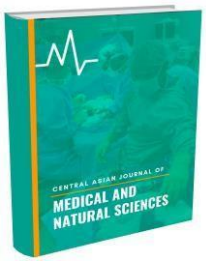

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Article

The Effects of Alpha Lipoic Acid Supplementation on The Serum Lipid Profile, Weight Loss, and Resistin Level in Women PCOS Treated with Metformin

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Abstract: Supplements such as Alpha Lipoic Acid are becoming more and more popular as more women look for natural remedies or prescription drugs to control their symptoms. Better health outcomes and an improved quality of life can result from combining these with a customized plan. Evaluation of the combined effects of metformin, and ALA, in PCOS in terms of weight loss, serum lipid profile, and insulin resistance is the goal of the current study. The randomized, single-blind, and actively controlled clinical trial was conducted in Babylon, Iraq, between September 2024 and March 2025. The participants were divided into two groups at random. Computer-generated random numbers were used for the random assignment. Glucophage (500 mg; Merck, West Drayton, UK) was administered once daily for 2 weeks followed by 2 times a day until end of study to patients in Group Met., while patients in Group Met.+ALA got metformin as in the first group plus ALA (600 mg, Batch no. 53642; neutec, Turkey) once/ day. Every treatment was administered for a total of twelve weeks. The average body mass index, cholesterol, triglycerides, and LDL all dramatically decreased after treatment, while HDL increased ($p < 0.001$). The effect of Met. plus ALA was significantly more pronounced than that of the other therapeutic modality ($p < 0.05$). Nevertheless, resistin serum levels were not substantially impacted by any of these treatment modalities ($p > 0.05$). In women with PCOS, alpha lipoic acid supplements are effective and safe ways to increase the results of metformin treatment in terms of weight loss and serum lipid profile improvement.

Keywords: Serum Lipids, Resistin, PCOS

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1. Introduction

Polycystic ovarian syndrome, or PCOS, affects millions of women globally [1]. It is estimated that the condition affects one in ten women of reproductive age [2]. It is a complicated hormonal disorder that affects both reproductive and metabolic health. Ovarian cysts, acne, excessive hair growth, and irregular menstrual periods are all symptoms of PCOS, which arises when hormonal signals are disrupted [3], [4]. Women with PCOS frequently have elevated androgen levels. Many women with this illness struggle with infertility, weight gain, and insulin resistance. High blood sugar levels are often the result of insulin resistance, which impairs the body's ability to control blood sugar [5].

In the long run, this could raise the risk of type 2 diabetes and heart disease. These risks need to be managed in order to protect public health [6]. Insulin resistance frequently makes PCOS symptoms worse. When its function is impaired, the body responds by

producing more insulin. Acne and excessive hair growth may be caused by increased testosterone brought on by raised insulin levels (4). Furthermore, this hinders ovulation, which complicates conception. More than 70% of women with PCOS have insulin resistance, which emphasizes the significance of this disease in treatment regimens [7].

Metformin is one medication that makes the body more sensitive to insulin. It reduces the body's requirement for insulin and helps lower blood sugar levels. In addition to improving insulin sensitivity, metformin can assist manage hormonal balance, which lowers high testosterone levels and promotes normal ovulation [8]. For instance, ovulation is often faster in women using Metformin who are attempting to conceive. Many people report lighter or more regular menstrual periods after taking it regularly, and some even report being able to conceive. It is a promising option for treating hormonal imbalances associated with PCOS [9].

It has been demonstrated that metformin increases women's chances of ovulation and improves menstrual regularity. It usually also helps with weight loss and improved blood sugar regulation. According to many women, these enhancements lead to more energy and less fatigue, which facilitates completing everyday duties (8,9). Most people have mild side effects including nausea, diarrhea, or stomach pain when they first start using Metformin. When the dosage is altered or time passes, these side effects typically improve [10].

Many women are exploring natural symptom management options in addition to using medications like Metformin. Attention is being drawn to the possible advantages of supplements such as alpha lipoic acid. Combining these strategies could provide a more effective means of raising quality of life. Understanding how each supplement functions is essential for making informed decisions [11], [12]. Alpha lipoic acid (ALA) is an antioxidant that helps shield the body from harm caused by free radicals. Cells must also be able to convert nutrients into energy. Because of these qualities, ALA is a popular choice for supporting metabolic health. Studies have demonstrated that ALA increases insulin sensitivity. It may also reduce inflammation and oxidative stress, which are prevalent in PCOS [12-14].

We can propose that these drugs and supplements work together to treat various facets of PCOS. ALA reduces oxidative stress, and metformin improves insulin sensitivity.

2. Material and Method

Study Design and Settings

Between September 2024 and March 2025, a randomized, single-blind, and actively controlled clinical trial was carried out in Babylon, Iraq. Before starting, the study received ethical approval from the College of Medicine/Al-Qadisiyah University committee and met with the Declaration of Helsinki's criteria. Informed consent was given by each subject.

Sample Size Estimation

A formula intended to produce a statistical power of more than 80% and a significance level below 0.05 was used to determine the sample size. We calculated the mean change (D) in insulin, our main outcome, to be 3.5 μIU/ml and the standard deviation to be 4.4 μIU/ml using data from a prior study [15]. The ultimate number was chosen at 15 participants each group after accounting for an anticipated 3 dropouts per group, even though the calculation showed that 12 individuals would be required for each group. A computer-generated sequence was used for randomization, and it was hidden in opaque, sequentially numbered envelopes that the researcher held.

Participants

The diagnosis of PCOS adhered to the Rotterdam criteria [16]. The following was the definition of the inclusion and exclusion criteria: PCOS-afflicted women aged 18–39 with a body mass index (BMI) <30 were deemed eligible for the analysis. Those with diabetes,

liver, kidney, thyroid, or heart problems, women who were menopausal, pregnant, or nursing, and those with high prolactin levels were not included. Participants who were taking hormonal treatments like oral contraceptives or drugs for ovulation induction were excluded, as were those who had used antioxidant supplements during the three months prior. Additionally, those who had been on a particular diet or exercise regimen, or who smoked or drank alcohol, were not recruited.

Grouping of Participants

Participants were randomly assigned to three different groups. The random assignment was carried out using computer-generated random numbers. Patients in Group Met. received Glucophage (500 mg; Merck, West Drayton, UK) single time a day for 2 weeks followed by 2 times daily until end of study; Group Met.+ALA patients were given metformin as in the first group along with ALA (600 mg, Batch no. 53642; neutec, Turkey) once/ day. All treatments were provided over a duration of 12 weeks.

Laboratory Analysis

Following a roughly 10-hour fast that began at 10 p.m. the night before, blood samples were collected in the morning and mixed by inversion for 15 minutes at room temperature. Centrifugation at 5000 × g for 5 minutes was used to extract the serum, which was then stored at -80°C until needed. We took care to avoid using serum samples that had been repeatedly frozen and thawed. Using an enzymatic colorimetric approach and a commercially available kit (biomaghreb), spectrophotometry was used to evaluate the serum lipid profile, which included total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein. The Friedewald equation was used to determine the serum levels of low-density lipoprotein. To measure resistin, an enzyme-linked immunosorbent test was used.

Body Mass Index

Calculation of body mass index (BMI) was as following: weight in kilogram was divided by square of height measured in meters.

Statistical Analysis

The Statistical Package for Social Science, version 26 (IBM, Armonk, NY), was used for all statistical analyses. Statistical significance was defined as a p-value of less than 0.05. Student t-test and post-hoc LSD multiple comparison tests were used to evaluate quantitative variables between groups. A related groups t-test was used to compare the post-treatment mean values to the baseline mean values in order to evaluate the therapeutic effect.

3. Results

Comparison of Age and Body Mass Index Across Groups

The current study enrolled 90 women with PCOS. The average of age of recruited women was 31.73 and 32.11 year in cohorts of Met., and Met. plus ALA, in that order. In terms of statistics, the difference in the average of age between cohorts of study exhibited no significance (p = 0.537), as explained in Table 1.

Table 1. Range of age and its average of enrolled PCOS patients according to group.

Characteristic	Met. group (45 member)	Met.+ ALA group (45 member)	*p*-value
Age (years)			
Average ±	31.73 ±2.77	32.11 ±3.01	0.537 N

StDev.		
Min.-Max.	28 -37	28 -37

N: none significance; StDev.: standard deviation

Prior to treatment course, the average BMI of Met. group, and Met. plus ALA group was 27.42 and 27.16 kg/m2, in that order. Statistically speaking, there was no significant variance in average BMI between cohorts of the investigation (p = 0.343). Post-treatment, the two forms of management showed significant decline in average BMI of PCOS women (p less than 0,001); however, the amount of decline using Met. plus ALA is the most fruitful with significant difference when contrast was made to other cohort (p less than 0,001), see Table 2.

Table 2. Range of BMI and its average of enrolled PCOS patients according to group pre- and post-treatment.

BMI (kg/m²)	**Met. group (45 member)**	**Met.+ ALA group (45 member)**	***p*-value**
Prior to therapy			
Average ± StDev.	27.42 ±1.23	27.16 ±1.41	0.343 N
Min.-Max.	25 -29	25 -29	
Post-therapy			
Average ± StDev.	26.33 ±1.19	25.29 ±1.20	<0.001 ***
Min.-Max.	25 -28.9	25.1 -28.9	
Related groups test	Lower than 0,001	Lower than 0,001	

N: none significance; ***: significant at p ≤ 0.001

Assessment of Serum Lipid Profile

Prior to treatment course, the average of cholesterol, triglyceride, high density lipoprotein (HDL) and low density lipoprotein (LDL) level of Met. group, and met. Plus ALA group were all comparable among study groups (p > 0.05). Post-treatment, the two forms of management showed significant decline in average cholesterol, triglyceride, and LDL concentrations and significant rise in HDL concentration of PCOS women (p less than 0.001); however, the amount of change using Met. plus ALA is the most prominent, Table 3.

Table 3. Range of serum lipids and their means prior to treatment and after completing course of treatment.

Hormone	**Met. group (45 member)**	**Met.+ ALA group (45 member)**
Cholesterol		
Prior to therapy	250.76 ±7.01	252.58 ±6.18
Post-therapy	216.27 ±5.46 *, b	230.38 ±7.46 *, a

Triglyceride			
	Prior to therapy	219.04 ±13.44	217.11 ±12.31
	Post-therapy	186.27 ±17.58*, b	193.09 ±14.33*, a
HDL			
	Prior to therapy	32.44 ±1.59	32.49 ±1.65
	Post-therapy	37.62 ±1.42*, a	35.36 ±2.04*, b
LDL			
	Prior to therapy	159.40 ±8.11	160.38 ±5.43
	Post-therapy	143.40 ±8.21*, b	149.40 ±5.71*, a

- *: significant paired t-test (before treatment vs. after treatment)
- a, and b, to indicate significant difference after performing student test

Range of RETN Level of Enrolled PCOS Patients and its Average According to Group Pre- and Post-Treatment

Prior to treatment course, the average RETN. level of Met. group, and Met. plus ALA group was 932.84, and 928.05, in that order. Statistically speaking, there was no significant difference in mean concentration between cohorts of the investigation ($p = 0.381$). Post-treatment, the two forms of management showed no significant changes in average RETN. concentration of PCOS women ($p > 0.05$), see Table 4.

Table 4. Range of RETN. level of enrolled PCOS patients and its average according to group pre- and post-treatment.

RETN. (ng/ml)	**Met. group (45 member)**	**Met.+ ALA group (45 member)**	***p*-value**
Prior to therapy			
Average ± StDev.	932.84 ±228.58	928.05 ±140.98	0.381 N
Min.-Max.	719 -1420	488.4 -1035.7	
Post-therapy			
Average ± StDev.	927.42 ±214.46	931.58 ±148.64	0.201N
Min.-Max.	652 -1315	462 -897	
Related groups t-test *P*-value	0.318 N	0.307 N	

N: none significance; StDev.: standard deviation

4. Discussion

In this study we tested two approaches in treating women with PCOS to evaluate their effects on body mass index, serum lipid profile and resistin levels. Following treatment, the two forms of management showed significant decline in average BMI of PCOS women; however, the amount of decline using Met. plus ALA is the most fruitful. This fact indicated that ALA supplementation is better than using metformin alone for weight reduction in women with PCOS.

In our study, after completing treatment course, the two modalities showed significant reduction in mean BMI of PCOS women; however, the amount of reduction using metformin +ALA was the greatest. Because of high incidence rate of obesity among

PCOS women and because of association between high BMI and pathogenesis of PCOS, weight reduction is an important goal when treating PCOS. Weight loss after treatment with metformin is well known, but, in this study, we have shown that administration of ALA may enhance this weight reducing effect.

In their recent study, Jannatifar et al. [17] evaluated the combination of metformin and ALA against metformin alone in women with PCOS; they reported reduction in mean BMI in both groups, but, unfortunately, the magnitude of weight reduction did not reach statistical significance. Therefore, our results are in disagreement with that of Jannatifar et al. [17].

Fruzzetti et al., [18] have declared that AlphaLA is connected to profound decline in mean weight in females with P-COS after being consumed for half- a year duration. In support for our observation, several previous studies have shown that ALA is efficient in significantly reducing weight when used in obese patients [19-21].

According to earlier research, ALA may have anti-obesity effects [21-23]. ALA supplementation has been demonstrated in animal studies to reduce body weight and fat mass by increasing energy expenditure and reducing food intake, potentially through the suppression of hypothalamic AMP-activated protein kinase (AMPK) activity [24, [25]. There are, however, few human trials on ALA supplementation, and the findings have been mixed. While some studies have found no effects of ALA on weight (26, 27), other clinical trials have suggested that ALA supplementation may aid in weight loss for overweight or obese people [21-23].

Regarding metformin's ability to help women with PCOS lose weight, it is commonly known that this medication aids in weight loss [28], [29]. There may be several different mechanisms at play when metformin affects body mass. Long-term follow-up data from the Diabetes Prevention Program suggest that the main way that metformin promotes weight loss is through increasing insulin resistance and decreasing consumption of calories. Moreover, metformin-induced changes in circadian rhythms and gastrointestinal physiology also influence lipid oxidation and storage in skeletal muscles, adipose compartments, and liver tissue [30]

In our study, and after completing treatment course, the two modalities showed significant reduction in mean cholesterol, triglyceride, and LDL concentration of PCOS women and significant rise of HDL level and that the amount of changes using metformin +ALA were better when compared to sole use of metformin. Firat et al., showed that use of ALA supplementation in PCOS is significantly associated with lowering effect of LDL [31]. Recent experimental study has also shown that ALA has the ability to significantly reduce total cholesterol and LDL [32]; however, two previous published papers made evaluation of supplementation of AlphaLA at profiles of fats in patients having P-COS [33, 34]. We believe that the anti-oxidant potential of ALA is an important mechanism in improving serum lipid profile in women with PCOS.

Indeed, there are previous observations that had been made by researchers supporting the anti-dyslipidemia effect connected to metformin drug [29, 35]. Based on several reports, this pharmacological agent has a protective act on profiles of lipid, enhancing, though in non-even manner, various dyslipidemia aspects; including, metformin-therapy has been correlated to greater levels of HDL-fraction, less LDL-fraction, and/or less levels of the lipid fraction triglyceride [36, 37].

Through a number of ways, metformin may be able to lessen the disruptions in lipid metabolism. Metformin slows the conversion of fatty-acids (free ones) to building blocks of lipoprotein in issues of hepatic organ via increasing insulin sensitivity, which lowers the rate of lipolysis. Metformin also decreases the amount of permanently glycated low-density lipoprotein cholesterol (LDL-C), which is eliminated from the circulation less effectively, by lowering plasma glucose levels. Additionally, metformin helps people with dyslipidemia by causing them to lose weight if they have impaired glucose metabolism.

According to Lin et al., weight loss after taking metformin is usually mild and mostly due to a decrease in body fat rather than an increase in energy expenditure [38].

In the current study, and after completing treatment course, the two modalities showed no significant change in mean resistin concentration of PCOS women. With respect to metformin, Basios et al. performed a study on 31 women with PCOS and found that treatment with metformin did not affected significantly the resistin level [39] and this finding is therefore similar to our finding. Moreover, in type 2 DM, treatment with metformin has been shown to lack an effect on serum resistin level [40] in support for our results. Probably the relative short duration of 3 months is the explanation for lack of significant change in serum resistin level.

5. Conclusion

In women with PCOS, alpha lipoic acid supplements are effective and safe ways to increase the results of metformin treatment in terms of weight loss and serum lipid profile improvement.

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