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A Narrative Review on impact of omega-3 fatty acids supplementation on lipid profile and adiponectin level in women with Polycystic Ovary Syndrome (PCOS)

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ABSTRACT
Polycystic ovary syndrome is endocrine related problems associated with infertility among women of reproductive age, results from multiple aetiological factors. However, precise causative factor and in-depth pathophysiological changes those occur during the progression of polycystic ovary syndrome (pcos) are poorly understood. Commonly seen symptoms in pcos are irregular ovulation, hyperandrogenism and presence of multiple cysts on ovaries. Most of research evidences has been reported the lowered level of adiponectin in pcos, derived from adipocytes. It was also validated that lowered adiponectin in pcos has been linked with the risk of developing metabolic syndrome such as alteration in lipid profile and significant increase of insulin resistance. Its imperative to find the effective means to reduce the risk of metabolic syndrome among pcos to decrease pathophysiological progression in pcos. Hence with this background present review was extensively dedicated to find the effectiveness of omega-3 fatty acids supplementation on adiponectin and lipid profile of pcos subjects.

Keywords: Poly Cystic Ovary Syndrome, Metabolic Syndrome, Omega 3 Fatty Acids

INTRODUCTION

Polycystic ovary syndrome (Stein -Leventhal syndrome) is a complex and highly prevalent metabolic problems appearing in the reproductive stage of female affecting the fertility, transpire as a consequence of endocrine alterations.[1] Women with PCOS is classically manifested with the symptoms of altered ovulation as oligo-amenorrhea with oligo- anovulation or anovulation leading to infertility, metabolic alterations associated with insulin resistance, lipid profile alterations, as a result of hormonal derangement, multiple cysts on ovaries and hyperandrogenism leading to acne, alopecia and hirsutism.[2,3] Lifestyle related factors, genetical factors featured with heterogenetic property are the major aetiological factors for PCOS. However, life style and genetical factors interlinked with obesity, altered gut microbiome are known to be predisposing factors for PCOS among women. Although array of aetiological factors has been shown to interlinked with PCOS from uterine to post-natal stage. However, précised causative factor and in-depth pathophysiological changes those occur during the progression of polycystic ovary syndrome (PCOS) are poorly understood and is still a zone of explorable research. From the World health Organisation report, it was revealed that global prevalence rate of PCOS among women of reproductive age is estimated to be 8 to 13 per cent (WHO, 2023).[4] In India it is estimated to be 10 per cent among women as derived from pooled data of different publications from Pubmed, Scopus, Google scholar and Cinhal based on Rotterdam and Androgen Excess Society (AES) criteria as reported by Bharali *et al*., in 2022.[2] Most of research studies revealed the higher prevalence rate of PCOS in urban compare to that of rural counterpart as reported in adolescents of Balaji hospital settings in Vellore, Tamil Nadu from India.[5] Another epidemiological study survey conducted in rural and urban women of Tamil Nadu revealed that odds of acquiring PCOS among urban women was found to be 0.1 per cent higher than that of rural women of same place.[6]

Obesity is one of the common prevalent problems among women with polycystic ovary syndrome leading to irregularities in the adiponectin level, which is being secreted through metabolically active adipocyte. Most of research findings revealed relative relation between the metabolic abnormalities and altered adiponectin levels in PCOS women.[7] It was reported that lipid profile variations, cardiovascular related problems, and endometrial

related cancer are two to six times more common in PCOS women than general population.[8] In type 2 diabetic subjects, it was also reported that, decreased level of circulating adiponectin levels are associated with increased level of metabolic syndrome components including higher intra-abdominal fat content.[9]

Adiponectin is peptide hormone, shown to play a vital role in regulation of lipid metabolic pathway, glucose level. This also plays a vital role in modulation and maintenance of insulin sensitivity by anti-inflammatory and anti-fibrotic property.[10] It was reported that, adiponectin has also role in energy control, body weight management and inflammation prevention. Signalling cascades for adiponectin has shown to affect satiety and energy homeostasis in hypothalamus.[11]

Life style modification as dietary intake modification by enhancing phytochemical rich foods intake and serving size optimisation, regular optimal physical activity inculcation, improvement in sleep pattern, stress management strategies usage has been shown to lower the risk of PCOS. Inclusion of dietary source with low glycaemic load and omeg-3 fatty acids source has been shown to improve high density lipoprotein. Further, it is crucial to strengthen the research evidences of interrelationship between omega-3 fatty acid source supplementation or dietary intake on adiponectin as well as lipid profile among PCOS women.[12]

Lipid profile alteration in PCOS- Predicted to be considered as one of the biochemical markers

Most of research evidences manifested the dyslipidaemia incidence among PCOS. It was also reported that apparently lower level of high-density lipoprotein presence in PCOS subjects. Triglyceride alterations was shown to be correlated with body mass index and insulin resistance. Research studies also indicated the higher incidence of dyslipidaemia among young PCOS women [13]. A study conducted to assess lipid profile among PCOS has shown the existence of mild hypercholesterolemia .[14] Subjects with PCOS often experiences the metabolic alterations known to pose the risk of highly prevalent health related problems *viz*., diabetes, obesity, hypertension and cardiovascular diseases.[15] A study conducted by inducing PCOS through high fat supplementation in rats has been reported the altered metabolic changes indicating change hyperlipidaemia .[16]

A prospective study conducted to know the lipid profile distribution among PCOS women attending the gynaecology clinic of Zagazig and Aln-Aharar Educational Hospital. Report of Lipid profile assessment showed the atherogenic lipid profile distribution among screened PCOS subjects.[17]

A cross-sectional study of prospective type in PCOS (n=76), between July 2014 and December 2016. Subjects were classified into two subgroups as hyperandrogenism (n=39) group and non-hyperandrogenism group (n=37). Triglyceride and testosterone level showed weak ($r = 0.232$, $p = 0.044$) and moderate ($r = 0.460$, $p = 0.001$) positive correlation with free testosterone index. Triglyceride was also found to be determinant of hyperandrogenism in PCOS subjects. Triglycerides, testosterone were associated with hyperandrogenism in PCOS female subjects.[18]

As compared to healthy individual (control group), biochemical parameters such as insulin resistance and triglyceride levels were found to be significantly high among PCOS women. However, HDL level was found to be low and ratio for TGL to HDL cholesterol was found to be correlated with insulin level in infertile women with PCOS.[19]

Sathyapalan & Atkin in 2010, reported the increase in LDL cholesterol in PCOS women, and statin therapy has shown the reduction in LDL cholesterol levels among PCOS women and concluded that diminished cholesterol synthesis in PCOS women, after the statin therapy is the clear indication of beneficial role to PCOS, as it helps in improving the adverse lipid profile, especially by reducing LDL levels in PCOS women. Since cholesterol is a substrate for ovarian steroidogenesis, decreased availability of cholesterol may result in lower androgen production.[20]

ω-3 fatty acids supplementation impact on lipid profile of PCOS women.

In PCOS women, twelve weeks of ω-3 fatty acids supplementation with Vitamin E has shown to reduce the low-density lipoprotein (LDL-C). The decreased expression of low-density lipoprotein receptor (LDLR) is driven through the inhibition of phosphatidylinositol 3-kinase and protein kinase B (PKB) pathway and modulation of the activity of the oxidative stress-induced nuclear factor-k-gene binding (NF-kB) pathway and is presented in in fig.1.[21] Through the activation of Peroxisome proliferator-activated receptor gamma (PPAR-g), ω-3 fatty acid supplementation can raise PON1 activity, HDL-C levels, and lower the TC/HDL and LDL/HDL ratio in serum as presented in figure 1.[22] In addition, ω-3 fatty acids supplementation also decreases the fatty acid absorption, which further reduces the liver's consumption of exogenous triglyceride.[23] As a result, ω-3 polyunsaturated fatty acids help PCOS patients with dyslipidaemia and help to prevent cardiovascular disease and metabolic related disease.[24]

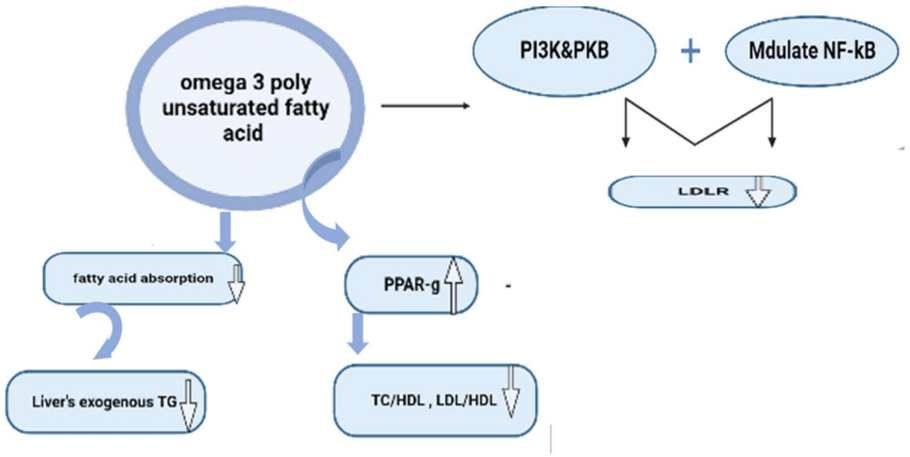

Figure 1. Mechanism of omega three fatty acids on lipid profile

Feeding trial conducted in PCOS rat model for 16 weeks to know the effect of multiple sources of poly unsaturated fatty acids *viz.,* synthetic as well food based Ω-3 sources of fish oil and flaxseed (*Linum usitatissimum*) on lipid profile. Forty-five rats (weight=130±10 g) were divided into 5 groups with nine numbers of rats in each group. Non-PCOS, with PCOS(PC) as control, supplementation with synthetic omega-3 with alpha lino lenic acid, ecosa pentaenoic acid and docosa hexaenoic acid (DHA), fish oil,linseed oil and given with the concentration of 300 mg per kg body weight through oral method with basal diet. However control group with PCOS and non PCOS received the purely basal diets. After the supplementation with synthetic omega-3 containing alpha lino lenic acid, linseed oil and fish oil has shown the reduced level of LDL-C. As compared to the PCOS control group. The highest high density lipoprotein with the mean value of 36.83±0.72 mg/dl was found in rats fed with fish oil basal diet.[25]

A double-blind clinical study was conducted in 88 patients with PCOS to evaluate the effect of omega-3 supplementation on PCOS symptoms including lipid profile parameters. The clinical trial was performed in 2015 in Alzahra and Shahid Beheshti Hospitals. Intervention group received omega-3 supplements with dose of 2 g/day for six months (two capsules), and control group received two capsules of olive oil. From the result it was revealed that omega 3 fatty acid has the effective role in achieving the desired values of HDL-cholesterol, LDL-cholesterol, triglyceride level along with, regularity of periods as compared to control group. Waist circumference (WC) was was also significantly get lowered in omega-3 as compared to control.[12]

Adiponectin relation with insulin resistance and incidence of insulin resistance in PCOS

Adiponectin is known to enhance the insulin sensitivity with anti-atherogenic and anti-inflammatory properties. Adiponectin appears to have a regulatory role in insulin resistance and atherosclerosis progression . Anti-atherogenic effects of adiponectin and its properties to improve and mimic metabolic and vascular actions of insulin and its influence on endothelial function.[26] Before the age of 40, diabetes or pre-diabetes strike more than 50% of those with PCOS. The way the body uses insulin directly affects the development of diabetes. People with PCOS may experience improved well-being by adhering to a diet that satisfies nutritional requirements, maintains a healthy weight, and encourages optimal insulin levels. Insulin resistance and compensatory hyperinsulinemia (HI) are present in 65–95 per cent of women with PCOS, including the vast majority of overweight and obese women and more than half of women of normal weight. However, it was reported that insulin resistance is more common in classical phenotype (Types A and B) of PCOs that is up to 80 per cent, followed by ovulating PCOS with 65 per cent of incidence and non-hyperandrogenaemia PCOS with 38 per cent.[24]

Homeostasis model of insulin resistance score (HOMA-IR score) assessment in obese PCOS adolescent girls has shown the higher insulin resistance score than non PCOS with the p value of 0.04 at 95 percent significance. It was found that HOMA insulin resistance score was independent with the degree of obesity among screened adolesent girls.[27]

Among 160 screened subjects with different phenotypes of PCOS, insulin resistance was detected in 74.4 percent (n=119). However, rate of insulin resistance was significantly different in all four phenotypes (*p*-value: 0.008) of PCOS. Higher rate of insulin resistance was observed in B phenotype with 91.90 per cent (n=34) followed by A phenotype with 74.7 per cent (n=62). Linear regression analysis revealed that HOMA-insulin resistance was significantly associated with classic A and B phenotype PCOS. Significant relation was observed

between HOMA insulin resistance and haemoglobin levels of PCOS subjects. Alongside, significant relation was also found with exercise, economic status as well as different phenotypes of PCOS.[28] A comparative cross-sectional study conducted in PCOS women and control subjects matched for age and Body Mass Index (BMI). Women with PCOS (n=32) had higher insulin secretion levels than controls with similar sample size (C-peptide: 4.98 ± 3.83 vs 3.25 ± 1.62 mUI/l; p = 0.02). Also, the HOMA-IR index was higher compared to that of women without PCOS (1.15 ± 0.90 vs 0.77 ± 0.38; p = 0.03) suggesting greater insulin resistance.[29]

Effect of omega-3 fatty acids on Adiponectin level

A study conducted with the objective to assess comparative analysis of the mRNA expression for adiponectin in PCOS and non-PCOS women matched with BMI. In this study 60 members from each group were examined for their adiponectin expression. Therefore present study noted marked down regulation of adiponectin. The decrease levels of adiponectin was observed in PCOS subjects. The detailed information on effect of supplementation with Ω-3 fatty acids on adiponectin level in PCOS condition obtained from different scientific research studies presented in table 1.

The study conducted on omega-3 fatty acid from fatty fish , has been shown the increased production of adiponectin, and decreased the production of Interleukin-6 (IL-6) proinflammatory adipokine.[30] Polyphenols being a major source of plant-based foods viz., fruits with citrus property, vegetables have shown the anti-inflammatory effects and predicted to help in the regulation and production of adipokines including adiponectin.[31]

Prebiotic foods has shown to promote the growth of beneficial microbiome, and have shown to posture the the production of adiponectin and decrease the production of proinflammatory adipokines.[32]

Table1: Omega 3 fatty supplementation effect on Adiponectin in PCOS subjects

Study subjects in number	Intervention period	Impact on adiponectin	Reference
n=32	56 days	Elevated experimental group	Mohammadi *et al*., 2012.[22]
n = 97	84 days	Elevated experimental group	Yang *etal*., 2018.[33]
n=50	42days	Elevated experimental group	Gammelmark *etal*., 2021.[34]
n=55	56days	Minimal changes in experimental group	Itariu *etal*., 2012.[35]
n=99	60 days	Minimal changes	Koh *etal*., 2012.[36]
n=17	56days	Elevated adiponectin	Kondo *etal*., 2010.[37]
n=126	84 days	Elevated adiponectin	Nomura *et al*., 2009.[38]
n=35	90days	Elevated adiponectin	Patel *et al*., 2007.[39]

CONCLUSION

Research evidences explored the direct association between adiponectin and metabolic alteration among PCOS women. Dietary modification with proven nutraceutical supplementation and physical activity as holistic approach could be the possible solution to reduce the complication of PCOS. Omega 3 fatty acids supplementation as one of the strategies known to bring positive change on serum adiponectin levels manifesting to reduce complications of PCOS.

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