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Original Research Article

Comparison of metformin and N-acetylcysteine on metabolic parameters in women with polycystic ovarian syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common disease that affects up to 10% of women of reproductive age, in which hyperandrogenism (HA), enlarged cystic ovaries, and chronic anovulation often co-exist with obesity, dyslipidemia and insulin resistance (IR). There is a need for an alternative to metformin with minimal side effects to improve insulin sensitivity and correct dyslipidemia in PCOS patients.
Methods: It was a prospective, Randomized controlled clinical trial. 116 PCOS patients, 58 each in two groups received either Metformin 500 mg TDS or N-acetylcysteine (NAC) 600 mg TDS for 3 months. Clinical and biochemical parameters contributing to metabolic syndrome (MS) and insulin resistance (fasting blood sugar (FBS), fasting insulin (FI), FBS:FI, HOMA-IR and QUICKI) were assessed at the start and end of the study. Results were compared between the two groups.
Results: Both treatment modalities resulted in a significant reduction in number of cases with IR (p=0.001) and MS. Fasting hyperinsulinemia improved in 15 % (p=0.12) and 30% (p=0.001) of patients while 12% (p=0.23) and 18% (p=0.049) improvement was seen in FBS:FI in MET and NAC group respectively. Similarly, improvement in HOMA-IR was 12% (p=0.30) and 32% (p=0.001) in MET and NAC group which is significant with NAC. QUICKI and impaired glucose tolerance showed significant improvement in both the groups with a p-value of 0.04 and 0.006, 0.035 and 0.046 respectively. Significant reduction was seen in triglycerides (p=0.048) in NAC group.
Conclusions: NAC is equally efficacious as metformin in improving parameters of insulin resistance and metabolic syndrome with minimal occasional side effects ensuring better compliance for a long-term therapy.

Keywords: Metformin, Metabolic syndrome, N-acetylcysteine

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common disease that affects up to 10% of women of reproductive age, in which hyperandrogenism (HA), enlarged cystic ovaries, and chronic anovulation often coexist with obesity, dyslipidemia and insulin resistance (IR).[1] The etiology of the syndrome has remained unknown although it has been revealed that IR lies at the core of its pathophysiology.[2,3] Obesity in women with PCOS is rather high, ranging from 30% to 60%, whereas hyperinsulinemia is present in more than 50% of patients with PCOS.[4,5] Furthermore, although about 70% of obese women with PCOS exhibit an exaggerated insulin secretion, this feature is also present in 20%–40% of lean PCOS.[6-8]

Chronic hyperinsulinemia results in different pathologies such as diabetes mellitus type 2, hypertension, cardiovascular diseases and metabolic syndrome.[1,9] Risk factors of cardiovascular diseases tend to accumulate in these women even at their young age and dyslipidemia in these patients is correlated with IR.[10-12] It has been proven

that IR results in a disturbed response of glucose to insulin stimulation in skeletal muscles and increase of hepatic glucose production as well as lipolysis.[13-15] While post-receptor dysfunction in the pathway of insulin activity has been introduced as the reason for insulin resistance, the underlying reason for such a dysfunction still remains equivocal.[16] On the other hand hyperinsulinemia accelerate the effect of luteinizing hormone on ovarian theca and androgen synthesis.[17,18] which inhibits ovulation through cessation of follicular maturity process.[19] As a consequence, unlimited exposure to estrogen following anovulation these women are at risk of endometrial cancer.[20]

Currently the treatment of PCOS is mainly symptomatic which includes oral contraceptive pills, clomiphene citrate, gonadotropins and laproscopic ovarian drilling. However, their long-term effects in terms of preventing the complications of PCOS, such as cardiovascular disease and diabetes are still unknown. Therefore, evaluation of insulin sensitizers for treating PCOS is essential as insulin resistance lies at its core pathophysiology.[6,21] Different studies have proven that treatment with insulin sensitizing agents results in decrease in plasma lipids, reduction in hyperandrogenism, regulation of menstrual cycles and promotion of both spontaneous and induced ovulation.[22,23] Metformin, an insulin sensitizer, is being used for long time in the treatment of PCOS.

Metformin improves the endocrine parameters of PCOS by decreasing the levels of insulin and androgens.[24,25] Problems associated with Metformin include gastrointestinal side effects like nausea, vomiting, abdominal discomfort, flatulence, indigestion, constipation, heartburn etc and increase in homocysteine levels in some patients which limits their long-term use.[26] Hyperhomocysteinemia is a risk for cardiovascular diseases, thromobophilia, pre-eclampsia and recurrent abortion. N-acetylcysteine (NAC) is a stable derivative of the aminoacid cysteine which has anti-oxidant properties and is required for the body's production of glutathione. Glutathione along with NAC are powerful anti-oxidants which protect insulin receptors against oxidant agents.[27] NAC probably influences insulin receptor activity.[6,28]

It is a mucolytic which is being approved to be used in COPD patients. NAC is not found in diet but is available as nutritional supplement so it is safe and has no documented side effects till now. It has proven activity on insulin secretion in pancreatic cells acting as an insulin sensitizer. It also has an anti-apoptotic activity protective against focal ischemia at the level of ovary. NAC reduces plasma homocysteine levels.[29] Therefore, the present study was planned to compare the metabolic effects of metformin and NAC in PCOS patients as both are insulin sensitizers and can be beneficial in PCOS patients in ameliorating the long-term complications. Also, NAC can substitute metformin as it has no side effects and can be safe for long term treatment.

METHODS

This was a prospective follow up study conducted in the Department of Obstetrics and Gynecology at the University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi from November 2012 to April 2014.

Inclusion criteria

Women in 15-45 years of age diagnosed as PCOS fulfilling at least two of the following three criteria (Rotterdam criteria 2003), after exclusion of other etiologies:

- Oligo or anovulation (fewer than six menstrual periods in preceding one year)
- Clinical and/or biochemical evidence of hyperandrogenism
- Ultrasound criteria used for diagnosis of polycystic ovary: presence of 12 or more follicles measuring 2-9 mm in diameter in at least one ovary and/or increased ovarian volume (>10 ml).

Exclusion criteria

- Pregnancy
- History of cigarette smoking, alcohol consumption
- Current or previous use (within 3 months) of oral contraceptives, antiandrogens, antidiabetics, statins, glucocorticoids or intake of any other hormone
- Known case of diabetes mellitus or diagnosed diabetic during investigation by OGTT
- Other factors for infertility like congenital adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, hyperprolactinemia, androgen secreting neoplasia
- Hepatic and kidney diseases and peptic ulcer
- Hypersensitivity to either Metformin or NAC.

Methodology

Informed written consent was taken from all the subjects. A detailed clinical history with specific reference to following points was elicited from all recruited women:

- Age at menarche
- Menstrual cycle pattern (regular, oligomenorrhoea, amenorrhoea)
- History of weight gain if any (recent/rapid)
- Excess hair growth
- Family history of PCOS, diabetes mellitus, hypertension, cardiovascular disease, obesity, infertility.

Detailed general physical and clinical examination was done with special emphasis on:

- Body mass index (BMI)
- Waist-hip ratio

- Blood pressure measurement (mmHg) in right arm sitting position
- Clinical evidence of hyerandrogenemia: Hirsutism (scored objectively by Ferriman-Gallwey score), acne (IADVL classification), androgenic alopecia.
- Presence of acanthosis nigricans.

All patients were subjected to pelvic USG (Wipro GE LOGIQ 500 using 5.0 MHz abdominal transducer) on day 2 or day 3 of cycle in menstruating women or on any day in patients with amenorrhoea. In sexually active women, transvaginal sonography was performed by the same machine using 7.0 MHz vaginal transducer.

Biochemical Parameters

20 ml of venous blood sample was taken after overnight fasting on day 2/day 3 of cycle in menstruating women or on any day in amenorrheic women. These were centrifuged immediately and sera were separated and stored at -20°C until assayed for the Serum lipid profile by auto analyzer- Triglycerides (TG), High Density Lipo-proteins (HDL), Very Low Density Lipo-proteins (VLDL), Low Density Lipo-proteins (LDL) (all measured in mg/dl).

- Fasting serum glucose by glucose oxidase-peroxidase method (mg/dl).
- 2-hour blood glucose after 75 gm oral glucose load taken after fasting state (mg/dl).
- Fasting serum insulin by commercial radioimmuno assay kits (µIU/ml) (Beckman Coulter, USA)
- Serum Total testosterone by Commercial Radio Immuno Assay kits (ng/ml) (Beckman Coulter, US).
- Serum Prolactin levels by ELISA (ng/ml)
- TSH levels (µIU/ml) by commercial radioimmuno assay kits.

Insulin resistance was diagnosed in the presence of one of the following:

- Increased fasting insulin (>15 µIU/ml)
- Ratio of fasting blood sugar: fasting insulin <4.5
- Impaired glucose tolerance- plasma glucose 140 mg/dl-199 mg/dl, 2hours after 75 gms oral glucose load
- Homeostatic model assessment (HOMA-IR) >2.5: fasting glucose (mg/dl) x Fasting insulin (mIU/l)/405
- Quantitative insulin sensitivity check index (QUICKI) <0.357:1/log [fasting insulin (µIU/ml)] +log [fasting glucose (mg/dl)].

Simple randomization using computer generated random numbers.

Patients were divided in 2 groups: Group MET received tablet Metformin 500 mg-OD 1st week, BD 2nd week, TDS 3rd week onwards. Group NAC received capsule N-acetylcysteine 600 mg-OD 1st week, BD 2nd week, TDS 3rd week onwards. Both groups received medication for 3 months.

Follow up details

All participants were instructed to take tablet once a day in the 1st week and twice a day in the 2nd week. They were asked to initially come after two weeks. If the patient was found to be intolerant to the medication, she was excluded from the study. Those with no or minimal side effects were counseled to continue therapy in a dosage of 1 tablet three times a day from the third week. From there on patients were called at 4 weekly intervals. At the end of 3 months, biochemical evaluations were repeated to report changes in metabolic parameters.

Statistical analysis

All statistical analysis was carried out using SPSS software version 17.0. Within and between the two groups, comparisons were obtained by repeated measure ANOVA. Unpaired t-test and chi-square were used to study the differences in anthropometric parameters. $P<0.05$ was considered significant. All values expressed as mean±standard deviation.

RESULTS

Number of patients showing improvement in other anthropometric parameters were comparable but even though at recruitment number of patients with DBP>85 were significantly higher in NAC group, there was 50% reduction in the number of patients in both groups showing improvement in DBP (Figure1).

After three months of therapy, there was a marginally non-significant decline in the mean of all the anthropometric parameters namely weight, BMI, waist circumference, hip circumference, WHR and diastolic blood pressure in both the groups but statistically significant decline in systolic BP was observed only in the NAC group (p=0.024) (Table 1).

All patients showing fasting hyperglycemia became euglycemic after metformin therapy (p=0.002) but this improvement was seen in only 50% patients in NAC group. However, this improvement was not statistically significant. Number of patients showing improved impaired glucose tolerance was not significant in either group.

30% and 33.33% women in MET and NAC group respectively had FG: I <4.5 at baseline while after treatment FG: I<4.5 was seen in 18.3% and 15.8% in the two groups respectively. This difference was significant only in NAC group (p=0.049) and not in MET group.

Table 1: Comparison of effects of therapy on anthropometric parameters.

Variable	Group MET		p-value	Group NAC		p-value
	Before*	After#		Before*	After#	
Weight (kg)	61.14±9.98	61.00±9.88	0.994	61.99±12.31	61.01±11.83	0.665
BMI (kg/m^2)	26.52±4.06	26.47±4.13	0.951	26.70±5.36	26.36±4.69	0.719
Waist (cm)	76.90±7.56	76.43±7.53	0.758	78.65±9.58	77.74±9.63	0.614
Hip (cm)	93.08±5.70	93.02±5.84	0.959	94.02±7.83	93.07±7.29	0.504
Waist/Hip	0.82±0.06	0.82±0.07	1.000	0.83±0.07	0.82±0.06	0.414
Systolic blood pressure	119.78±8.83	118.12±9.68	0.377	121.72±9.21	117.54±10.33	0.024
Diastolic blood pressure	77.12±6.86	76.18±6.57	0.490	79.70±7.54	78.00±7.19	0.220

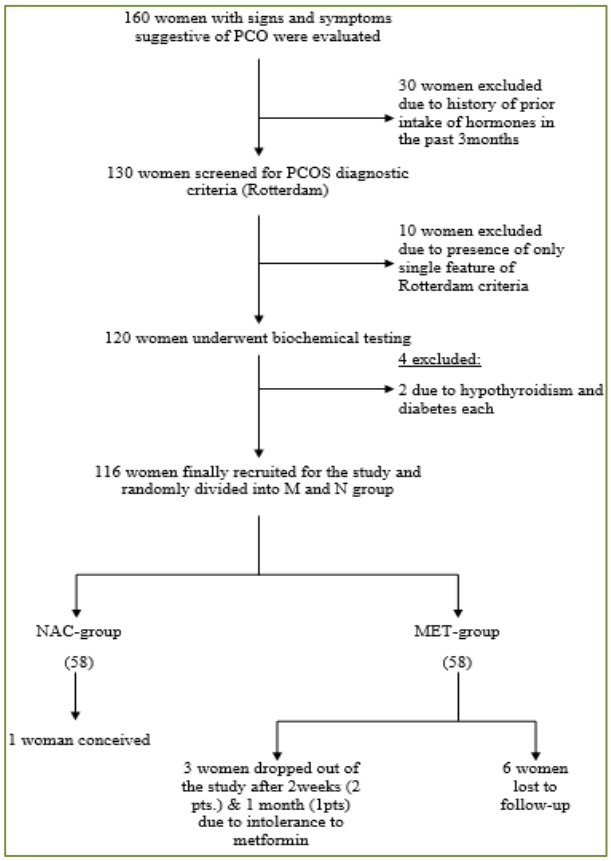

Figure 1: Consort statement indicating the procedure of recruitment.

Fasting hyperinsulinemia was seen in 38.7% and 45.6% in MET and NAC group respectively at recruitment followed by a decline to 22.4% and 15.7% in two groups after therapy which was significant in NAC group (p=0.001). 46.7% and 61.4% patients had HOMA-IR value >2.5 (one of the marker of insulin resistance) at start of therapy in MET and NAC group respectively while 34.5% and 29.8% had HOMA-IR >2.5 after therapy which was significant in NAC group (p=0.001) not in MET group.

QUICKI <0.35 was seen in 63.2% and 73.6% of patients in MET and NAC group respectively at baseline whereas it was found in 40.8% and 40.3% in two groups after therapy. This was significant in both the groups (p=0.04 and p=0.006).

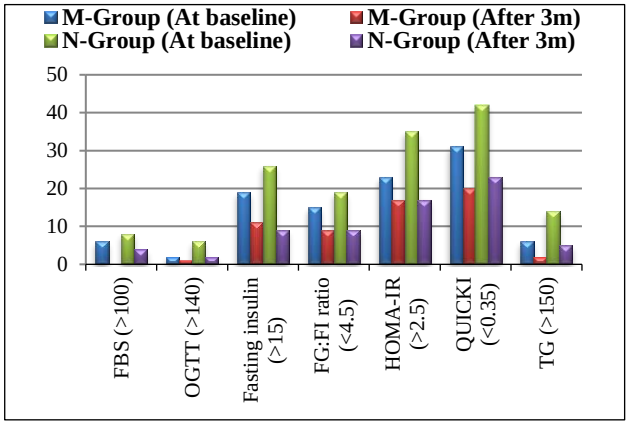

Figure 2: Comparison of number of patients showing Improvement metabolic parameters after 3 months of therapy.

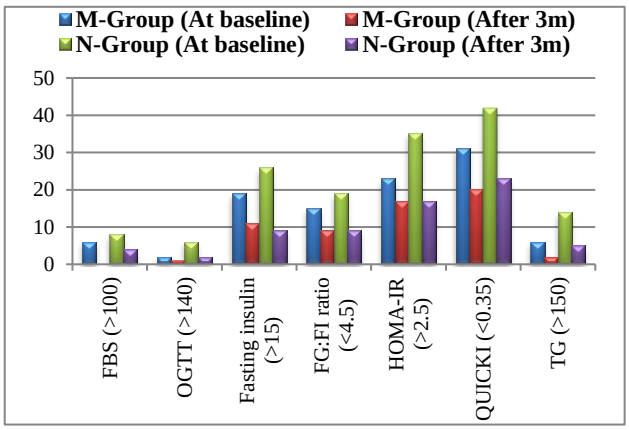

Figure 3: Comparison of number of patients showing Improvement metabolic parameters after 3 months of therapy.

Similarly, 12.2% and 24.5% patients had hypertriglyceridemia (TG>150 mg/dl) at recruitment in MET and NAC group respectively while only 4.08% and 8.7% had hypertriglyceridemia after therapy. This

decrease in the number of patients was found to be significant in NAC group (p=0.04) not in MET group (Figure 3). There was significant improvement in parameters of insulin resistance viz. fasting insulin, FG:FI, OGTT, HOMA-IR and QUICKI in the two groups. Similarly, there was drop in TG, LDL, VLDL and testosterone in the two groups after 3 months of medication while there was significant decline in testosterone in NAC group only (p=0.049) (Table 2).

There was a significantly higher prevalence of cases with MS in the NAC group at baseline (8/49 vs 16/59; p=0.001). Both MET and NAC brought about a significant reduction in the number of cases with MS (p=0.09 for MET and 0.002 for NAC). There was 75% reduction in cases with MS after Met therapy (from 8 cases to 2) whereas only a 32% reduction was observed in the NAC group (16 cases to 11) and this difference remained significant (2/49 vs 11/57; p=0.002) (Table 3).

Table 2: Comparison of effects of therapy on metabolic parameters.

Variable	Group MET		p-value	Group NAC		p-value
	Before*	After#		Before*	After#	
Fasting Blood Sugar (mg/dl)	88.25±9.80	82.85±8.87	0.005	89.04±10.81	83.46±9.21	0.007
Fasting Insulin (µIU/ml)	13.54±7.65	10.00±6.59	0.015	16.05±10.12	9.59±5.35	0.001
F.B.S / F.I.	8.42±0.08	12.24±0.08	0.001	7.50±0.11	11.63±0.06	0.0001
OGTT (mg/dl)	111.68±20.25	102.51±22.20	0.035	113.02±21.47	105.95±17.13	0.046
Homa-IR	3.00±1.86	2.02±1.38	0.003	3.59±2.30	1.98±1.13	0.0001
QUICKI	0.33±0.01	0.36±0.01	0.0001	0.33±0.01	0.36±0.01	0.0001
TG (mg/dl)	111.94±32.41	105.72±29.20	0.321	124.71±47.64	110.32±28.17	0.048
LDL (mg/dl)	91.62±18.98	89.76±18.77	0.626	96.18±24.60	89.62±22.78	0.142
HDL (mg/dl)	39.04±8.60	38.72±9.52	0.861	40.93±9.43	41.44±9.90	0.778
VLDL (mg/dl)	21.71±6.11	20.09±5.61	0.178	23.50±9.52	21.11±5.97	0.111
HDL/LDL	0.44±0.14	0.45±0.15	0.733	0.45±0.17	0.49±0.19	0.238

At baseline 81.6% patients (40/49) in MET group were insulin resistant fulfilling one or more of the diagnostic criteria. The corresponding data for the NAC group was 91% patients (52/57). This baseline prevalence of IR was comparable between the two groups (p=0.16). Post therapy IR was documented in 42% (21/49) and 58% (33/57) in MET and NAC groups respectively, revealing a 50% reduction in either group. Both treatment modalities resulted in a significant reduction in number of cases with IR (p=0.001). However, the number of cases with IR after treatment remained comparable between the two groups (21 vs 33; p=0.17) (Table 4). 13 (26.5%) patients in MET group and 3(5%) patients in NAC group reported the above side effects while on therapy (Table 5).

Table 3: Comparison of number of cases with metabolic syndrome in two groups after therapy.

No. of criteria fulfilled for diagnosis	MET group Baseline	MET group After 3m	NAC group baseline	NAC group After 3m
3	6	2	12	10
4	2	0	3	1
5	0	0	1	0
n	49	49	57	57

Table 4: Comparison of number of cases with insulin resistance in two groups after therapy.

No. of parameters fulfilled	MET-Group (n=49) Baseline	MET-Group (n=49) After 3m	NAC-Group (n=57) baseline	NAC-Group (n=57) After 3m
1	13	4	13	14
2	10	4	13	14
3	8	5	15	5
4	9	8	10	0
5	0	0	1	0

Table 5: Comparison of side effects in two groups.

Side effects	MET group (n=49)	NAC group (n=57)
Nausea	6	0
Heartburn	7	0
Constipation	0	2
Lassitude	0	1

DISCUSSION

In the present study, three months therapy of Metformin and NAC were compared for their effects on parameters of insulin resistance and dyslipidemia in women with PCOS. Confounding factors like smoking, alcoholism or any medical disorders which might affect the drug metabolism were excluded from the study. Known cases of Diabetes and Hypertension were also excluded. 106 PCOS women completed the study of 3 months therapy, 49 and 57 receiving Metformin and NAC respectively.

Age of patients ranged from 16-35 years with a mean of 22.75 years. Since patients were recruited from general OPD and not from an infertility clinic about 60% were unmarried and nearly a quarter were teenagers, with main complaints being menstrual irregularities (85%), weight gain (28%) or symptoms of clinical hyperandrogenism (26%). All the symptoms were equally distributed in the two groups at the time of recruitment showing no baseline bias.

Family history of PCOS associated comorbidities could be elicited in as high as 45% cases (diabetes mellitus in 29% cases) and this despite a large number of patients being not aware of diabetes, CAD etc. in the immediate family members. Strong associations of Diabetes or glucose intolerance in up to 40% of first degree relatives of PCOS has been reported by Fox R.[30] While some studies have reported family history of CAD and PCOS in PCOS, no such history could be elicited from the patients in the present study.[30,31]

The mean BMI of the study population was found to be 26.56 kg/m^2 with 79 % and 77% in MET and NAC group respectively having a BMI >23 kg/m^2. Reported prevalence of obesity in women with PCOS by Majumdar et al range from 30% to 60% in Asian/ Indian women.

The range of waist circumference was found to be 62-108 cms with a mean of 76.89 cms and 78.64 cms in MET and NAC group respectively with waist circumference of >80 cm in 30.6 % and 35% of patients in the two groups. Despite the mean waist circumference of patients being <80 cm and comparable in two groups WHR remained higher than 0.81 in 63.3% and 64.9 % of patient in MET and NAC group, indicating predominance of central obesity in these women. Higher percentage of increased WHR in present study is similar to that reported by other studies.[33-35]

The mean of systolic BP was 118.12 and 117.54 mmHg while diastolic BP were 77.12 and 79.70 mmHg in MET and NAC group respectively at recruitment. Systolic hypertension was seen in about 7% cases (3 in MET and 4 in NAC group) and five (10%) in MET and twenty (35%) in NAC-group had diastolic hypertension similar to the prevalence of 10-15% reported by Majumdar et al on Indian population.[35] The prevalence of prehypertension was seen in 20-30% cases. However, recruitment bias came to light for distribution of cases with diastolic hypertension being significantly higher in NAC group (20 v/s 5, p<0.002).

Baseline biochemical and hormonal parameters were comparable between the two groups. FBS >100 mg/dl and IGT was seen in 8 women (16.3%) in MET gp. and in 14 (24.5%) in NAC group. As high as 30-40% of impaired glucose tolerance reported in various studies suggests that PCOS is probably a pre-diabetic condition.[36] This lower range of abnormal FBS and IGT in the present study could be probably due to the younger age of PCOS cohort.

Taking a cut-off of >15 µIU/ml, fasting hyperinsulinemia was seen in nineteen (38.7%) and twenty-six (45.6%) patients. The cutoff point used to define IR appears to be different among various ethnic groups. Kauffman et al.[37] found that in regard to diagnosing IR with a fasting insulin level, a cutoff point of ≥20 µU/mL was appropriate for white women, but in Mexican American women, a cutoff point of ≥23 µU/mL should be used. This lower fasting insulin cutoff point was specifically chosen to reduce the bias of our results toward a falsely low rate of IR.

Similarly, fasting glucose insulin ratio <4.5 was seen in 15 (30.6%) and nineteen (33.3%) pts with a mean of 13.54 µIU/ml, 8.42 in MET group and 16.05 µIU/ml, 7.50 in NAC group respectively.

Twenty-three (46%) and thirty-five (61.4%) patients had abnormal HOMA-IR >2.5 and thirty-one (63.2%) and forty-two (73.6%) had abnormal QUICKI <0.35 in MET and NAC group respectively. Insulin resistance was observed in 26% patients according to HOMA-IR by Jolanta et al on western population. A higher percentage of IR was seen which might be due to Indian subjects.[38]

Similar mean of fasting glucose while higher values of fasting insulin and HOMA-IR was reported by a study done on 100 subjects (50 in MET and 50 in NAC group) by Gayatri K on Indian population while OGTT and QUICKI were not taken as an assessment for insulin resistance in that study.[39]

In the present study, HDL<50 mg/dl was seen in 45 (91.8%) and 49 (85.9%) pts with mean of 39.04 and

40.06 mg/dl in MET and NAC group respectively while TG >150 mg/dl was seen in 6 (12.2%) and 14 (24.56%) patients in two group. It is consistent with other studies which report that dyslipidemia can be seen up to 70% of PCOS patients.

At recruitment, 71% and 79% of the women met the ultrasonographic criteria of Rotterdam in MET and NAC group respectively which is similar to PCO morphology on USG reported in 70-100% of women in several studies.

After 3 months of intervention

After three months of therapy there was decline in mean of all the anthropometric parameters viz weight, BMI, waist circumference, hip circumference in both the groups but more in N-group while WHR decreased in NAC group after therapy but remained same in MET group. There was significant number of patients who lost weight among the two groups, however, the pre-and post-treatment differences in the other anthropometric parameters were not statistically significant between the two groups.

Gayatri K et al also reported decrease only in weight and no other anthropometric parameters in NAC group and not in the MET group similar to the present study.[40] On the other hand Salehpour et al reported significant improvement in all the parameters in NAC group as compared to placebo after six weeks treatment.[40] In the study by Fulghesu et al wherein, 31 out of 37 women were obese, NAC did not show any significant change in BMI.[6] Similar observation of no significant change in BMI or WHR after six weeks of either NAC or MET was made by Elnashar et al.[41]

There was significant improvement in mean of parameters of insulin resistance viz fasting blood sugar, fasting insulin, fasting glucose insulin ratio, HOMA-IR and QUICKI in the two groups more in NAC group. All cases of fasting hyperglycemia became euglycemic after Metformin while this change was observed in only 50% cases after NAC. However, as the number of cases with hyperglycemia were small (6 and 8), this difference was not statistically significant.

Significant improvement in OGTT values were observed in both the groups, more so in the MET group (p=0.03 and 0.046). There are as yet probably no published studies comparing OGTT between metformin and NAC groups. Significant number of patients exhibited lowering of Fasting hyperinsulinemia only in NAC group (p=0.001). Similarly, FG:FI as well as HOMA-IR values improved in significantly higher number of patients only in NAC group (p=0.049 and p=0.001) as compared to MET group (p= 0.23 and 0.3). QUICKI showed significant improvement in both the groups with a p-value of 0.04 and 0.006 in the two groups. This is similar to the study by Gayatri K et al, who observed, significant improvement in all the parameters of insulin resistance viz fasting insulin levels, fasting glucose insulin ratio and HOMA-IR only with NAC therapy as compared to metformin therapy.[39]

In a study by Salehpou et al, there was significant drop in serum fasting glucose, fasting insulin and HOMA-IR but the rise in glucose insulin ratio was not found to be significant.[40] Treating 20 PCOS women, Kilicdag noticed that despite the insignificant change in fasting plasma glucose, insulin levels dropped significantly and decline in HOMA-IR was statistically significant in NAC compared with placebo.[8] On the contrary Elnashar reported significant drop in FPG and serum insulin among patients who received metformin and not in NAC group.[41] Fulghesu, assessing insulin sensitivity using colompe euglycemic hyperinsulinemic technique, showed increased sensitivity to insulin and significant decline in insulin area under curve after oral glucose tolerance test after treatment with NAC while fasting plasma glucose (FPG), fasting insulin and glucose area under the curve remained unchanged.[6]

The study showed significant decrease in mean of TG, LDL, VLDL and HDL/LDL ratio with significant increase in HDL within the two groups while not significant among the groups. Similar results were reported by Salehpour and Fulghesu showing significant decrease in total cholesterol, LDL, TG and significant rise in HDL on NAC therapy while no significant improvement was reported by Oner.[6,40,42] Of the Fourteen patients with TG >150 mg/dl, 9 showed normal TG levels in the NAC group (p=0.04) while no significant decrease was seen in the MET-group.

Metabolic syndrome was seen in 35% (16.3% patients in MET group) at recruitment while only 4% remained in this category after therapy whereas 28% patients were having metabolic syndrome in NAC group which dropped to 19% after 3 months. Both MET and NAC brought about a significant reduction in the number of cases with MS (p=0.09 for MET and 0.002 for NAC). According to International Diabetes Federation criteria, one third of Asian PCOS patients have metabolic syndrome. At baseline 81.6% patients (40/49) in MET group were insulin resistant fulfilling one or more of the diagnostic criteria. The corresponding data for the NAC group was 91% patients (52/57). This baseline prevalence of IR was comparable between the two groups (p=0.16). Post therapy IR was documented in 42% (21/49) and 58% (33/57) in MET and NAC groups respectively, revealing a 50% reduction in either group.

More than 50% insulin resistance is generally reported in PCOS patients5. This high value in the present study might be due to lower cut off considered for fasting insulin (>15 µIU/ml) while other studies5 reporting a lower prevalence in the range of 30-40% have considered a fasting insulin cutoff value of >20 µIU/ml. Taking a cut off of >20 µIU/ml, 25% insulin resistance was seen in the

present study. NAC was well tolerated by study population with mild side effects of constipation or lassitude reported only by one or two patients in the initial two weeks which however did not result in discontinuation of treatment. Patients on metformin more frequently complained of nausea and heartburn which might be the reason for drop out of 9 patients in this group. Similar high dropouts were reported by Oner in metformin group suggesting the reason to be gastrointestinal side effects while NAC was well tolerated by study subjects.[42] Different studies done by Gayatri, Salehpour and Fulghesu also reported that NAC showed no adverse effects.[6,39,40]

CONCLUSION

Metformin therapy resulted in improvement in weight, fasting blood sugar and parameters of insulin resistance while no improvement in lipid profile was recorded. NAC therapy resulted in improvement in weight, systolic BP, fasting blood glucose, parameters of insulin resistance and lipid profile. Significant and comparable reduction in number of cases with IR and MS was seen in both treatment groups. Side effects of metformin were much higher resulting in non- compliance of treatment. NAC with minimal occasional side effects ensured completion of study by all participants. Superiority of NAC over metformin in ameliorating insulin resistance and metabolic syndrome is evident from this study of 106 patients.

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