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Review

Effect of omega-3 fatty acids supplementation on insulin resistance in women with polycystic ovary syndrome: Meta-analysis of randomized controlled trials

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ABSTRACT

Background: Several studies have shown that omega-3 polyunsaturated fatty acids (PUFA) may improve insulin resistance in various diseases. However, the possible effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation on insulin resistance in PCOS still remains unclear. We evaluated the effect of omega-3 PUFA supplementation on insulin resistance in women with PCOS in a meta-analysis.

Methods: Literature searches of MEDLINE, PubMed Central and EMBASE for publications in English were conducted up to December 2015. We included all randomized controlled trials (RCTs) that investigated effects of omega-3 fatty acids supplements on insulin resistance in women with PCOS. Results are summarized as mean differences (MD) with 95% confidence intervals (CI). Effect sizes of eligible studies were pooled using random-effects models (the DerSimonian-Laird estimator). We assessed the potential sources of heterogeneity using the standard $\chi 2$ test.

Results: Of 1202 papers, three RCTs were eligible for inclusion which involved 72 cases and 73 controls. The dose range for omega3 supplement was 1.2 g to 3.6 g and the duration of follow-up was from 6 to 8 weeks. There was no significant effect of omega-3 fatty acids supplements compared to placebo on insulin resistance (MD: 6.18; CI; −3.347, 15.382; p = 0.208) and HOMA −IR (MD: 0.276; 95% CI = −1.428, 1.981; p = 0.751) in women with PCOS.

Conclusion: The results provide an evidence that supplementation with omega-3 fatty acids may not have a beneficial effect on improving insulin resistance in women with PCOS.

Contents

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1. Introduction

Polycystic ovary syndrome (PCOS) is the most common and complex endocrine disorder that affect fertility of women in their reproductive age [1,2]. Prevalence of PCOS in the general population is 5%–18% that varies according to the diagnostic criteria [3,4]. PCOS is characterized by hyperandrogenism and ovulatory dysfunction [5,6]. This syndrome is also related to dyslipidemia, insulin resistance, type 2 diabetes and risk factors of cardiovascular disease such as elevated levels of high-sensitivity C-reactive protein(hs-CRP) and acute phase proteins [7,8]. Insulin resistance with hyperinsulinaemia is common in PCOS which is also seen in 50–70% of lean and obese women with this syndrome [9,10]. Moreover, PCOS is a proinflammatory disease with increased level of tumor necrosis factor alpha (TNF-α) and Interleukin-6 (IL-6) in obese and lean women which may lead to insulin resistance [4,11]. Insulin resistance may play a key role in the pathogenesis of PCOS, and hyperinsulinemia may lead to hyperandrogenaemia by stimulation of androgen synthesis through Theca cells and reducing hepatic production of sex hormone-binding globulin (SHBG) [10,12].

Lifestyle and nutritional interventions along with weight loss are successful treatment for women with PCOS [6,13]. Dietary factors such as anti-inflammatory foods may have important role in improving metabolic disorders of this syndrome [6,14]. Among dietary factors, omega-3 fatty acids especially marine n-3 PUFA (eicosapentaenoic acid (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA)) have anti-inflammatory, anti-obesity and anti-insulin resistance functions [14–16]. Omega 3 fatty acids can improve insulin sensitivity by decreasing production of inflammatory cytokines including TNFα, IL-6 and increasing secretion of anti-inflammatory adiponectin [17]. Although several studies have shown effect of omega-3 fatty acids on insulin resistance in different conditions, but there are controversial results in studies on PCOS patients [6]. Thus, in current meta-analysis we intend to investigate the effect of omega-3 supplementation on insulin resistance in women with PCOS.

2. Methods

2.1. Search strategy and selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses was used for writing this systematic review and meta-analysis [18].

We searched databases including MEDLINE, EMBASE and PubMed Central for all relevant published studies up to December 2015 with no language restriction. We used medical subject headings (MeSH) and text words to identify potential interest articles. Search terms included: (“Fatty Acids, Omega-3” OR “n-3 polyunsaturated fatty acid” OR ‘omega-3 polyunsaturated fatty acid’ OR "ω-3fatty acid" OR “polyunsaturated fatty acid” OR “eicosapentaenoic acid” OR “docosahexaenoic acid” OR “fish oil” OR EPA OR DHA OR ALA OR PUFA OR “alpha-linolenic acid” OR fat OR “fatty acid” OR “docosapentaenoic acid” OR n-3 OR omega-3 OR “n-3 fatty acid”) AND (“polycystic ovarian syndrome” OR PCO OR PCOS OR “polycystic ovary” OR “Polycystic Ovary Syndrome”). First, there was no limitation on RCT, animals or human studies. Then, among the all received articles, RCTs were identified by reading titles, abstracts, population and study design in order to select relevant articles for inclusion/exclusion criteria.

2.2. Eligibility criteria

Studies were eligible for inclusion if they fulfilled the following criteria: a) the study design was a RCT, b) the intervention was oral omega-3 supplementation, c) the outcomes of interest were insulin resistance, d) the population of interest was adults (aged >18 years).

Studies were excluded if those were cross-sectional, review articles, duplicated publications and animal or cell culture studies.

2.3. Quality assessment

We used Jadad scoring system to assess the quality of the included studies [19]. The Jadad scale contains questions which describe randomization, randomization scheme and withdrawal in intervention and placebo group [20]. In this scoring system each study get from zero to five points. Low quality studies received score of $\leq$2 and high quality studies a score of $\geq$3 [20].

2.4. Data extraction and statistical analysis

The following data were extracted from full text of selected studies: general characteristics of the study (first author’s name, year of publication, the study design, the country where the study was conducted, number of cases and controls, total supplement dose and duration of follow-up), characteristics of the participants (study population, age, BMI) and result (means and standard deviations for insulin and HOMA-IR in baseline and After intervention). Heterogeneity of studies was assessed using the I^2 statistics. A random-effects model (the DerSimonian-Laird estimator) was used if heterogeneity was more than 50%, to calculate the pooled mean difference (MD).

All statistical analysis was performed using STATA software version 12 (STATA Corp, College station, Texas).

3. Results

3.1. Study selection

The flow chart of the study is presented in Fig. 1. The initial search identified 1202 studies through PubMed and Scopus; 808 studies remained after removing duplicates. The title and abstract of remaining studies were reviewed and irrelevant studies were excluded. A total 6 studies were eligible for inclusion in the meta-analysis. One study had no control group, one study was overlapped and in another study there was limited data [10,21,22]. Finally, 3 randomized controlled trials were included in this meta-analysis.

3.2. Characteristics of included studies

Characteristics of the included studies were summarized in Table 1. The Rotterdam diagnostic criteria and the NIH criteria were used in all studies whereas one study investigated only overweight/obese PCOS women [23,24]. These studies were published in Iran [25], Australia [24] and USA [26] which included 72 cases