SI by applying the MINIMOD program to FSIVGTT data. Hepatic insulin resistance was assessed by calculating Homeostasis Model Assessment (HOMA: [(fasting insulin (μ U/ml) $\times$ fasting glucose (mg/dl))/405]. Early insulin secretion was assessed by calculating AIR_g from FSIVGTT. Pancreatic function was assessed by calculating the area under the curve (AUC) for insulin during OGTT and calculating β -cell function during FSIVGTT. β -cell compensation for insulin resistance was assessed by calculating DI from AIR_g and SI.

Statistical analysis

The SAS software, version 9.1 (SAS Institute Inc, Cary, NC) was used. Descriptive statistics were calculated for each outcome in each intervention group of patients, before and after intervention. The data were log-transformed in order to improve the normality of residuals and homoscedasticity of errors where appropriate before analysis. Paired t-test was performed to determine the significance of within-group change in each outcome, for each intervention. Inter-group comparisons were performed by analysis of covariance (ANCOVA), adjusted for the baseline values. When the overall difference among the groups was significant in ANCOVA, post-hoc pair wise group comparisons were performed using the Bonferroni multiple comparisons procedure to determine which groups significantly differed from each other. The longitudinal trajectories for changes in glucose and insulin during OGTT were estimated by repeated measures analysis of variance. Individual

trajectories for changes in glucose and insulin were estimated from linear random-effects models. Each observed level was entered as the dependent variable. Treatment, time, and treatment $\times$ time interaction term were entered as independent variables. The coefficients for the interaction term were to estimate the additional changes in glucose and insulin level over time associated with treatment. To account for between-subject heterogeneity in the change of glucose or insulin level, intercept and time were modeled as random effects. Because we studied the differences at 6 weeks after intervention, we only included the subjects ($n=51$) with the endpoint measurements in the analysis. For those subjects, there were no missing endpoint values. A two-sided p -value <0.05 was considered significant.

RESULTS

There were no significant differences in the baseline data of the three intervention groups.

Diet

Macronutrient intake did not change significantly during the study. Baseline diet contained $1,945 \pm 127$ kcal, 33.8% fat, 50.4% carbohydrate, 16.4% protein, 15.0 ± 1.2 g fiber, 282 ± 73 mg cholesterol, 4.48 ± 0.59 g n-6 PUFA and 0.43 ± 0.07 g n-3 PUFA. The diet at the end of the study contained $1,735 \pm 145$ kcal, 34.8% fat, 48.2% carbohydrate, 16.9% protein, 15.7 ± 1.5 g fiber, 214 ± 4 mg cholesterol, 4.16 ± 0.53 g n-6 PUFA and 0.43 ± 0.06 g n-3 PUFA (excluding the PUFA from the supplements).

Anthropometric variables (Table 2)

Weight, BMI, fat mass and waist circumference did not change during the intervention.

Glucose homeostasis variables (Table 2 and Figure 1)

Fasting glucose, insulin, adiponectin, leptin, and HOMA did not change in any of the intervention groups.

When the baseline results were compared to after-study results, within group comparisons showed that fish oil increased serum glucose at 120 min (from 6.9 ± 0.4 to 7.7 ± 0.4 , $p = 0.0355$) and tended to increase insulin at 60 min (from $1,028 \pm 159$ to $1,201 \pm 213$ pmol/l, $p = 0.0941$) while decreasing the Matsuda index (from 2.43 ± 0.37 to 1.96 ± 0.25 , $p = 0.0378$). Fish oil tended to decrease the early insulin response measured by FS-IVGTT (AIRg) ($p=0.0871$). However, when overall glycemia was considered, fish oil caused a small but significant decrease in HgBA1 from $5.5 \pm 0.09\%$ to $5.4 \pm 0.09\%$ ($p = 0.0030$).

During fish oil treatment, the change in adiponectin correlated inversely with the changes in fasting glucose ($r = -0.6041$, $p = 0.0102$) and $AUC_{Glucose}$ ($r = -0.4334$, $p = 0.0822$). In addition, the change in hs-CRP correlated positively with the changes in fasting insulin ($r = 0.6176$, $p = 0.0245$) and triglyceride ($r = 0.6348$, $p = 0.0198$), and inversely with the change in Matsuda Index ($r = -0.06348$, $p = 0.0299$).

Flaxseed oil tended to increase glucose at 30 min of OGTT (from 8.3 ± 0.4 to 8.9 ± 0.5 mmol/l, $p = 0.0883$) but did not increase insulin at any time point. The change in hs-CRP was correlated inversely with the changes in HDL-cholesterol ($r = -0.5243$, $p = 0.0448$) and Matsuda Index ($r = -0.4585$, $p = 0.0857$).

Soybean oil increased glucose levels at 30 min (from 7.7 ± 0.4 to 8.3 ± 0.3 mmol/l, $p = 0.0333$) during OGTT with borderline increase in glucose at 90 min ($p = 0.0941$); $AUC_{Glucose}$ increased significantly (from 14.82 ± 0.61 to 16.37 ± 0.72 , $p = 0.0122$). Soybean oil tended to increase insulin at 90 min (from 757 ± 144 to 949 ± 132 pmol/l, $p = 0.0558$).

During IVGTT, soybean oil tended to decrease early insulin response (AIRg) ($p = 0.0848$). The change in $AUC_{Insulin}$ correlated with the change in leptin ($r = 0.5010$, $p = 0.0571$).

The overall intergroup comparison showed that DI response tended to differ among the three intervention groups ($p = 0.0621$).

Fasting lipids and hs-CRP

When after intervention levels compared to the baseline, both fish and flaxseed oils decreased serum triglyceride significantly ($p = 0.0154$ and $p = 0.0176$, respectively) while soybean oil had no significant change. There was a significant inter group difference in triglyceride response change ($p = 0.0368$), which was primarily due to the difference between fish oil vs. soybean oil interventions (Bonferroni post-hoc test $p = 0.0545$). None of the oils altered serum total-cholesterol, HDL-cholesterol or apoprotein B. However, there tended to be inter group differences in the LDL-C response ($p = 0.0678$) as fish and flaxseed oils tended to increase LDL-C while soybean oil tended to decrease it.

Androgens

After intervention, soybean oil reduced testosterone significantly (from 3.33 ± 0.73 to 3.05 ± 0.76 nmol/l, $p = 0.0216$) and tended to reduce SHBG (from 18.4 ± 2.4 to 16.2 ± 2.5 nmol/l, $p = 0.0858$), without affecting DHEAS. Fish and flaxseed oils did not affect testosterone, SHBG or DHEAS.

DISCUSSION

The primary objective of the study was to compare the effects of the essential vs. the long chain n-3 PUFA (flaxseed vs. fish oils). The secondary objective was to compare the n-3 vs. n-6 PUFA rich oils (flaxseed and fish oils vs. soybean oil). Fish and soybean tended to have similar effects on glucose homeostasis, which differed from the effects of flaxseed oil. On the other hand, fish and flaxseed oils tended to have similar effects on the lipid metabolism, which differed from the effects of soybean oil.

Changes in glucose homeostasis have two-fold relevance in PCOS. First, PCOS patients have increased insulin resistance and a higher risk of developing impaired glucose tolerance and type 2 diabetes. Second, changes in glucose homeostasis affect lipid metabolism and androgen production ¹⁴.

This study demonstrated that, when compared to the baseline, fish oil increased glucose levels during OGTT and tended to increase insulin levels during the second half of OGTT and decreased insulin sensitivity index (Matsuda), without significantly affecting fasting glucose, insulin or HOMA. Although the late insulin response tended to increase, the early insulin response measured by FS-IVGTT (AIRg) tended to decrease. Recent literature indicated that the patterns of change during OGTT point to the site of insulin resistance ¹⁵. Increased fasting glucose, insulin and HOMA suggest increased hepatic insulin resistance. On the other hand, increased glucose and insulin levels during the second half of OGTT and decreased Matsuda Index suggest increased peripheral insulin resistance. Accordingly, fish oil appeared to increase peripheral insulin resistance and decrease early insulin secretion. However, the late increase in insulin secretion compensated for the insulin resistance because disposition index tended to increase, and HgBA1c decreased. Notably, flaxseed oil did not change glucose homeostasis significantly, except for the increase in 30 min-OGTT glucose.

To our knowledge, differential effects of different n-3 PUFA have not been investigated in PCOS patients. In healthy men and women, fish oils have not affected insulin sensitivity or

early phase insulin response, regardless of the background fat intake or n-6/n-3 PUFA ratio^{16, 17}. In diabetic patients, low dose of fish oil supplementation has not affected hepatic or peripheral insulin resistance¹⁸ while a high-dose increased glucose levels and decreased peripheral glucose utilization¹⁹. Several earlier studies have demonstrated increased glucose levels during fish oil treatment in diabetic patients⁶. A recent population study indicated that fish consumption may be associated with increased risk of diabetes²⁰. Flaxseed oil has not altered fasting glucose, insulin or HgBA1c in diabetic patients either²¹. These findings are in contrast with the data from animal models which have consistently shown that n-3 PUFA increase insulin sensitivity and glucose utilization⁶. Studies in human muscle have demonstrated that monounsaturated fatty acid and PUFA contents of the cell membrane correlate directly with the glucose uptake²². A potential explanation for the failure of n-3 PUFA in increasing insulin sensitivity in PCOS may relate to the underlying mechanism: Glucose uptake requires binding of insulin to its receptor in the cell membrane, followed by serial phosphorylation steps that occur in the insulin receptor (IR) and its substrate (IRS). Phosphorylation of tyrosine residues in the IR and IRS-1 advances insulin signaling. In contrast, serine phosphorylation of the IRS-1 reduces insulin signaling and glucose transport. n-3 PUFA overcomes insulin resistance by preventing serine phosphorylation of IRS-1²³. Women with PCOS have intrinsic increase in serine phosphorylation of IRS-1²⁴. It is conceivable that n-3 PUFA cannot reverse this intrinsic abnormality, and therefore, cannot correct insulin resistance. To test this hypothesis, effects of n-3 PUFA in PCOS vs. healthy control women need to be compared.

During fish oil treatment, the changes in adiponectin levels correlated inversely with the changes in fasting glucose and AUC_{Glucose}. This is consistent with the well recognized role of adiponectin in promoting insulin sensitivity. Experimental data indicate that adiponectin lowers fasting glucose by reducing hepatic glucose output and increases peripheral insulin sensitivity by promoting lipid oxidation²⁵. Although we have not observed any significant increase in adiponectin during fish oil intervention, studies in animal models and humans have reported significant increase^{17, 26, 27}. In addition, hs-CRP correlated directly with the changes in fasting insulin and triglyceride, and inversely with the change in Matsuda Index. This is consistent with the well established role of inflammation in insulin resistance and metabolic syndrome²⁸.

Similar to fish oil, soybean oil also decreased early insulin response, increased glucose and insulin levels during the second half of OGTT and tended to decrease Matsuda Index--all pointing to increased insulin resistance and impaired early insulin secretion. The change in AUC_{Insulin} correlated with the change in leptin. This finding can be explained by the strong correlation between serum leptin and obesity²⁹ as well as the role of insulin in leptin secretion from the adipose tissue³⁰. The main difference between fish oil vs. soybean oil treatments was that the disposition index tended to increase during fish oil intervention but tended to decrease during soybean oil intervention. These findings suggest that glucose disposal to the peripheral tissues was maintained during fish oil but not during soybean oil intervention. The similarities between the effects of fish and soybean oils were unexpected because the major PUFA in the fish oil belong to the n-3 class whereas in soybean oil to the n-6 class (Table 1). Although there is limited information about the effects of soybean oil on glucose homeostasis, in vitro studies in rat pancreas have shown that soybean oil can decrease³¹ or increase³² insulin secretion.

When the changes in lipid metabolism were considered, both fish and flax seed oils decreased triglyceride and tended to increase LDL-cholesterol. It is well established that long chain n-3 PUFA in fish oil decrease triglyceride and increase LDL-cholesterol⁷. Effects of flaxseed oil on triglyceride and LDL-cholesterol have been variable³³. The literature about the effects of soybean oil on plasma lipids is not readily comparable to our

study because most published reports have tested the effects of hydrogenated soybean oil or soybean itself.

An important finding was that none of the supplements affected the hs-CRP levels. In PCOS, obesity and central obesity both have been associated with elevated hs-CRP levels³⁴. We had expected fish oil and flaxseed oil to lower hs-CRP due to their well recognized anti-inflammatory effects^{35–37}, while soybean oil increases hs-CRP because n-6 PUFA are pro-inflammatory³⁸. Although population studies in the USA^{35, 39} and Greece⁴⁰ have shown inverse relationships between hs-CRP and n-3 PUFA intake, a study in Japan also showed inverse correlation between intake of n-6 essential PUFA and hs-CRP⁴¹, suggesting that n-6 PUFA can also be anti-inflammatory. The results obtained from cross-sectional population studies may not be directly applicable to prospective intervention studies because neither our intervention nor a recent report from Gillingham et al⁴² found a decrease in hs-CRP during n-3 PUFA supplementation. Changes in hs-CRP correlated with the changes in insulin resistance markers, consistent with the well accepted role of inflammation in increased insulin resistance⁴³.

In conclusion, our findings indicate that long chain vs. essential n-3 PUFA rich oils from marine vs. plant sources exert specific effects on glucose homeostasis in PCOS patients. The long chain n-3 PUFA rich fish oil and n-6 PUFA rich soybean oil supplements can decrease early insulin secretion, can impair glucose tolerance and increase hyperinsulinemia. On the other hand, the essential n-3 PUFA rich flaxseed oil does not have any adverse effects. It is necessary to monitor blood glucose in PCOS patients after starting any PUFA supplementation.

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ABBREVIATION LIST

PCOS	polycystic ovary syndrome
PUFA	polyunsaturated fatty acid
OGTT	oral glucose tolerance test
FS-IVGTT	frequently sampled intravenous glucose tolerance test
LDL	low density lipoprotein
HDL	high density lipoprotein
IRS	insulin receptor substrate
AUC	area under the curve
SHBG	sex hormone binding globulin
DHEAS	dehydroepiandrosterone
HOMA	Homeostasis Model Assessment

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Figure 1.

Effects of fish, flaxseed and soybean oils on serum glucose and insulin during oral glucose tolerance test (continuous lines: baseline; broken lines: after treatment; *, $p < 0.05$; Mean $\pm$ SEM; $n = 17$ in each group).

Table 1

Fatty acid composition (% weight) of the supplements

	Fish oil	Flaxseed oil	Soybean oil
<u>Saturated fats</u>			
Palmitic acid (16:0)	5.0	5.7	9.7
Stearic acid (18:0)	2.1	4.0	3.6
<u>Monounsaturated fats</u>			
Oleic acid (18:1, n-9)	4.6	19.2	20.2
<u>Polyunsaturated fats</u>			
Linoleic acid (18:2, n-6)	0.8	16.2	42.9
Linolenic acid (18:3, n-3)	0.6	54.5	5.7
Eicosapentanoic acid (20:5, n-3)	39.5	0.1	0.1
Docosahexanoic acid (22:6, n-3)	27.5	0	0.1

Table 2

Changes in anthropometric parameters, glucose homeostasis variables, plasma lipids and androgens during fish oil, flaxseed oil or soybean oil supplementations for six weeks in women with polycystic ovary syndrome.

	Fish Oil (n=17)		Flaxseed Oil (n=17)		Soybean Oil (n=17)		ANOVA (Weight adjusted)
	Pre	Post	Pre	Post	Pre	Post	
Age (years)	31.7 ± 1.9	---	29.4 ± 1.6	---	28.9 ± 1.0	---	
Anthropometrics							
Weight (kg)	100.0 ± 5.2	100 ± 5	94.1 ± 8.2	94.5 ± 8.2	90.0 ± 5.9	90.5 ± 5.5	--
BMI (kg/m ²)	36.3 ± 1.9	36.6 ± 1.8	35.0 ± 2.5	35.1 ± 2.6	33.2 ± 1.8	33.3 ± 1.7	0.8418
Waist (cm)	99.3 ± 4.1	100.1 ± 3.8	95.0 ± 5.1	95.0 ± 5.0	94.7 ± 3.8	95.5 ± 3.8	0.5911
Fat mass (kg)	37.9 ± 3.8	38.5 ± 3.7	34.7 ± 4.2	34.1 ± 4.7	37.0 ± 4.1	35.3 ± 2.8	0.9471
Fasting parameters							
Glucose (mmol/l)	5.44 ± 0.17	5.38 ± 0.11	5.16 ± 0.05	5.33 ± 0.17	4.94 ± 0.11	5.05 ± 0.11	0.5584
Insulin (pmol/l)	153 ± 17	158 ± 15	173 ± 40	188 ± 33	122 ± 17	132 ± 15	0.8005
HgBA1 (%)	5.5 ± 0.1	5.4 ± 0.1 [†]	5.5 ± 0.1	5.4 ± 0.1	5.4 ± 0.1	5.3 ± 0.1	0.8911
Adiponectin (ng/ml)	7.5 ± 1.0	8.5 ± 1.3	8.0 ± 1.2	7.6 ± 1.3	6.5 ± 1.2	6.2 ± 1.1	0.1988
Leptin (ng/ml)	29.8 ± 3.5	29.4 ± 3.2	27.1 ± 3.3	28.5 ± 4.0	28.1 ± 3.4	30.6 ± 4.3	0.4042
HOMA	5.46 ± 0.68	5.55 ± 0.58	5.91 ± 1.47	6.78 ± 1.43	3.92 ± 0.59	4.32 ± 0.53	0.4208
Oral Glucose tolerance test							
ISIMatsuda	2.43 ± 0.37	1.96 ± 0.25 [*]	2.46 ± 0.41	2.36 ± 0.38	3.27 ± 0.42	2.86 ± 0.42	0.4903
AUC _{Glucose}	15.65 ± 0.61	16.48 ± 0.61	15.93 ± 0.44	15.71 ± 1.00	14.82 ± 0.61	16.37 ± 0.72 [*]	0.6973
AUC _{Insulin}	1,760 ± 229	1,979 ± 236	1,924 ± 333	1,778 ± 319	1,292 ± 194	1,458 ± 194	0.2311
Intravenous glucose tolerance test							
ΔIRg	893 ± 171	786 ± 129 [†]	627 ± 81	666 ± 94	669 ± 89	550 ± 74	0.1469
DI	1212 ± 189	1441 ± 239	956 ± 173	965 ± 113	1,784 ± 436	1100 ± 158	0.0621
SI	1.53 ± 0.24	1.78 ± 0.40	1.60 ± 0.23	2.98 ± 1.30	3.13 ± 0.76	2.45 ± 0.51	0.4028
B cell function	319 ± 63	331 ± 50	370 ± 51	343 ± 53	343 ± 49	315 ± 42	0.9651
Fasting lipids and CRP							
Triglyceride (mmol/l)	1.47 ± 0.15	1.20 ± 0.14 [*]	1.62 ± 0.24	1.31 ± 0.17 [*]	1.39 ± 0.17	1.45 ± 0.19	0.0368

	Fish Oil (n=17)		Flaxseed Oil (n=17)		Soybean Oil (n=17)		ANOVA (Weight adjusted)
	Pre	Post	Pre	Post	Pre	Post	
Age (years)	31.7 ± 1.9	---	29.4 ± 1.6	---	28.9 ± 1.0	---	0.1625
Total-C (mmol/l)	4.95 ± 0.21	5.10 ± 0.21	4.69 ± 0.23	4.69 ± 0.23	4.92 ± 0.18	4.61 ± 0.21	0.0678
LDL-C (mmol/l)	3.29 ± 0.18	3.44 ± 0.21	2.77 ± 0.16	2.93 ± 0.18	2.87 ± 0.21	2.56 ± 0.26	0.7764
HDL-C (mmol/l)	1.06 ± 0.05	1.11 ± 0.05	1.17 ± 0.08	1.17 ± 0.05	1.22 ± 0.09	1.22 ± 0.08	0.4381
ApoB (mg/dl)	83 ± 5	86 ± 5	65 ± 12	64 ± 2	77 ± 4	77 ± 6	0.9575
hs-CRP (mg/l)	3.6 ± 0.8	3.2 ± 0.8	3.1 ± 0.7	3.6 ± 1.0	3.5 ± 0.8	3.3 ± 0.6	
Androgens							
Testosterone (nmol/l)	2.95 ± 0.69	2.85 ± 1.11	2.95 ± 0.18	2.78 ± 0.62	3.33 ± 0.73	3.05 ± 0.76*	0.7843
SHBG (nmol/l)	17.2 ± 2.5	17.2 ± 2.8	17.7 ± 3.5	16.3 ± 3.7	18.4 ± 2.4	16.2 ± 2.5	0.3896
DHEAS (μmol/l)	392 ± 70	392 ± 65	491 ± 75	504 ± 55	705 ± 57	653 ± 68	0.4933

* Within group significance $p < 0.05$

† Within group significance $p = 0.0871$