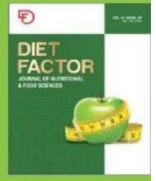




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### Review Article

# Therapeutic Role Of Omega-3 Fatty Acids In Improving PCOS And PCOS Related Complications

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### ABSTRACT

To our insight, despite a few preliminaries investigating the helpful impact of n-3 polyunsaturated unsaturated fats (PUFA) on Polycystic Ovarian Syndrome (PCOS), not many studies are done to examine the impacts of n-3 PUFA utilization on PCOS inconveniences. In this manner, our point was to write a review to explore the potential impact of omega 3 and related components. Data base search was conducted through PubMed, Google scholar, Scopus, EMBASE. Omega-3 fatty PUFAs were explored for their effects on PCOS, mechanisms regulating these pathologies and associated consequences. Omega 3 PUFA helps in management of PCOS by causing weight reduction, maintaining glycemic and hormonal balance and enhancing the endothelial capacity. Patients are observed to show improvements in symptoms of PCOS after using Omega 3 PUFAs. They have various positive impacts on these patients which will be discussed in detail in this review. Accordingly, more preliminaries are justified to examine attractive instruments for explaining the metabolic and hormonal impacts of these specialists in PCOS.

## INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is viewed as one of the most well-known female endocrine issues with a prevalence of 5-10 % globally [1]. Omega-3 PUFAs may apply advantageous consequences for PCOS, including the upgrade of endothelial capacity, helps in reducing weight, improving glycemic load and hormonal homeostasis, and reducing inflammation. Past investigations have shown that an eating regime containing omega-3 PUFAs, particularly long-chain PUFAs, altogether worked on the clinical appearances of dyslipidemia, vascular endothelial functioning, and insulin obstruction in patients with PCOS. Komal *et al.* discovered that fish oil contains EPA and DHA that lowers body weight and metabolic inconsistencies in an animal model. One meta-investigation including 591 PCOS patients from nine randomized controlled preliminaries (RCTs) showed that supplementation with omega-3 PUFAs further improved HOMA-IR and adiponectin levels and lipid profiles [2].

The logic behind the phenomenon of PCOS is not buttoned-down; even with this, a mixture of specifications, involving genetics or epigenetics, ecological components, and disclosure to elevated leveled androgen prenatally are studied to supposedly showcase a part in the outbreak of the disease. Previously it has been studied that ecological components might serve as central components in the prevalence and cure of the disease. In the ecological components, dietary modifications are one of the essential and administrable components [3].

For the analysis of PCOS, the most common criteria which should be examined are FSH, LH, and androgen levels. Elevated LH level drives to an elevation in androgen amount, which raises the evolution of PCOS [3]. Remedial choices of PCOS bounds from pharmacological to surgical. Oral contraceptive pills (OCP) prescribed for half a year alleviates hyperandrogenism and normalize menstruation [4]. It also decreases the serum 25 hydroxyvitamin D level, which can alter bone health. Metformin, an insulin sharpener, upgrades the condition of women suffering from PCOS by reducing the



increased criteria as insulin, androgen, rotating free T levels, at the same time elevating sex hormone-binding globulin and insulin-like growth factor-binding protein [5,6].

Metformin medication during and before the IVF or sperm injection in females with PCOS restrains from the danger of OHSS [7]. Whereas the negative consequences of metformin are lactic acidosis, tiredness, severe drowsiness, cold skin, muscle ache, labored breathing, slow/irregular heartbeat, stomach ache, nausea, vomiting, and diarrhea [9]. Steroid hormonal mediations are one more form to cure PCOS. Antiandrogens are administrated to deal with androgenism. N acetylcysteine and some others are administrated to deal with the resistivity of insulin. These remedies are useful to some degree, but not completely. These remedial methods are also not free from negative effects. The importance and danger of medicine lean on the host elements. The use of these hormone controllers for a longer period of time can become a reason for obesity, cancer, psychiatric problems, along with some other issues [11]. Alteration of lifestyle, like eating habits, nutritional products, workout, and psychological remedies, must be the go-to medication for PCOS as they have no harmful effects [10].

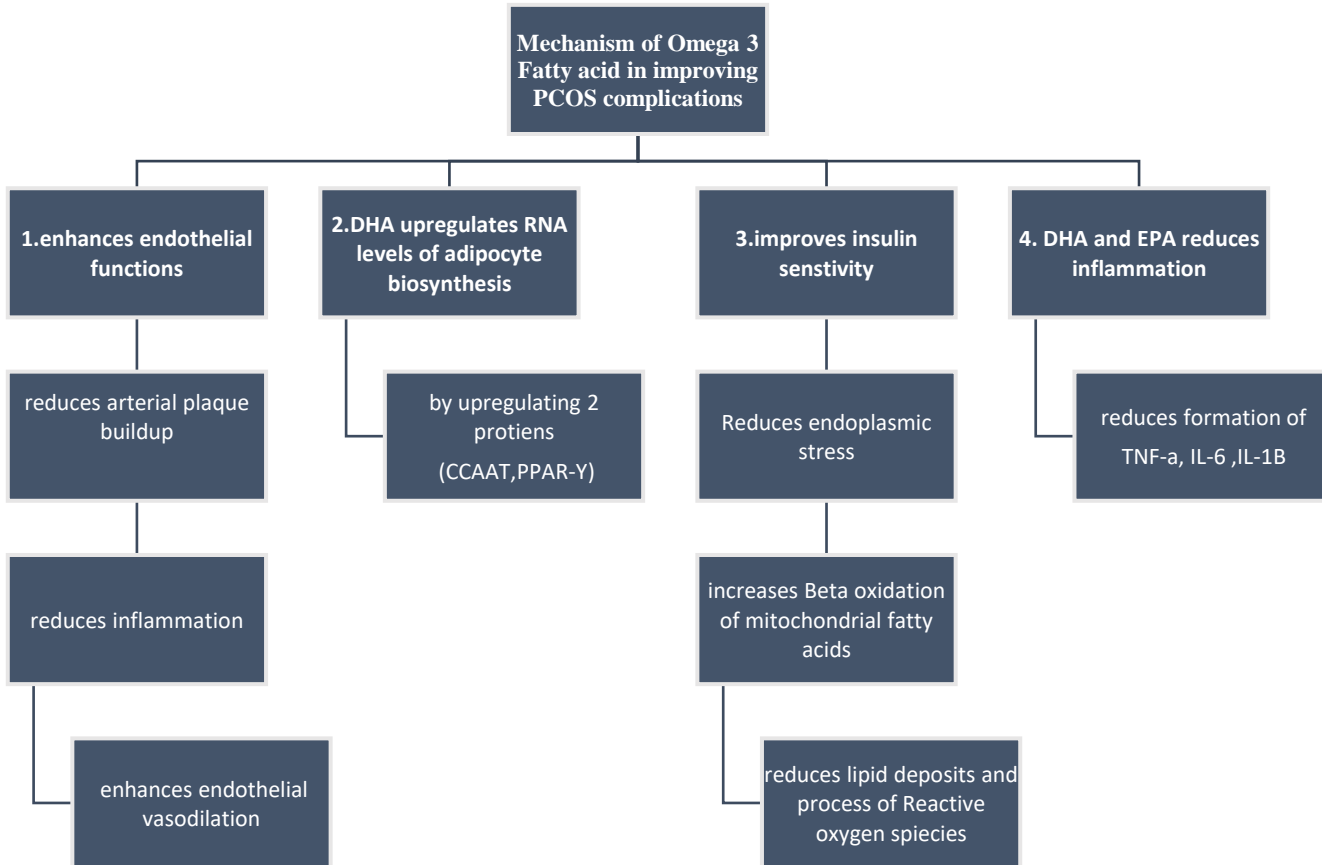
Around the world, pervasiveness assessment of PCOS is greatly fluctuating, starting from 2.2 percent to as above as 26 percent. It is also linked with cognitive deterioration in addition to stress and some other mood swings. Many females with PCOS also suffer from overweight or obesity, boosting up androgen release while decreasing function of reproduction and most probably facilitating the expansion of PCOS. Metabolic irregularities like dyslipidemia, insulin resistance, then disorders like diabetes, obesity, cancer, infertility, along with coronary heart diseases, could be identified with PCOS [11]. Sensitive oxygen breeds and antioxidants stay stable in an ordinary person, but as soon as this balance is interrupted, oxidative stress evolves that might drive to multiple diseases. Elevated oxidative stress adds up to the hazards of CVD in females having PCOS [12].

Though excellent medication for PCOS is not completely found, a number of ways are desirable, along with a mixture of one or more of the greatest compelling mediational design, like change in eating pattern and living style, numerous professionals consider exercise and diet to be the initial step in treating PCOS [13,14]. For example, digestible fats like PUFA along with  $\omega-3$  and  $\omega-6$  fats are considered in relationship to PCOS. Food origins of n-3 PUFA are confined compared to n-6 PUFA origin. Alpha-linolenic acid ALA is rich in plant sources and is rich in products like flaxseeds [14].

Omega-3 PUFA is affirmed to apply its beneficial properties in signaling pathways and inaction of transcription. Gene expression is one illustration of the desirable system of n-3 PUFA utilization is certainly affecting wellbeing indicators. Utilization of PUFA foods lowers the danger of recurring disorders, which is exceptionally correct regarding the dangerous aspects of the metabolic diseases in patients suffering from PCOS, dyslipidemia, damaged endothelial function, and insulin resistance [16,17]. Nutritional mediation serves as an encouraging approach for the medication of PCOS, PUFAs have health benefits such as anti-inflammatory, insulin sensitivity, cellular discrimination, and ovulation [18,19].

### **Mechanism of omega -3 fatty acids:**

There are many mechanisms for how omega 3 fatty acids work in our bodies (Figure 1). 1. Omega-3 PUFAs upgrade endothelial function by decreasing the development of plaque in the blood vessel and improving endothelial-subordinate vasodilation. 2. Omega-3 PUFAs, particularly DHA, activate mRNA levels of adipocyte protein, CCAAT/enhancer-restricting proteins (C/EBPs), and peroxisome proliferator-actuated receptor  $\gamma$  (PPAR- $\gamma$ ), and these two unique groups control fat biosynthesis. 3. Omega-3 PUFAs improve insulin sensitivity by reducing the stress of the endoplasmic reticulum, increasing  $\beta$ -oxidation of mitochondrial unsaturated fats and mitochondrial uncoupling, decreasing lipid stores, and developing ROS; hence this process improves insulin responsiveness. 4. EPA and DHA work as lowering inflammation in the body by decreasing the TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , which are produced by the process of lipopolysaccharide (LPS) as well as downregulating the outflow of the outer layer of monocytes and endothelial cells [20]



**Figure 1:** Mechanism of Omega 3 Fatty acid in Improving PCOS complications

### Obesity and omega 3

Approximately 40 %-50 % of patients with PCOS are observed to be overweight and is viewed as a significant factor for PCOS. The fatter in the body can prompt fat tissue dysfunction, which is associated with the pathological mechanisms of MetS and disturbed insulin obstruction in the liver and skeletal muscle. It is found that teenagers with a higher waist circumference and increased BMI are deficient in n-3 PUFA, especially DHA. Functioning of an endocrine organ is done by adipose tissues, which can emit a few adipokines and chemicals, for example, leptin and adiponectin, and cytokines, for example, interleukin-6 (IL-6) [21].

Obesity can be treated with an active lifestyle and dietary modifications. Regular bioactive mixtures, such as n-3 PUFA, are considered safe in contrast with different treatment modalities. There are many studies that showed that n-3 PUFA, especially EPA and DHA, increase the metabolism of the body, improves body composition, and decreases body weight [21]. Few investigations have detailed great results of omega-3 utilization on obesity. For example, BMI diminished fundamentally day by day with the oral organization of 1,500 mg omega-3 for quite a long time [22-24].

## Insulin Resistance

Insulin resistance is the response of peripheral tissue to decreased insulin. This disease appears particularly in the lean muscle and liver, with multiple drawbacks in glucose metabolism associated with the abnormal adjustment in GLUT4. Skeletal muscle plays a considerable part in IR. gluconeogenesis, glycogenolysis are not regulated properly due to insulin resistance, leading to abnormal glucose output [25]. IR has been recorded in thirty percent of skinny and seventy-five percent of obese people with PCOS while insulin resistance is greater in overweight and older people [26]. Obesity leads to insulin resistivity IR, which is responsible for metabolic syndrome [21]. IR plays its part in hyperandrogenism in PCOS in 2 noticeable ways:

1) stimulant of androgen cells with luteinizing hormone LH and elevated androgen cells leads to excessive man-like hair growth low fertility in females.

2) Elimination of sex hormone constricting globulin fusion from the liver [27]. Sex hormone-binding globulin is a plasma protein of androgen or estrogen, so all reductions in sex hormone-binding globulin levels can lead to hyperandrogenism in PCOS patients. There are few findings that display the properties of n-3 on insulin resistance. Oner and Muderris found that levels of insulin were automatically reduced by taking n-3 for six months, contrarily no changes were observed in glucose level and Homeostatic model assessment index. Another study was conducted in which 30 people took 2 grams of fish oil for about twelve weeks; serum insulin levels were improved respectively [28]. Mirmasoumi *et al.* recorded a decline in insulin levels after distributing 1 gram of flaxseed oil n-3 fatty acid daily for twelve weeks [29]. Furthermore, insulin decline was seen after twelve weeks of supplementation with omega 3 acids and vitamin [10].

## Inflammation

Constant low-grade inflammation is common in obesity. White blood cells in the adipose tissue can raise IR in type 2 diabetes and obesity. PCOS devotes itself to a proinflammatory state, and a link between inflammation and IR has been recorded. Furthermore, inflammatory modulators increase PCOS that is escorted by glucose stimulation of proatherogenic routes [30]. Omega 3 PUFA controls multiple inflammatory markers like adhesion molecules and cytokines, TNF  $\alpha$ , IL6, and interleukin1 $\beta$ . Many studies have recorded that EPA and DHA reduce the TNF $\alpha$ , interleukin 6, and interleukin-1 $\beta$ . While other research has demonstrated that EPA and DHA might result in elevation of the cytokines IL-10 absorption, which is anti-inflammatory [31]. There are multiple records proposing that PUFAs can lessen inflammation of patients with PCOS [32]. Three grams of fish oil or 5000 IU of cholecalciferol daily automatically declined CRP and IL-1 [33]. One more research says that flaxseed oil supplementation declined high sensitivity C-reactive protein. At the same time, Rahmani indicated that taking 1 gram of fish oil daily for twelve weeks regulated PPAR $\gamma$  and lowered gene expression of Interleukin 1 and 8 [10]. Undoubtedly, a lot of earlier research has affirmed the effectiveness of omega 3-PUFA in PCOS.

## Adipokines

Adjustments of adipokines are examined as a particular problem of PCOS; still it is not completely accepted that either this dysregulation is insignificant to PCOS problems like obesity, hyperinsulinemia, and hyperandrogenism, or is precisely associated with PCOS [34]. Adiponectin or leptin is present in the adipokines, which are excreted from adipocytes [34]. Anti-inflammatory adipokines are declined in obese people, while inflammatory adipokine is increased in comparison with slim individuals [35]. The greater leptin absorption in the obese individual is because of resistance of leptin which is linked to more inflammation, that includes TNF $\alpha$  and C-reactive protein. In inclusion to the inflammatory feedbacks of adipokines, adiponectin and leptin can balance hunger and energy consumption, which concludes that alterations in these can bring insulin sensitivity in the body. Omega 3 PUFA taken from plant and marine origins has positive effects in modulating the anti-inflammation of adipokines [36]. An increase of adiponectin and depletion of leptin was recorded by omega 3 PUFAs control in former research [37], which is linked with improvised functioning of skeletal muscles mitochondria and, therefore, elevated glucose levels.

There are multiple researches linked with n-3 and adipokines, and research recorded an elevation of adiponectin by n-3 fatty acids supplements of eight weeks. According to Mejia-Montilla, when patients with PCOS were given n-3 FA for twelve weeks, elevated adiponectin levels were seen. In addition to that, research was followed in PCOS patients, who were given

n-3 supplements three pills per day elevated adiponectin absorption [38]. Sufferers of PCOS consumed capsules of 4 grams n-3 fatty acids daily, giving 1200 mg n-3 LC PUFA, for eight weeks elevated adiponectin levels and improved PCOS.

### Omega 3 and Hormonal factors

Hyperandrogenism is treated as the essential character of PCOS [39] and is generally linked to extra excretion of luteinizing hormone LH by the pituitary glands or connected with elevated levels of insulin or IR [40]. Insulin generates increased androgen creation that leads to hirsutism. The development of a reproductive system is associated with the advancement of luteinizing hormone absorption and LH/FSH ratio, associated with arachidonic acids. Arachidonic acids ARA can stimulate steroidogenic acute regulatory protein StAR, which transmits cholesterol to the focal part of the mitochondrial membrane, which is initial and essential to drive both androstenedione and testosterone. So, absorption of ARA can execute luteinizing hormone-stimulated steroidogenesis, while current information advocates that low ARA is linked to omega 3 levels [39].

Jamilian recorded reduced testosterone by fifty thousand IU of vitamin D every two weeks and two thousand mg of fish oil daily for twelve weeks, while according to one more study, flaxseeds oil and vitamin E for twelve weeks in females with PCOS proceeded a compelling decrease in androgenic hormone [11]. An identical result of n-3 utilization on hormonal factors in females with PCOS was seen in which members were given 1500 mg of n-3 per day for six months. Serum luteinizing hormone and testosterone levels declined, and SHBG levels elevated automatically [23]. Females with PCOS were supplemented with three pills of omega 3 of EPA:180 mg and DHA:120 mg every day for eight weeks. Mean luteinizing hormone reduced in n-3 members, and the mean innovation in luteinizing hormone/Follicle-stimulating hormone ratio in these groups was compelling; furthermore, the authors recorded no essential revolution in prolactin levels [39].

### CONCLUSIONS

Dietary fats play a very important component in improving conditions like PCOS. This review highlighted the most important complications that can be caused by the PCOS. Omega 3 fatty acids proved to be the best natural treatment for PCOS as these are not harmful for the body and have no other side effects compared to medications like metformin and birth control.

### REFERENCES

1. Salek M, Clark CC, Taghizadeh M, Jafarnejad S. N-3 fatty acids as preventive and therapeutic agents in attenuating PCOS complications. *EXCLI journal*. 2019; 18:552-558. doi: 10.17179/excli2019-1534
2. Faghfoori Z, Fazelian S, Shadnoush M, Goodarzi R. Nutritional management in women with polycystic ovary syndrome: A review study. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2017 Nov 1;11: S429-432. doi.org/10.1016/j.dsx.2017.03.030
3. Akram M, Roohi N. Endocrine correlates of polycystic ovary syndrome in Pakistani women. *Journal of the College of Physicians and Surgeons Pakistan*. 2015;25(1):22-26. [www.jcpsp.pk/archive/2015/Jan2015/07.pdf](http://www.jcpsp.pk/archive/2015/Jan2015/07.pdf)
4. Patel, S. Polycystic ovary syndrome (PCOS), an inflammatory, systemic, lifestyle endocrinopathy. *The Journal of Steroid Biochemistry and Molecular Biology*, 2018, 182: 27-36. doi.org/10.1016/j.jsbmb.2018.04.008
5. Yousuf SD, Rashid F, Mattoo T, Shekhar C, Mudassar S, Zargar MA, Ganie MA. Does the oral contraceptive pill increase plasma intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and tumor necrosis factor- $\alpha$  levels in women with polycystic ovary syndrome: a pilot study. *Journal of pediatric and adolescent gynecology*. 2017;30(1):58-62. doi.org/10.1016/j.jpag.2016.06.010
6. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. *Human reproduction update*. 2015;21(5):560-574. doi.org/10.1093/humupd/dmv025
7. Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Marjoribanks J, Macedo CR. Metformin treatment before and during in vitro fertilization or intracytoplasmic sperm injection in women with polycystic ovary syndrome: summary of a Cochrane review. *Fertility and sterility*. 2015;104(3):542-4. doi.org/10.1016/j.fertnstert.2015.05.038
8. Nasri H, Rafeian-Kopaei M. Metformin: current knowledge. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*. 2014;19(7):658-665. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4214027/>

9. Szosland K, Pawłowicz P, Lewiński A. Prolactin secretion in polycystic ovary syndrome (PCOS). *Neuroendocrinology Letters*. 2015;36(1):53-8. <https://www.nel.edu/userfiles/articlesnew/NEL360115A11.pdf>
10. Rahmani E, Samimi M, Ebrahimi FA, Foroozanfard F, Ahmadi S, Rahimi M, Jamilian M, Aghadavod E, Bahmani F, Taghizadeh M, Memarzadeh MR. The effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression of lipoprotein (a) and oxidized low-density lipoprotein, lipid profiles and biomarkers of oxidative stress in patients with polycystic ovary syndrome. *Molecular and cellular endocrinology*. 2017; 439:247-55. [doi.org/10.1016/j.mce.2016.09.008](https://doi.org/10.1016/j.mce.2016.09.008)
11. Khan A, Karim N, Ainuddin JA. The triad of PCOS, infertility and metformin. *Journal of Bahria University Medical and Dental College*. 2019;9(1):67-71. [doi.org/10.51985/JBUMDC2018144](https://doi.org/10.51985/JBUMDC2018144)
12. Allahbadia GN, Merchant R. Polycystic ovary syndrome and impact on health. *Middle East Fertility Society Journal*. 2011;16(1):19-37. [doi.org/10.1016/j.mefs.2010.10.002](https://doi.org/10.1016/j.mefs.2010.10.002)
13. Geetha V, Chakravarthula SN. Chemical composition and anti-inflammatory activity of *Boswellia ovalifoliolata* essential oils from leaf and bark. *Journal of forestry research*. 2018;29(2):373-81. [doi.org/10.1007/s11676-017-0457-9](https://doi.org/10.1007/s11676-017-0457-9)
14. Ghasemifard S, Hermon K, Turchini GM and Sinclair AJ. Metabolic fate (absorption,  $\beta$ -oxidation, and deposition) of long-chain n-3 fatty acids is affected by sex and by the oil source (krill oil or fish oil) in the rat. *British Journal of Nutrition*, 2015. 114(5), 684-692. [doi.org/10.1017/S0007114515002457](https://doi.org/10.1017/S0007114515002457)
15. Gray B, Steyn F, Davies PSW and Vitetta L. Omega-3 fatty acids: a review of the effects on adiponectin and leptin and potential implications for obesity management. *European Journal of Clinical Nutrition*, 2013 67(12), 1234-1242. [doi.org/10.1038/ejcn.2013.197](https://doi.org/10.1038/ejcn.2013.197)
16. Li S, Wen W, Gong X, Huang X and Chen N. Variation of lipids and fatty acids composition in the tissues of wild devil stinger (*Inimicus japonicas*) during sexual maturation. *Aquaculture and Fisheries*, 2018. 3(3), 115-121. [doi.org/10.1016/j.aaf.2018.05.004](https://doi.org/10.1016/j.aaf.2018.05.004)
17. Khani B, Mardanian F, Fesharaki SJ. Omega-3 supplementation effects on polycystic ovary syndrome symptoms and metabolic syndrome. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*. 2017;22. doi: 10.4103/jrms.JRMS\_644\_16
18. Zhang X, Wang H, Yin P, Fan H, Sun L, Liu Y. Flaxseed oil ameliorates alcoholic liver disease via anti-inflammation and modulating gut microbiota in mice. *Lipids in health and disease*. 2017;16(1):1-10. [doi.org/10.1186/s12944-017-0431-8](https://doi.org/10.1186/s12944-017-0431-8)
19. Zhu L, Sha L, Li K, Wang Z, Wang T, Li Y, Liu P, Dong X, Dong Y, Zhang X, Wang H. Dietary flaxseed oil rich in omega-3 suppresses severity of type 2 diabetes mellitus via anti-inflammation and modulating gut microbiota in rats. *Lipids in health and disease*. 2020;19(1):1-6. [doi.org/10.1186/s12944-019-1167-4](https://doi.org/10.1186/s12944-019-1167-4)
20. Lu L, Li X, Lv L, Xu Y, Wu B, Huang C. Dietary and serum omega-3 polyunsaturated fatty acids and PCOS: A matched case-control study. *The British Journal of Nutrition*. 2021:1-31. doi: 10.1017/S0007114521003007
21. Albracht-Schulte K, Kalupahana NS, Ramalingam L, Wang S, Rahman SM, Robert-McComb J, Moustaid-Moussa N. Omega-3 fatty acids in obesity and metabolic syndrome: a mechanistic update. *The Journal of nutritional biochemistry*. 2018;58:1-6. [doi.org/10.1016/j.jnutbio.2018.02.012](https://doi.org/10.1016/j.jnutbio.2018.02.012)
22. Oner G, Muderris II. Efficacy of omega-3 in the treatment of polycystic ovary syndrome. *Journal of Obstetrics and Gynaecology*. 2013;33(3):289-91. [doi.org/10.3109/01443615.2012.751365](https://doi.org/10.3109/01443615.2012.751365)
23. Nomura S, Taniura T, Shouzu A, Omoto S, Suzuki M, Okuda Y, Ito T. Effects of sarpogrelate, eicosapentaenoic acid and pitavastatin on arteriosclerosis obliterans-related biomarkers in patients with type 2 diabetes (SAREPITASO study). *Vascular health and risk management*. 2018;14:225. doi: 10.2147/VHRM.S171143
24. Pizzini A, Lunger L, Demetz E, Hilbe R, Weiss G, Ebenbichler C, Tancevski I. The role of omega-3 fatty acids in reverse cholesterol transport: A review. *Nutrients*. 2017;9(10):1099. [doi.org/10.3390/nu9101099](https://doi.org/10.3390/nu9101099)
25. Lepretti M, Martucciello S, Burgos Aceves MA, Putti R, Lionetti L. Omega-3 fatty acids and insulin resistance: focus on the regulation of mitochondria and endoplasmic reticulum stress. *Nutrients*. 2018;10(3):350. [doi.org/10.3390/nu10030350](https://doi.org/10.3390/nu10030350)
26. O'Connor A, Gibney J, Roche HM. Metabolic and hormonal aspects of polycystic ovary syndrome: the impact of diet. *Proceedings of the Nutrition Society*. 2010;69(4):628-35. doi: [doi.org/10.1017/S0029665110002016](https://doi.org/10.1017/S0029665110002016)
27. Günalan E, Yaba A, Yılmaz B. The effect of nutrient supplementation in the management of polycystic ovary syndrome-associated metabolic dysfunctions: A critical review. *Journal of the Turkish German Gynecological Association*. 2018;19(4):220. doi: 10.4274/jtgga.2018.0077

28. Amini M, Bahmani F, Foroozanfard F, Vahedpoor Z, Ghaderi A, Taghizadeh M, Karbassizadeh H, Asemi Z. The effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Journal of Psychosomatic Obstetrics & Gynecology*. 2020;1-9. doi.org/10.1080/0167482X.2018.1508282
29. Mirmasoumi G, Fazilati M, Foroozanfard F, Vahedpoor Z, Mahmoodi S, Taghizadeh M, Esfeh NK, Mohseni M, Karbassizadeh H, Asemi Z. The effects of flaxseed oil omega-3 fatty acids supplementation on metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Experimental and Clinical Endocrinology & Diabetes*. 2018;126(04):222-228. doi: 10.1055/s-0043-119751
30. Escobar-Morreale HF, Luque-Ramírez M, González F. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. *Fertility and sterility*. 2011;95(3):1048-1058. doi.org/10.1016/j.fertnstert.2010.11.036
31. Calder, P.C. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochemical Society Transactions*, 2017, 45(5) :1105-1115. doi.org/10.1042/BST20160474
32. Talari HR, Poladchang S, Hamidian Y, Samimi M, Gilasi HR, Ebrahimi FA, Asemi Z. The effects of omega-3 and vitamin E co-supplementation on carotid intima-media thickness and inflammatory factors in patients with polycystic ovary syndrome. *Oman Medical Journal*. 2018;33(6):473. doi: 10.5001/omj.2018.88
33. Jamilian M, Samimi M, Mirhosseini N, Ebrahimi FA, Aghadavod E, Talaei R, Jafarnejad S, Dizaji SH, Asemi Z. The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome. *Journal of Affective Disorders*. 2018;238:32-38. doi.org/10.1016/j.jad.2018.05.027
34. Baldani DP, Skrgatic L, Kasum M, Zlopasa G, Kralik Oguic S, Herman M. Altered leptin, adiponectin, resistin and ghrelin secretion may represent an intrinsic polycystic ovary syndrome abnormality. *Gynecological Endocrinology*. 2019;35(5):401-405. doi.org/10.1080/09513590.2018.1534096
35. Farimani AR, Hariri M, Azimi-Nezhad M, Borji A, Zarei S, Hooshmand E. The effect of n-3 PUFAs on circulating adiponectin and leptin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Acta diabetologica*. 2018;55(7):641-652. doi.org/10.1007/s00592-018-1110-6
36. Kang YE, Kim JM, Joung KH, Lee JH, You BR, Choi MJ, Ryu MJ, Ko YB, Lee MA, Lee J, Ku BJ. The roles of adipokines, proinflammatory cytokines, and adipose tissue macrophages in obesity-associated insulin resistance in modest obesity and early metabolic dysfunction. *PloS One*. 2016;11(4):e0154003. doi.org/10.1371/journal.pone.0154003
37. Hariri M, Ghiasvand R, Shiranian A, Askari G, Iraj B, Salehi-Abargouei A. Does omega-3 fatty acids supplementation affect circulating leptin levels? A systematic review and meta-analysis on randomized controlled clinical trials. *Clinical endocrinology*. 2015;82(2):221-228. doi.org/10.1111/cen.12508
38. Nadjarzadeh A, Dehghani-Firouzabadi R, Daneshbodi H, Lotfi MH, Vaziri N, Mozaffari-Khosravi H. Effect of omega-3 supplementation on visfatin, adiponectin, and anthropometric indices in women with polycystic ovarian syndrome. *Journal of reproduction & infertility*. 2015;16(4):212. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4819211/>
39. Stein JD, Andrews C, Musch DC, Green C, Lee PP. Sight-threatening ocular diseases remain underdiagnosed among children of less affluent families. *Health Affairs*. 2016 1;35(8):1359-1366. <https://doi.org/10.1377/hlthaff.2015.1007>
40. Liepa GU, Sengupta A, Karsies D. Polycystic ovary syndrome (PCOS) and other androgen excess-related conditions: can changes in dietary intake make a difference?. *Nutrition in clinical practice*. 2008;23(1):63-71. doi.org/10.1177/011542650802300163