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Review Article

THERAPEUTIC EFFECT OF OMEGA-3 FATTY ACID IN POLYCYSTIC OVARIAN DISEASE

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ABSTRACT

Polycystic ovarian disease is the most common endocrine condition in reproductive-aged women. Its common characteristics are reproductive, metabolic, endocrine, and psychological changes in women. We review here the therapeutic effect of omega-3 polyunsaturated fatty acids on polycystic ovarian disease (PCOD). Therefore, the aim of conducting a review was to study the possible effects and their mechanism. A comprehensive systematic search was conducted in MEDLINE/PubMed, Google Scholar, and SCOPUS, to find studies investigating omega-3 fatty acids as a preventative or therapeutic agent for the attenuation of PCOD complications. Subsequently, the impact of omega-3 on PCOD, inflammation, insulin resistance, obesity, and hormonal imbalance were discussed. Although most of the studies in patients with PCOD reported an improvement in many complications after administration of omega-3 supplements, there is a distinct shortage of studies investigating the dietary intake of these types of fatty acids. A balanced amount of omega-3 fatty acid is important for prevention and reducing complications of PCOD.

Keywords: Omega-3, Fatty acids, PCOD, PUFA

INTRODUCTION

Polycystic ovarian disease (PCOD) is the most common female reproductive disorder in women aged 15 to 48 years. It is an endocrine and metabolic disorder in women, reflecting major hormonal imbalance and long-term complications [1].

PCOD is a disease affecting approximately 6 to 10% of women in their reproductive age [2]. PCOD was first discovered by the American gynecologist F Stein and M Leventhal in 1935 as an accumulation of many fluid-filled sacs in follicles of ovary [3]. There are several characteristics of PCOD like irregular menstrual cycles, amenorrhea and

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oligomenorrhea, acne or hirsutism, enlarged ovary, insulin resistance, obesity, and infertility.

Polycystic Ovary Syndrome (PCOS), also known as Polycystic Ovary Disease, is the most common disorder affecting women of childbearing age. PCOD is a heterogeneous disease with a variety of signs and symptoms and severe disturbance of endocrine and metabolic functions [2]. Recently, European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) stated a refined definition of PCOD: particularly the presence of 2 out of the subsequent 3 criteria: (i) oligo- and/or anovulation; (ii) hyperandrogenism (clinical and/or biochemical); (iii) polycystic ovaries, with the exclusion of different etiologies [4].

Clinically, PCOD women diagnosed with associated inflated sterility risks like dysfunctional hemorrhage, endometrial and ovarian cancer, form a pair of polygenic disorder [5]. Additionally, several endocrine abnormalities in PCOD result from metabolic alteration like dyslipidemia, obesity, metabolic syndrome, insulin resistance, and hyperinsulinemia [6]. PCOD phenotype is a prominent clinical issue from the symptomatic and therapeutic point of view [7]. The specific causes are not known for PCOD till now, but some of the factors that can affect are environmental factors, genetic factors, sedentary lifestyle, etc.

The cure for PCOD are firstly, lifestyle changes, dietary modification, behavioral therapy, physical activity, and exercise. The nutritional intervention & therapeutic approach represent a favorable strategy for the treatment of PCOD [8]. Omega-3 fatty acids, mainly polyunsaturated fatty acids, play a very effective role to prevent anovulation. Omega-3 fatty acids have been found to have very health benefits like anti-inflammatory properties, anti-insulin resistance, and anti-obesity properties [9]. Evidence suggests that role of omega-3 fatty acid supplementation increase insulin sensitivity, and decrease plasma triglyceride, reduce oxidative stress, and plasma adiponectin level, and reduce hyperinsulinemia in adults [10].

A good source of omega-3 fatty acid is Alpha-linolenic acid which is found in plant-based diets such as flax seed oil and walnut, Animal-based diet like fish oil is rich in docosahexaenoic acid which is also a source of omega-3 fatty acid. These fatty acids are essential for our body’s functions and activities. The essential fatty acids are not synthesized in our body and are only fulfilled through the diet [11].

In PCOD, there is an imbalance of sex hormones, that causes ovarian cysts and irregular menstrual cycle or amenorrhea. These complications have been mainly attributed to the suppression of the follicle-stimulating hormone (FSH) secretion by an

excess androgen produced from the theca cells of the ovary [12].

Pathophysiology of PCOD (Fig.1)

Hyperandrogenism is the key feature of PCOS. This causes a direct increase in the production of androgen probably by an increased level of insulin in the ovaries and a decrease in sex hormone-binding globulin (SHBG). This protein keeps testosterone in its bound forms & thus reduces the free testosterone level in the body [14].

In addition to this, patients with PCOS have high levels of luteinizing hormone, in which level of androgen is elevated and secondarily

It leads to the disturbance of the menstrual cycle, infertility, hirsutism, acne, alopecia. Elevated LH levels play a vital role in the development of reproductive and metabolic disorders, based on the evidence. Firstly, LH stimulates androgen production in ovarian theca cells, resulting in hyperandrogenemia and halted follicle development [15]. Secondly, an increased frequency of LH pulses disrupts the synthesis of estrogen and FSH, thereby inhibiting follicle growth and ovulation. Thirdly, LH enhances the ovarian secretion of IGF-1, which further promotes LH binding and androgen production in theca cells, contributing to the development of polycystic ovaries in patients with PCOS [16].

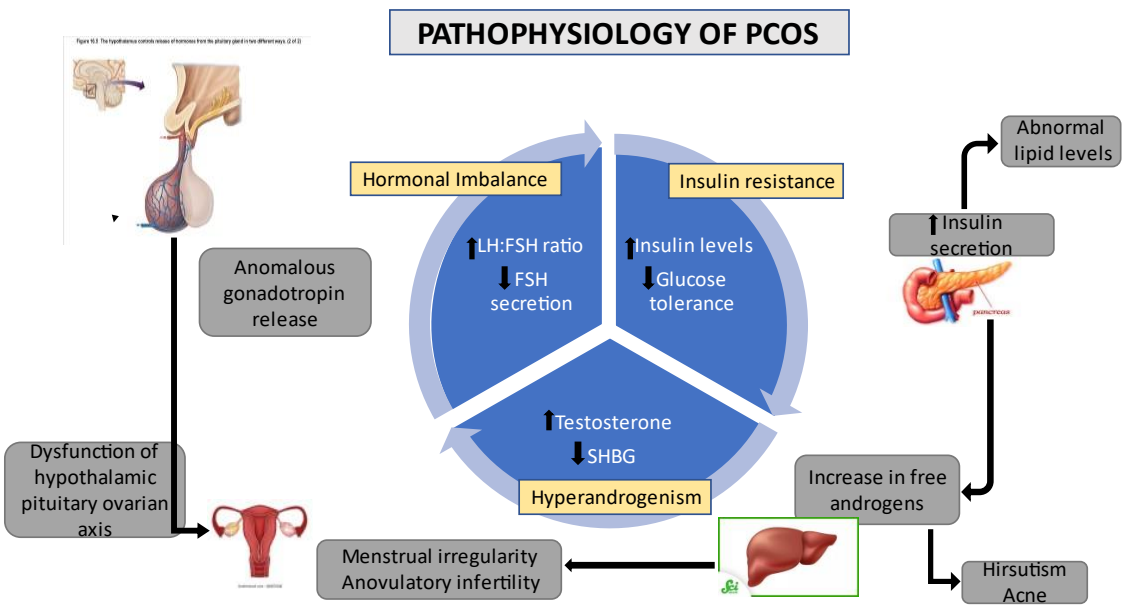

Fig. 1. Pathophysiology of Poly Cystic Ovarian Syndrome

Physiological mechanism of omega-3 polyunsaturated fatty acid

Polyunsaturated fatty acids (PUFAs) are categorized into omega-3 (n-3) and omega-6 (n-6) fractions. Omega-3 PUFAs are primarily synthesized from α-linolenic acid, while omega-6 PUFAs are synthesized from linoleic acid (LA) [17]. Linoleic acid can be metabolized to n-6 via desaturase, resulting via biosynthesis of gamma-linolenic acid (GLA), dihomo—gamma-linolenic acid (DGLA), and finally AA. The largest amount of arachidonic acid (AA), however, is found in phospholipids membranes, competing with n-3 acids for metabolism and with their products for receptors [18].

Under the action of cyclooxygenase (COX) enzymes, arachidonic acid (AA) is converted into prostaglandins (PG), thromboxanes, and leukotrienes. Eicosanoids, mainly epoxyeicosatrienoic acids (EETs) and 20 hydroxyeicosatetraenoic acid (20-HETE), are produced throughout cytochrome P450 (CYP) enzyme activity [19]. However, as a result of AA metabolism mediated by lipoxygenase (LOX) enzymes, including 5-, 8-, 12-, and 15-LOX, from which, in turn, HPETE acids are adequately produced, followed by HETE and oxo-ETE (Fig. 2) [20]. 5-oxo ETE and 12-HETE are potent chemo-attractants for basophils, eosinophils, monocytes, and neutrophils. Moreover, 15 HETE stimulates

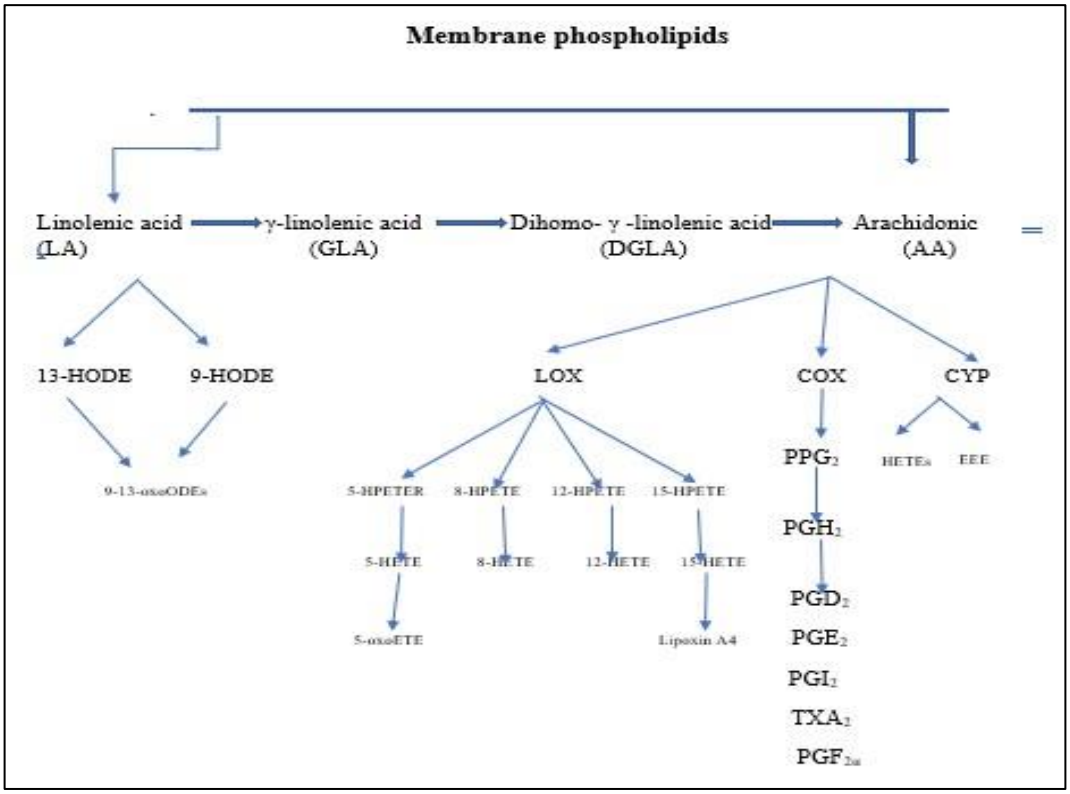

Fig. 2. Synthesis of inflammatory mediators from linoleic acid (LA) and metabolic acid (AA). LOX-lipoxygenase, HETE- hydroperoxyl eicosatetraenoic acid, HPETE-Hydroperoxyeicosatetraenoic acid, HODE-hydroxyoctadecadiene acids, COX-cyclooxygenase, CYP-cytochrome P450, HETEs- hydroxyeicosatetraenoic acids, EETs-epoxyeicosatrienoic acids, PG- prostaglandins, TX-thromboxane.

mitogenesis of endothelial cells, increasing the activity of granulocytes and lymphocytes [21].

Omega 3 fatty acid and insulin resistance

Insulin resistance is a condition where the peripheral tissues have a diminished response to insulin. Insulin resistance is commonly encountered in spread to muscles and liver causing a negative impact of glucose metabolism which is attributed to defective regulation of glucose transporter [4]. Among the complications related to insulin resistance are the suppression of gluconeogenesis, glycogenolysis in the liver, and reduction of glucose output.

Omega-3 fatty acid protest glucose tolerance and avoid the accumulation of lipid mediators by up-regulating the mRNA expression of insulin-stimulated glucose transporter 4 (GLUT4) insulin receptors substrate-1 (IRS-1) and glycogen synthase-1 (GYS). Additionally, by reducing endoplasmic reticulum stress, increasing β-oxidation of mitochondrial fatty acid and mitochondrial uncoupling as well as limiting lipid deposits and reactive oxygen species, generation omega-3 PUFA could further improve insulin sensitivity.

Omega-3 fatty acid and obesity

Overweight and obesity are observed in 40-50% of PCOS patients and are considered a major risk factor for PCOS [22]. Excess weight accumulation can cause dysfunction in adipose tissue, which is mechanistically linked to the development of metabolic syndrome and associated complications, including insulin resistance in the liver and skeletal muscle.

Natural bioactive compounds, such as n-3 PUFA, have minimal side effects and may be a safer alternative compared to other treatment options. There are a variety of putative mechanisms by which n-3 PUFA, particularly EPA, and DHA could work in improving body composition, modulating energy metabolism, and reducing body weight [23].

It has been shown that DHA, in dosages of >50 μM, could facilitate the differentiation of adipocytes by up-regulation of mRNA levels of adipocyte protein [24]. N-3 PUFA of marine origin may have the potential to control the number and size of adipocytes by influencing their differentiation and apoptosis [25].

Omega-3 fatty acid and inflammation

Omega-3 PUFA also has also have anti-inflammatory properties. Omega-6 PUFA arachidonic acid (AA) is stored in cell membranes and is released upon cell stimulation. It is then metabolized by proinflammatory lipid mediators, such as prostaglandins and leukotrienes in the AA cascade, which exacerbates existing inflammation. Omega-3 PUFA are also stored in cell membranes, where they replace AA,

thereby reducing its storage. Although omega-3 PUFA are also metabolized by proinflammatory lipid mediators in the AA cascade, their active metabolites are considered to be less potent than those of AA, shifting the balance toward reduced inflammation [26]. DHA-rich fish oil extends survival in a mouse model of systemic lupus erythematosus, a common autoimmune disease [27].

The key factors involved are resolvins and neuroprotectins derived from omega-3 fatty acids, especially DHA, which are produced at the conclusion of an inflammatory response. [28] RvE1 plays an active role in halting leukocyte movement to the inflamed area, enhancing the removal of inflammatory cells and debris, and inhibiting cytokine production, thus facilitating the resolution of acute inflammation. [29]

CONCLUSION

In this review, we find out that Omega-3 supplementation in PCOD, promotes indirect benefits by changing the metabolic profile associated with the disease. For the hormonal profile and biomarkers of the inflammatory process, positive results were observed for the reduction of CRP levels. However, the great heterogeneity in the studies to standardize the dosages and the timing of administration.

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