RESEARCH ARTICLE

Study of N-Acetyl Cysteine Plus Metformin Versus Metformin Alone in Treatment of Iraqi Women with Polycystic Ovarian Syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most common hormonal abnormality in reproductive-age women. The reproductive features include increased androgen production and disordered gonadotropin secretion leading to menstrual irregularity, skin problems, and infertility. In addition to these important reproductive manifestations, PCOS has metabolic characteristics that include prominent defects in insulin action and β-cell function. Treatment should be individualized based on the patient's presentation. Few medications were approved for the most common symptoms of PCOS, leading to the off label use of approved medications for other indications. One of the most common medications being used off-lable is metformin. Dietary supplementation such as N-acetyl cysteine has been recommended for PCOS therapy because it has at least one functional property in the PCOS-induced pathway.

Objective: To compare the effect of N-acetyl cysteine plus Metformin and Metformin alone for their efficacy and safety in Iraqi women with polycystic ovary syndrome.

Patients and Methods: 45 women diagnosed with PCOS according to Rotterdam criteria were randomly assigned into two treatments group, group 1 received N-Acetyl Cysteine (1800 mg/day) plus Metformin (1500 mg/day), and group 2 received metformin (1500 mg/day). Body mass index (BMI), menstrual regularity, clinical signs of hyperandrogenism, serum levels of various hormones follicular stimulating hormone (FSH), luteinizing hormone (LH) and testosterone), in addition to the clinical outcome assessed by ultrasonography, were evaluated before and after 3 months of treatment.

Results: After 3 months and compared to pre-treatment values, a significant difference in pregnancy rate, BMI, menstrual cyclicity, clinical hyperandrogenism manifestations (only Hirsutism), hormonal profile, and ultrasound findings (only the percentage of mature follicle > 9 mm in size) were found in N-Acetyl Cysteine plus Metformin groups; while in Metformin group only significant effect on serum testosterone level observed. Both treatment groups had no significant effect on acne, androgenic alopecia, and ovary volume. When the effects of both treatment approaches were compared, no significant difference was observed in BMI, clinical hyperandrogenism manifestations, side effects, serum testosterone, and serum FSH level. Adjunctly used N-Acetyl Cysteine showed significantly higher effects on menstrual cyclicity, serum LH level, and mature follicle than metformin alone.

Conclusions: N-acetylcysteine plus Metformin is superior to metformin alone, affecting the menstrual cycle, serum LH level, and follicle maturation. Due to the lack of adverse effects, N-acetylcysteine can be regarded as an appropriate substitute for insulin-reducing medication in PCOS treatment.

Keywords: Acne, N-acetylcysteine, Metformin, Polycystic ovary syndrome, Testosterone.

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INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most prevalent endocrine condition affecting women during their reproductive period.[1] The heterogeneous state of PCOS is characterized by irregular anovulatory cycles, hyperandrogenism, and/or polycystic ovarian appearance.[2,3] While not necessary for diagnosis, the presence of insulin resistance (IR) and hyperinsulinemia is common and puts those affected at increased risk of diabetes and cardiovascular disease. Therefore, PCOS has a negative effect on endocrine, metabolic,

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and cardiovascular health.[4] PCOS is considered a multifactorial condition with distinct genetic, metabolic, endocrine, and environmental disorders.[5]

The first-line therapy for PCOS is a lifestyle change, which involves diet management and exercise, with weight restriction being particularly important for PCOS patients. Because of the wide range of clinical and psychological disorders involved with PCOS, treatment should be symptom-based.[6]

Metformin (MET) has been reported to reverse PCOS-related metabolic disorders where ovulatory activity has been restored, normal menstrual periods, and circulating androgen and insulin levels have decreased.[7,8]

NAC is an N-acetylated derivative of cysteine, a sulfur-containing endogenous amino acid that serves as a precursor to the antioxidant glutathione.[9] Fortunately, supplementing with NAC will help women with PCOS reduce their IR. Reduced circulating insulin levels will cause a substantial drop in testosterone levels as well as the free androgen index.[10] Inflammation and oxidative stress are often higher in women with PCOS. Studies indicate that women with PCOS have glutathione levels that are nearly half as low as those without the condition.[11,12]

NAC has anti-inflammatory activity by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and modulating pro-inflammatory cytokine synthesis.[13] It functions primarily as an antioxidant and is essential for the body's glutathione formation. Enhanced glutathione synthetase hormone (GSH) synthesis reduces OS, preventing hyperinsulinemia-induced IR and protecting insulin receptors from oxidant agents such as malonyl dialdehyde, homocysteine, and lipoprotein that are elevated in PCOS.[14-16]

PATIENTS AND METHODS

This prospective, comparative, clinical study was conducted at a gynecology outpatient clinic in Baghdad Teaching Hospital /Medical City, Baghdad/ Iraq, from December 2020 till May 2021. Forty-five patients diagnosed with PCOS were included in the study. The individuals were randomly selected from those who attended the clinic. Our Inclusion criteria were as follows: (1) Female age 18 to 45 year, (2) Diagnosed as having PCOS according to Rotterdam criteria that included: oligo ovulation or anovulation, clinical or biochemical hyperandrogenism and/ or polycystic ovaries (by pelvic ultrasound). Our Exclusion criteria were as follows: (1) Congenital adrenal hyperplasia, (2) Thyroid dysfunction, (3) Hyperprolactinemia, (4) Cushing's syndrome, (5) Androgen-secreting neoplasia, (6) Diabetes mellitus, (7) Use medication change insulin hemodynamic, (8) Use medication affect carbohydrate metabolism, (9) Use hormonal drugs, multivitamins, and anti-obesity drugs within last 3 months, (10) sever concurrent cardiovascular disease, (11) Severe hepatic or kidney disease, and (12) poor patient compliance to the study.

The patients were randomized into two groups: Group 1 includes 19 patients treated only with 500 mg MET three times daily, and Group 2 includes 25 patients treated with 600 mg NAC three times daily plus MET 500 mg three times daily.

Each subject's medical history was obtained, focusing on age, marital status, and menstrual cycle history. If the patient was married, the number of pregnancies, living and dead babies, and any previous abortions were all asked for, and if she was infertile, the type and duration of infertility were also asked for. Furthermore, all subjects were asked for the presence of Hirsutism, acne, and/or androgenic alopecia. The height and weight were determined then BMI was calculated. Transvaginal ultrasonography was done. Transabdominal ultrasound was done in women who were virgins or who declined transvaginal examination. The imaging report contained details, including ovarian volumes and follicle counts, as well as any relevant observations such as the existence of a mature follicle (> 9 mm in diameter).

The hormonal profile was performed on all patients' second to the fourth day of the menstrual cycle. Blood samples were collected for patients with amenorrhea or oligomenorrhea regardless of the cycle's duration. All patients were subjected to basal investigations, including (serum FSH, serum LH, and serum testosterone).

Outcomes Measures

the changes in menstrual regularity, clinical signs of hyperandrogenism, BMI, ultrasound features, and hormonal assay were set as the study's primary outcome. The secondary outcomes included any adverse effects of the drugs used.

Statistical Analysis

Data analysis was carried out using the available statistical package of SPSS-27 (Statistical Packages for Social Sciences-version 27). The significance of difference of different means (quantitative data) was tested using students-t-test for the difference between two independent means or paired-t-test for a difference of paired observations (or two dependent means), or ANOVA test for difference among more than two independent means. The significance of difference of different percentages (qualitative data) was tested using the Pearson Chi-square test (χ^2-test) with an application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the p-value was equal to or less than 0.05.

RESULTS

Before treatment, there was no statistically significant difference in age between groups (26.31 ± 5.24 vs. 26.16 ± 5.38, p = 0.962), Marital status (p = 0.936), type of infertility (p = 0.058), and duration of infertility (p = 0.081).

Table 1 showed that 4 out of 14 (28.6%) of married women in (NAC+MET) group got pregnant, while no pregnancy occurred in M*Et al*one group. However no statistically significant difference in pregnancy rate between the two groups (p = 0.064).

Table 2 showed no statistically significant difference in frequency of mense and BMI (p = 0.626 and p = 0.565, respectively) between the two groups before treatment. After 3 months treatment there was a statistically significant effect on menstrual cyclicity with (NAC + MET) (p = 0.0001*), while

Table 1: Assessment of basic data and the effect on pregnancy rate.

		NAC + MET	*MEt alone*	*p-value*
Age (years)		*26.31 ± 5.24*	*26.16 ± 5.38*	*0.962*
Marital status	single	12 (46.2 %)	9 (47.4%)	0.936
	married	14 (53.8%)	10 (52.6%)	
Type of infertility	Primary	2 (14.3%)	5 (50%)	0.058
	Secondary	12 (85.7%)	5 (50%)	
Duration of infertility (years)		3.93 ± 3.02	2.65 ± 1.80	0.081
Pregnancy rate	Positive	4 (28.6%)	-	0.064
	Negative	10 (71.4%)	10 (100%)	

Table 2: Assessment of the effect on menstrual cyclicity and body mass index

		NAC + MET		*MEt alone*		
NO		*%*	*NO*	*%*		*p-value*
Frequency of menses Before	Amenorrhoea	3	13.6	5	26.3	0.626
	Oligomenorrhea	16	72.7	12	63.2	
	Regular cycle	3	13.6	2	10.5	
Frequency of menses After	Amenorrhoea	-	-	1	5.3	0.034*
	Oligomenorrhea	5	22.7	12	63.2	
	Regular cycle	17	77.3	6	31.6	
p-value comparing	Before x After	0.0001*		0.112		
BMI before (Kg/m2		28.15 ± 5.63		28.83 ± 4.02		0.565
BMI After (Kg/m2)		27.63 ± 5.67		28.22 ± 4.10		0.996
p-value comparing	Before x After	0.003#		0.055		

Table 3: Assessment of the effect on clinical hyperandrogenism

		NAC+MET		*MEt alone*		
NO		*%*	*NO*	*%*		*p-value*
Hirsutism before	yes	9	40.9	6	31.6	0.536
	no	13	59.1	13	68.4	
Hirsutism after	yes	3	13.6	4	21	0.529
	no	19	86.4	15	79	
p-value comparing	Before x After	0.042*		0.46		
Acne before	yes	2	9.1	3	15.8	0.513
	no	20	90.9	16	84.2	
Acne after	yes	1	4.5	2	10.5	0.463
	no	21	95.5	17	89.5	
p-value comparing	Before x After	0.578		0.631		
Androgenic alopecia Before	yes	3	13.6	2	10.5	0.762
	no	19	86.4	17	89.5	
Androgenic alopecia After	yes	1	4.5	2	10.5	0.463
	no	21	95.5	17	89.5	
p-value comparing	Before x After	0.294		-		

no significant effect in the MET group (p = 0.112) compared to pre-treatment values. Greater effect on menstrual irregularity was observed in (NAC + MET) compared to M*Et al*one group (p = 0.034). Table 2 showed that there was a statistically significant effect on BMI with (NAC+MET) (p = 0.003); while no significant effect in MET group (p = 0.055) compared to pre-treatment values. However no statistically significant difference in BMI between the 2 groups (p = 0.996).

Table 3 showed that there was no statistically significant difference in Hirsutism, acne, and androgenic alopecia (p = 0.536, p = 0.513, and p = 0.762, respectively) between the 2 groups before treatment. After 3 months of treatment, there was a statistically significant effect on Hirsutism with (NAC+MET) (p = 0.042), while no significant effect in the MET

group (p = 0.46) compared to pre-treatment values. However no statistically significant difference in Hirsutism between the 2 groups (P=0.529). Both groups showed no statistically significant difference in acne and androgenic alopecia after 3 months of treatment.

Table 4 showed no statistically significant difference in FSH, LH, FSH/LH ratio, and testosterone level (p = 0.330, p = 0.276, p = 0.713, and p = 0.318, respectively) between 2 groups before treatment.

Figures 1-4 showed that after 3 months treatment there was statistically significant effect on FSH (6.14 ± 1.73 vs 6.83 ± 2.28, p = 0.006), LH (7.97 ± 3.08 vs. 6.55 ± 2.56, p = 0.0001), FSH/LH ratio (1.398 ± 0.721 vs. 1.011 ± 0.400, P=0.001) and testosterone level (21.21 ± 12.49 vs. 18.31 ± 10.13, p = 0.010) with (NAC+MET), while no significant effect in MET group on FSH (6.67 ± 1.69 vs. 7.17 ± 2.19, p = 0.098), LH (9.13 ± 3.66 vs. 8.96 ± 3.57, p = 0.635), FSH/LH ratio (1.486 ± 0.790 vs. 1.350 ± 0.675, p = 0.094), only significant effect on testosterone level (26.62±19.6 vs. 25.57 ± 18.55, p = 0.013). Table 4 showed that there was greater effect on LH level was observed in (NAC+MET) compared to M*Et al*one group (p = 0.017).

Figures 5 and 6 showed that there was no statistically significant difference in ovary volume (both sides) in (NAC + MET) and M*Et al*one groups after 3 months treatment compared to pre-treatment values (9.74 ± 4.9 vs. 9.53 ± 4.58, p = 0.087 and 12.04 ± 4 vs. 12.05 ± 3.99, p = 0.147, respectively of left ovary) and (9.51 ± 3.64 vs. 9.29 ± 3.68, p = 0.064 and 11.25 ± 3.21 vs. 11.24 ± 3.12, p = 0.851, respectively of right ovary).

Table 5 showed that there was no statistically significant difference in the percentage of the mature follicle (above 9 mm in size) (p p =0.769) between 2 groups before treatment.

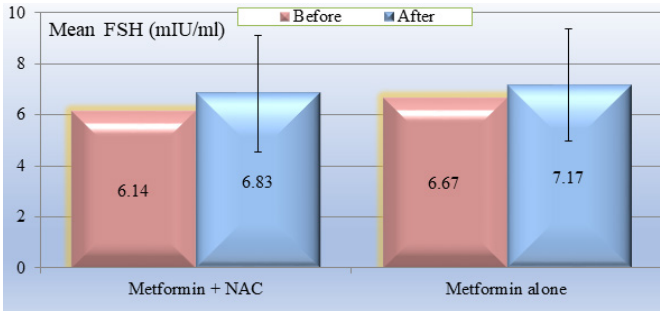

Figure 1: Mean FSH before and after treatment.

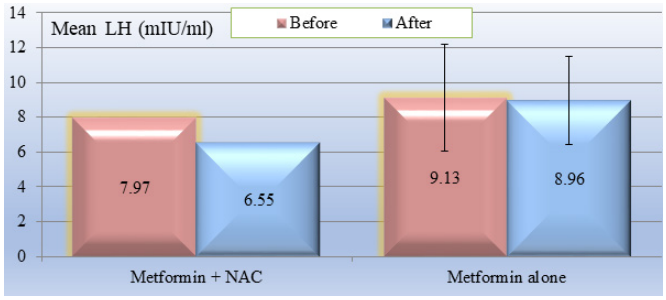

Figure 2: Mean LH before and after treatment.

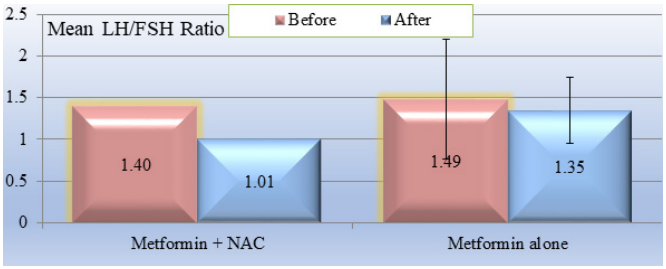

Figure 3: Mean LH/FSH ratio before and after treatment.

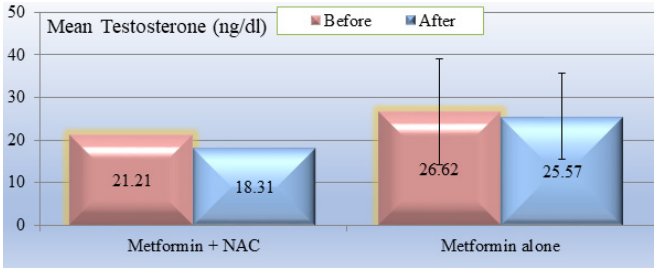

Figure 4: Mean testosterone before and after treatment.

Table 4: Comparison of the effect on the hormonal profile and ovary volume (both sides) in between groups.

	p-value (NAC + MET VS. MEt alone)
FSH Before	0.330
FSH After	0.629
LH Before	0.276
LH After	0.017#
LH/FSH ratio before	0.713
LH/FSH ratio after	0.054
Testosterone before	0.318
Testosterone after	0.145
Left ovary volume before	0.114
Left ovary volume after	0.090
Right ovary volume before	0.115
Right ovary volume after	0.078

Table 5: Assessment of the effect on mature follicle (above 9 mm in size)

		NAC+MET		*MEt alone*		
NO		*%*	*NO*	*%*		*p-value*
Mature follicle before	yes	3	13.6	2	10.5	0.769
	no	19	86.4	17	89.5	
Mature follicle after	yes	16	72.7	7	37	0.021*
	no	6	27.3	12	63	
p-value comparing	Before x After	p = 0.0001*		p = 0.056		

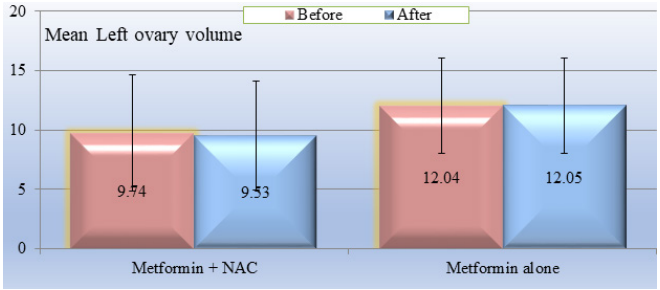

Figure 5: Mean left ovary volume before and after treatment.

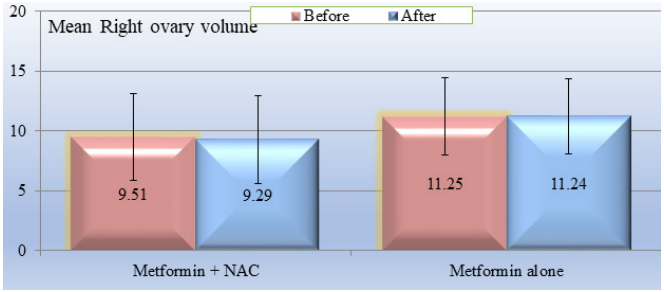

Figure 6: mean right ovary volume before and after treatment.

After 3 months of treatment, there was a statistically significant effect on follicle maturation with (NAC+MET) (p = 0.0001), while the small but not significant effect in the MET group (P=0.056) compared to pre-treatment values. Greater effect on follicle maturation was observed in (NAC+MET) compared to M*Et al*one group (p = 0.021).

DISCUSSION

PCOS is the most frequent cause of anovulatory infertility, affecting a significant percentage of women of reproductive age.[17] In the present study, 4 out of 14 (28.6%) of married women in (NAC+MET) group got pregnant, while no pregnancy occurred in M*Et al*one group. The results of this study about the MET effect were compatible to a systematic review by Costello *et al*. observed inconclusive outcomes on the effects of MET in the treatment of anovulatory infertility.[18] In the present study, the pregnancy rate increased when NAC was used as an adjunct to MET, while Thakker *et al*. conducted a study to see if NAC was more helpful than placebo or MET. Women who took NAC had a 3.5 times higher chance of becoming pregnant than those who took a placebo, while women on NAC were 60% less likely to become pregnant than those on MET.[10]

The endometrium undergoes hyperplasia in PCOS women due to estrogen's unopposed action, and this can manifest as a normal and regular menstrual cycle, regular cycle with menorrhagia, oligomenorrhea, or amenorrhea followed by menorrhagia.[19] One clinical trial compared MET and NAC use over 24 weeks; the results show that both groups had equal efficacy in terms of improved menstrual cyclicity,[20] While in the present study, the results show that NAC+MET had more efficacy in terms of improved menstrual cyclicity than M*Et al*one.

Obesity is a prevalent finding in PCOS women, and it is thought that PCOS is linked to genetics as well as environmental variables such as diet, lifestyle, and hormone levels.[21]

Glueck *et al*. observed that the change in BMI was inversely related to the duration of MET therapy. Women who used MET for less than three months lost an average of 2.4 pounds, whereas those who took it for more than six months dropped an average of 16 pounds.[22] NAC effects on BMI in the present study were compatible with one study conducted on 100 women with PCOS who were randomly assigned into 2 treatment groups, MET Group (500 mg three times a day) and NAC Group (600 mg three times a day). After 24 weeks of treatment, There was a significant reduction of BMI in the NAC Group.[23]

Increased levels of LH and coexisting IR are important contributors of hyperandrogenism. Hyperandrogenism in PCOS women clinically presents as Hirsutism, acne, and androgenic alopecia. With regard to NAC and MET effect, in one study compared the effects of MET with NAC for 24 weeks. Both treatments resulted in a significant decrease in hirsutism score compared with baseline values,[20] While in the present study, M*Et al*one resulted in insignificant improvement in Hirsutism compared with baseline values. This may be due to the longer duration of treatment (24 weeks) compared to the duration of the present study (12 weeks).

A disruption in the secretion rhythm of GnRH causes a relative increase in LH to FSH release in PCOS. Normally, the ratio of LH to FSH is 1:1, but in PCOS, it is >2:1.[24] The disruption of normal ovarian or adrenal function results in excess androgens production. NAC results of this study were compatible with the results of Gayatri *et al*., who compared NAC with MET. They observed a significant decrease in serum LH, FSH, and LH/FSH ratio in the NAC group, whilst in the MET group, there was a decrease in serum LH, but there was an insignificant decline in serum FSH and LH/FSH ratio. Also, there was a decline in testosterone levels in both groups.[25] The decrease in testosterone levels was highly correlated with the decrease in insulin levels. The reported reduction in testosterone and improvements in LH, FSH, and LH/FSH in our patients after treatment with NAC as an additional treatment to MET compared to M*Et al*one seemed to be independent on improvement in insulin sensitivity only. NAC appeared to have a synergistic effect in all types of PCOS, including those caused by IR and those caused by tissue OS.

As one of the diagnostic criteria for PCOS, ultrasonography imaging of both ovaries is critical. In comparison to normal ovaries, there is an increase in ovary volume (size) due to an increase in the number of follicles (12 or more measuring 2-9 in diameter) and stromal volume. The presence of a single PCO is sufficient to provide the diagnosis. NAC effects were compatible within one study that found that the average number of mature follicles was significantly higher in patients receiving (CC+NAC) than patients receiving (CC+placebo).[26] In addition to its insulin-sensitizing, androgen-reducing, and antioxidant effects, NAC preserves more follicles in the ovary through its anti-apoptotic mechanism.[27]

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