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Changes in plasma metabolites and glucose homeostasis during omega-3 polyunsaturated fatty acid supplementation in women with polycystic ovary syndrome

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ABSTRACT

Background: Both fish (FO) and flaxseed oils (FLX) are n-3 polyunsaturated fatty acids (PUFA). Fish oil contains long chain while FLX contains essential n-3 PUFA. We demonstrated that FO altered insulin secretion and resistance in polycystic ovary syndrome (PCOS) women but FLX did not. Surprisingly, the effects of FO were similar to those of the n-6 PUFA-rich soybean oil (SBO). Since increased branched chain (BCAA) and aromatic amino acids (AA) affect insulin secretion and resistance, we investigated whether FO, FLX and /or SBO affect plasma metabolites, especially AA.

Methods and findings: In this six-week, randomized, 3-parallel arm, double-blinded study, 54 women received 3.5 g/day FO, FLX or SBO. In 51 completers (17 from each arm), fasting plasma metabolites were measured at the beginning and at the end.

As compared to FLX, FO and SBO increased insulin response and resistance as well as several BCAA and aromatic AA. Pathway analysis indicated that FO exerted the largest biochemical impact, affecting AA degradation and biosynthesis, amine, polyamine degradation and alanine, glycine, L-carnitine biosynthesis and TCA cycle, while FLX had minimal impact affecting only alanine biosynthesis and L-cysteine degradation.

Conclusion: Effects of FO and SBO on plasma AA were similar and differed significantly from those of the FLX. The primary target of dietary PUFA is not known. Dietary PUFA may influence insulin secretion and resistance directly and alter plasma AA indirectly. Alternatively, as a novel concept, dietary PUFA may directly affect AA metabolism and the changes in insulin secretion and resistance may be secondary.

1. Introduction

Polyunsaturated fatty acids (PUFA) are powerful modulators of lipid and glucose metabolism. Their actions are considered to be class specific as the PUFA from omega-3 (n-3) vs. n-6 have different and usually opposing actions. For example, n-3 PUFA lower serum triglycerides while n-6 PUFA lower total cholesterol and low density lipoprotein (LDL)-cholesterol [1]. Experimental studies suggest that n-3 PUFA decrease, whereas n-6 PUFA increase insulin secretion; and both n-3 and n-6 PUFA increase insulin sensitivity [2]. Although the findings of experimental vs. clinical studies agree on lipid metabolism, they vary a great deal regarding glucose homeostasis.

Significant gaps in knowledge exist regarding the biological effects of PUFA. For example, no distinction has been made between the effects of long-chain vs. essential n-3 PUFA. Flaxseed oil is a rich source of the essential n-3 PUFA α-linolenic acid (ALA, 18:3) while fish oil contains the long chain n-3 PUFA eicosapentanoic acid (EPA, 20:5) and docosahexanoic acid (DHA, 22:6). Although ALA can be converted to EPA in vivo, this is very inefficient in humans [3]. Despite that, in clinical practice these oils are used interchangeably. However, the choice of the exact type of oil used is important because ALA is metabolized differently than EPA and DHA. While ALA competes with the n-6 essential PUFA linoleic acid (LA, 18:2) for Δ6 desaturase and interferes with production of arachidonic acid (AA, 20:4), EPA and DHA compete at more distal steps at the cyclooxygenase and lipooxygenase [4].

We had compared the effects fish, flaxseed and soybean oils on glucose homeostasis in polycystic ovary syndrome (PCOS) [5]. This syndrome provides an excellent clinical model because the affected young women are insulin resistant; at least 50% of PCOS patients have metabolic syndrome; one third of patients have glucose

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intolerance; and one out of five develops type 2 diabetes before the age of 40 years. Hyperinsulinemia aggravates reproductive dysfunction by stimulating ovarian androgen production, by reducing sex hormone binding globulin (SHBG); thus by increasing bioavailable testosterone. Treatment of insulin resistance increases fertility in PCOS [7].

We assessed insulin resistance and secretion using oral and frequently sampled intravenous glucose tolerance tests (OGTT and FS-IGT, respectively). Unexpectedly, fish and soybean oils caused similar changes in glucose homeostasis; furthermore, their effects were distinctly different than those of flaxseed oil [6]. These observations challenged the widely accepted concept that "the biological effects of PUFA are specific To their omega class" The similarities between the effects of n-3 PUFA rich fish oil and n-6 PUFA rich soybean oil suggested complex regulatory mechanisms.

Several studies employing the metabolomics technology suggest perturbations of branched chain amino acid (BCAA) and aromatic AA metabolism in insulin resistance and obesity [8]. Obese, insulin resistant individuals demonstrated a characteristic increase in fasting plasma concentrations of BCAA: (valine, isoleucine, leucine) and their catabolic byproducts such as glutamate, α-ketoglutarate, C3 and C5 acylcarnitines [9–12]. We also found direct correlations between serum BCAA ad insulin resistance parameters in women with metabolic syndrome [13]. Similar findings were observed in a subpopulation of the Framingham Cohort where a few AA (leucine, isoleucine, valine, phenylalanine, tyrosine) could predict the five-fold increase in type 2 DM [12]. Therefore, we investigated the effects of fish, flaxseed and soybean oils on BCAA and other primary metabolites in PCOS.

2. Research design and methods

2.1. Subjects

The study was approved by the Institutional Review Board of University of California, Davis and registered with the NIH. The subjects were recruited between September 2007 and February 2010, and were included in the study after signing the written informed contents. Clinical characteristics of the patients, the study protocol, clinical studies and the results have been reported previously [6].

Women between the ages 20 and 45 years and with a body mass index (BMI) of 25–45 kg/m^2, fulfilling the NIH criteria for PCOS by having ovarian dysfunction (amenorrhea; no periods for >6 months, or oligomenorrhea: <6 periods/year; clinical 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 [7]. Patients were excluded if they used oral contraceptives, anti-androgenic medications, insulin sensitizers, d-chiro inositol, lipid lowering drugs 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.

2.2. Consort statement

As shown in Fig. 1, 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) or had other

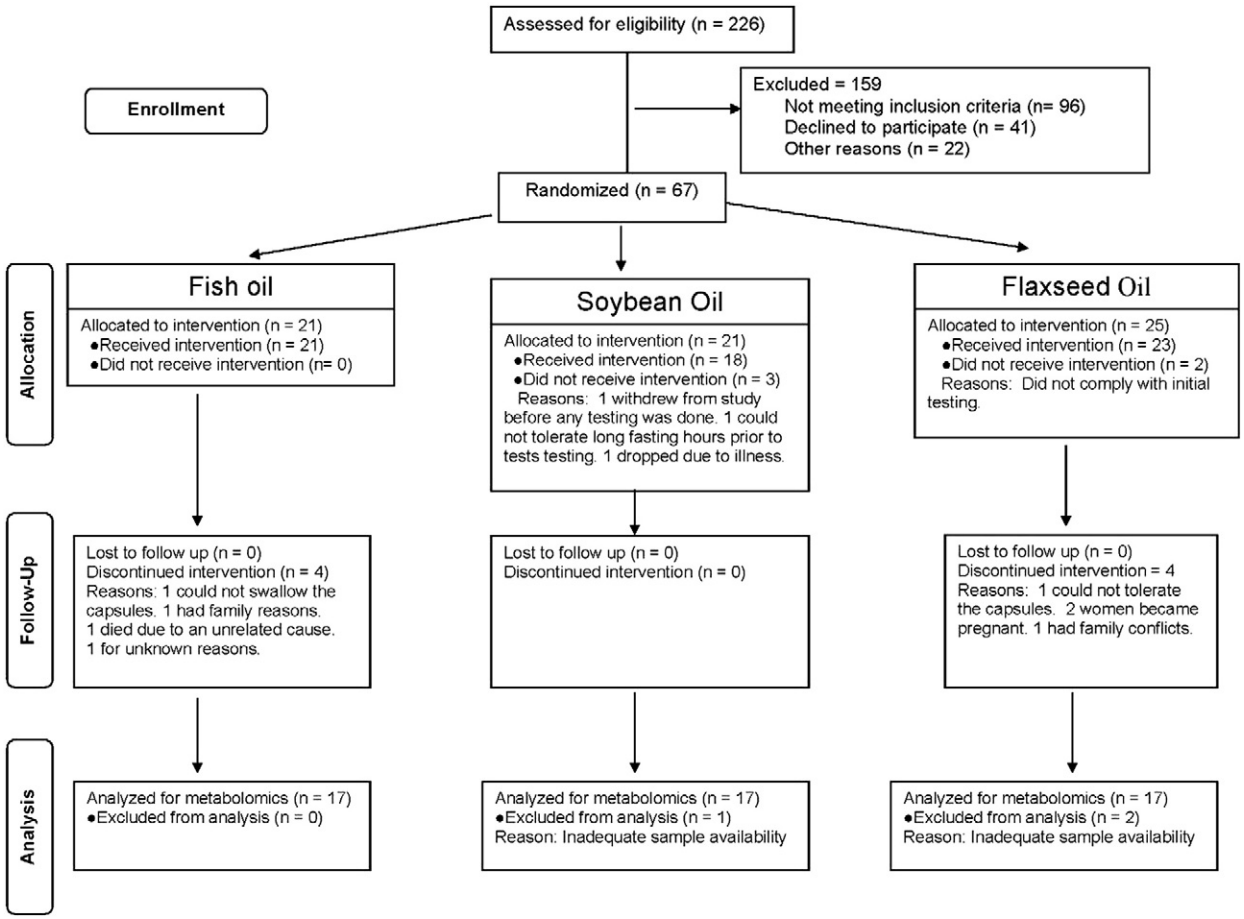

Fig. 1. Consort diagram.