A Study Of N-Acetyl Cysteine On Clinical, Metabolic Parameter And Hormonal Profile In Women With Polycystic Ovarian Syndrome

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Abstract: Background: Polycystic ovary disease (PCOD) is a common endocrine disorder, which is mainly characterized by infertility, anovulation, hyperinsulinemia, dyslipidaemia, biochemical imbalance. In our present study we have evaluated the effect of NAC in women suffering from PCOD in terms of their clinical, metabolic and hormonal parameters. Material And Methods: We conducted this prospective study for a period of 5 months on 60 women who are affected with PCOD (diagnosed by Rotterdam criteria) of age group 18–30 year, visiting OPD of obstetrics and gynaecology department of Acharya Vinobha Bhave Rural Hospital (AVBRH) Jawaharlal Nehru Medical College (J.N.M.C) located in Sawangi (Meghe), Wardha. Patients who had oligo/amenorrhoea, hirsutism (hyperandrogenism) and ultrasound finding (Polycystic ovaries) were included in this study. Clinical, metabolic parameter and hormonal profile were measured pre and post treatment with NAC. Result: Fifty-six patients who received tab N acetylcysteine 600 mg three times a day, shown improvement in BMI, waist circumference, WHR, fasting glucose, fasting insulin and total testosterone level after a period of 3 months but no significant reduction in weight. Conclusion: It has been concluded that longer treatment with N-acetyl cysteine may result in more desirable outcomes and more effective control of clinical symptoms of PCOS, hyperandrogenism, and carbohydrate parameters. So, NAC can be used as a insulin sensitizer drug for PCOS women. [T A Natl J Integr Res Med, 2021; 12(6): 9-13]

Key Words: PCOS, ENDOCRINE DISORDER, WOMEN, INFERTILITY, NAC

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Introduction: Polycystic ovary diseases (PCOD) are common endocrine disorders, which affects approximately 5% to 15% of women of reproductive age[1-3]. PCOD is a heterogenous, multisystem endocrinopathy in women of reproductive age with the ovarian expression of various metabolic disturbances and a wide spectrum of clinical feature such as obesity, menstrual abnormalities and hyperandrogenism.

This disease was described by and named as Stein-Leventhal syndrome in 1935. To diagnose PCOD, adrenal and androgen-producing ovarian tumour should be excluded. PCOD is mainly characterized by infertility anovulation, hyperinsulinemia, dyslipidaemia, biochemical imbalance which shows increased androgen levels, increased luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio and higher androgen level leads to metabolic disorders such as cardiovascular diseases, type 2 diabetes, hypertension and endometrial cancer later in life[4-6]. For the diagnosis of PCOD, the Rotterdam criteria (2003) are generally followed[7]. It states that at least two of three criteria should be present. These criteria are as follows: 1. Oligo/amenorrhoea and/or anovulation, infertility. 2. Hirsutism/acne (Hyperandrogenism) 3. Ultrasound finding (Polycystic ovaries, with the exclusion of other aetiologies).

According to Androgen Excess and PCOS (AE–PCOS) Society, Definition of PCOS is biochemical or clinical hyperandrogenism which is associated with ovulatory dysfunction which is expressed in the form of oligo-anovulation or ultrasound finding of polycystic ovaries whereas the National Institute of Health (NIH) criteria says that PCOD is a clinical and/or biochemical hyperandrogenic and chronic anovulatory state[8]. The exact aetiology of the syndrome has remained unknown, a number of theories have been postulated in genesis of PCOD. Some of well-known factors which may influence the onset of PCOD are lifestyle changes, sedentary life, diet and stress. Although it has been revealed that, insulin-resistance (IR) and synthesis of high levels of androgen is core pathophysiology[9], insulin-resistance causes decreases insulin receptor activity in skeletal muscles which reduces glucose

uptake by skeletal muscle and increase lipolysis and glucose production by hepatic cells[10]. Hyperinsulinemia induces LH to cause theca-cell hyperplasia and secret androgens, testosterone and epi- androstenedione[11].

N-Acetyl cysteine (NAC) is prodrug of both the amino acid reduced glutathione and L-cysteine, NAC works as antioxidant at cellular levels and reduces glutathione at higher doses. Therefore, NAC improves insulin secretion in response to glucose and insulin receptor activity in human erythrocytes[12]. Decreased insulin will decrease the testosterone and free androgen level[13]. Its antioxidant action prevents endothelial damage, protection against focal ischemia, pro inflammatory cytokine release, and protease activity[14]. In our present study we have evaluated the effect of NAC in PCOD women on their clinical, metabolic and hormonal parameters.

Material & Methods: Subjects: We conducted this study on 60 women who are affected with PCOD (diagnosed by Rotterdam criteria) of age group 18–30 year, visiting OPD of obstetrics and gynaecology department of Acharya Vinobha Bhave Rural Hospital (AVBRH) Jawaharlal Nehru Medical College (J.N.M.C) located in Sawangi (Meghe), Wardha, Maharashtra in central India. This was a prospective study done for period of 5 months from August 2020 to December 2020.

Patients who are hypersensitive to NAC, presence of infertility factors other than anovulation, pelvic organic pathologies, thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinemia, Cushing's syndrome, impaired glucose tolerance or diabetes mellitus, androgen secreting neoplasia, pregnancy, history of cigarette smoking, alcohol consumption, pregnancy, current or previous use (within 3 months) of oral contraceptives, antiandrogens, statins, glucocorticoids or intake of any other hormone consumption of medications affecting carbohydrate metabolism, severe kidney or hepatic diseases and active peptic ulcer were considered as exclusion criteria. Patients who had oligo/amenorrhoea, hirsutism (hyper androgenism) and ultrasound finding (Polycystic ovaries) were included in this study.

Clinical Evaluation: After getting approval from the ethical committee and patient's written informed consent, the main presenting complaint in all the patients were noted and detailed clinical and general physical examination was performed with special emphasis on: weight of patient, Body mass index (BMI), waist circumference, waist-hip ratio (cut off value of waist circumference is 85 cm or more and hip circumference measurement around the widest portion of the buttocks, with the tape parallel to the floor). Blood pressure measurement (mmHg) in right arm sitting position, physical features of hyperandrogenaemia: Hirsutism (scored objectively by Ferriman-Gallwey score), androgenic alopecia, acne (IADVL classification), presence of acanthosis nigricans, menstrual disturbance like secondary amenorrhea (absence of vaginal bleeding for at least 6 months), oligomenorrhea (interval between menstrual periods < 35).

Biochemical Parameters: Blood investigation included were serum TSH, serum fasting glucose level, serum fasting insulin, serum fasting glucose/insulin ratio and serum total testosterone were measured by enzyme immune assay (EIA).

Patients constituting 60 cases were given N-acetyl cysteine 1800mg/day (600 mg three times daily). All patients were advised to maintain their routine physical activity and avoid any change in their life style and nutrition and not to undergo any new pharmacotherapy during the study. Each patient received the treatment for 3 months.

Patients were asked to report any possible adverse effects. At the end of 3 months of treatment, the clinical and biochemical evaluations were repeated. The statistical analysis was done using latest version of SPSS software.

Results: During the study a total 60 patients were taken for study but four patients dropped out treatment. Ultimately, evaluation limited for 56 patients who received tab N acetylcysteine 600 mg three times a day. After a period of 3 months clinical features, carbohydrate metabolic parameters and reproductive hormone levels were again measured. Number of patients showing improvement in anthropometric parameters namely BMI, waist circumference, WHR. Mean BMI which was 29.38 before treatment with NAC shown statistically significant difference after treatment which was 26.18 ($p < 0.05$). Same results were found with waist circumference and WHR; mean WHR was 0.94

before treatment and 0.91 after treatment ($p < 0.05$), mean waist circumference was 96.19 before giving NAC treatment shown statistically significant improvement after NAC which was 92.71 ($p < 0.05$) but there was no significant reduction of weight ($p > 0.05$). Metabolic and hormonal parameter also showed the improvement. Post treatment reduction in fasting glucose and fasting insulin was statistically significant ($p < 0.05$), fasting glucose was 112 before treatment,92 after treatment; likewise fasting insulin was 24.23 pre-treatment and 18.21 post treatment with NAC. Serum testosterone level was decreased and shown statistically significant improvement ($p<0.05$).

Table 1: Effect Of N Acetylcysteine On Clinical, Metabolic And Hormonal Parameters

	Before Treatment (N=56)	After Treatment (N=56)	P Value
Weight	66.20	63.17	0.1037
BMI	29.38	26.18	0.0000
WC	96.19	92.71	0.00016
WHR	0.94	0.91	0.00486
Glucose (Fasting)	112	92	0.0000
Insulin (Fasting)	4.23	18.21	0.0000
Fasting Glucose/Insulin Ratio	4.89	6.01	0.0000
Total Serum Testosterone	2.1	1.6	0.00015

Discussion: A prospective observational study was carried out on 56 women in Dept. of Obstetrics and Gynaecology Acharya Vinobha Bhave Rural Hospital (AVBRH) Jawaharlal Nehru Medical College (J.N.M.C) located in Sawangi (Meghe), Wardha, Maharashtra in central India from august 2020 to December 2020. This study was conducted with the objective to assess the efficacy of N acetyl cysteine on physical, Metabolic Parameter and biochemical hormonal Profile in women with polycystic ovarian syndrome. Increased insulin resistance and compensatory hyperinsulinemia play a key role in the pathogenesis of PCOS. Chronic insulin excess is a high-risk factor for gestational and non–insulin dependent diabetes, may exert effect on endocrine impact on the ovary, insulin has been shown to directly stimulate androgen secretion than in normal ovaries.

Hyperandrogenism lowers the level of hepatic sex hormone binding globulin (SHBG), as a result level of testosterone in serum rises leading to hirsutism. On the basis of the above considerations, it seems very important to test the efficacy of insulin-lowering drugs in patients with PCOD; thus, we wanted to analyze the potential insulin-sensitizing properties of NAC in patients with PCOD.

NAC is recognized by the Department of Health as a medicine that fluidizes bronchial mucous secretions. In vivo and in vitro studies have demonstrated that NAC represents a precursor in GSH biosynthesis and is deacetylated into cystine. NAC works as a antioxidant in non–insulin-dependent diabetic patients significantly reduced intraerythrocytic GSH disulfide (GSSG) concentrations and this prevents oxidative stress on endothelial cells[15]. NAC increases the insulin sensitivity by increasing its consumption.

Clinical Parameters: In our study after 12 weeks of treatment with N acetyl cystine shown significant improvement in BMI, WC and WHR (Table 1). Others authors also found the same result in BMI[16]. Two another study reported the same in view of clinical parameters[17,18]. Eight studies with a total of 910 women with PCOS were randomized to NAC found no significant difference in change in body mass index[19].

Metabolic Parameter: In this study there is significant reduction in fasting insulin, fasting glucose and fasting glucose/insulin ratio (Table 1). Another study done in Rome in 2002 demonstrated that NAC treatment improves the peripheral insulin sensitivity and lipid profile in patients of PCOS[20]. The results of our study were comparable with the study done by other authors where the improvement in the carbohydrate metabolic parameters is similar to the improvements in their study[17,21,22].

Hormonal Parameter: In our study, total serum testosterone showed significant reduction. A study done by Nidhi Chandil et al in 2018 and Gayatri et al in 2010 also found the same result

as ours that significant fall in serum total testosterone level[17,21]. Another study done in 2002 in Italy documented the same about the NAC effect on total testosterone, free androgen[20]. A randomized controlled clinical trial done in 2014 on 910 PCOS women found no significant change in testosterone[19].

Conclusion: In our study insulin sensitizer used as first line therapy for PCOS women. It has been concluded from our study that, longer treatment with N-acetyl cysteine may result in more desirable outcomes, such as more effective control of clinical symptoms of PCOS, hyperandrogenism, and carbohydrate parameters.

So far less adverse effects have been reported for NAC as it is an amino acid. NAC with minimal occasional side effects ensured completion of study by all participants.

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