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ROLE OF N-ACETYL CYSTEIN, METFORMIN AND VITAMIN D3 WITH CALCIUM ON METABOLIC PROFILE IN PCOS

Dr.Veena Gupta Professor, Department of Obstetrics and gynecology, M.L.N.Medical College, Allahabad

Dr. Amita Yadav Assistant professor, Department of Obstetrics and gynecology, M.L.N.Medical College, Allahabad - Corresponding author

ABSTRACT

Objective – This study was aimed to evaluate the role of N-Acetyl cystein, metformin and vitamin D3 with calcium on the metabolic profile in PCOS .

Material and Methods-The present study was conducted in the department of obstetrics and gynecology ,Motilal Nehru medical college, Allahabad over a period of 12 months. The study was carried out in 66 women of reproductive age group. The diagnosis of PCOS was made if the patients had two out of three Rotterdam criteria.

RESULT- Reduction in fasting plasma glucose among all the three groups was statistically insignificant (p=0.1135)). Post treatment greater reduction in fasting plasma glucose was seen in N-acetyl cysteine(p=0.0001) compared to Metformin and Vitamin D3 with Calcium (p=0.0002 and p=0.0028 respectively) The difference in mean value of fasting plasma glucose/ fasting insulin ratio between Group 1 and Group 2 was insignificant. (p>0.05) and between Group 2 and Group 3 (p<0.05) as well as in Group 1 and Group 3 (p<0.01) was significant.

CONCLUSION- Highly significant changes brought by a 12 week course of treatment with NAC suggested that, longer treatment with N-acetyl cysteine may result in more desirable outcomes, such as more effective control of clinical symptoms of PCOS.

KEYWORDS : PCOS, n-acetyl cystein, metformin,vitamin D3, fasting plasma glucose,fasting insulin level.

INTRODUCTION-

Polycystic ovarian syndrome (PCOS) is considered to be the most prevalent endocrinopathy in reproductive age group, affecting 5-10% of women worldwide ***(R.Aziz et al, 2004)[1].*** In India more than 25% reproductive women are suffering from PCOS. It is characterized by the combination of hyperandrogenism, chronic anovulation and polycystic ovaries with the clinical manifestation of oligomenorrhea /amenorrhea, acne, hirsutism, and infertility. The characteristic polycystic ovary develops when a chronic anovulatory state persist for a long time. Hormonal profile of PCOS compared to normal cycling women exhibit increased serum luteinizing hormone (LH) concentration and increased LH:FSH ratio.

Current incidence of PCOS {5-6%} is fast increasing lately due to change in lifestyle and stress. It is also becoming a common problem in adolescents, developing soon after puberty. Amongst infertile women,about 20% infertility is attributed to anovulation caused by PCOS. Some of the women who develop cardiovascular disease, hypertension,endometrial cancer and type 2 diabetes later in life appear to have suffered from PCOS in early years. ***Jakubowicz et al (1997)[2]***

Increased insulin resistance is significantly associated with the long-term risks of metabolic syndrome and cardiovascular disease ***Ganie et al (2011)[3]***

- Etiology of the syndrome has remained unknown although it has been revealed that, synthesis of high levels of androgen and insulin-resistance (IR) lies at the core of its pathophysiology (AN Schuring) [4]. 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 (L Poretsky et al)[5]. Insulin resistance is a pathophysiological contributor in around 50-80% of women with PCOS. Insulin alter the ovarian steroidogenesis independent of gonadotrophin secretion in PCOS. Insulin and insulin like growth factor I (IGF-I) receptor are present on ovarian stromal cells. A specific defect in early step of insulin receptor mediated signaling was identified in 50 % patient of PCOS. (Ehrmann DA et al)[6].

Aim and Objective

The purpose of the study was to know the effect of N-acetyl cysteine (NAC), Metformin and Vitamin-D3 with Calcium on fasting plasma glucose, fasting insulin and fasting glucose/insulin ratio.

Material and method- The present study was done in the Swaroop Rani Nehru hospital, Department of Obstetrics and Gynaecology, MLN Medical College, Allahabad over a period of 12 months. The study was carried out in 66 women of reproductive age group, with characteristics of PCOS fulfilling two out of three rotterdom criteria in the age group of 15-40 years Women with systemic and endocrine disorders, late onset Congenital Adrenal Hyperplasia, Cushing's Syndrome, Thyroid dysfunction, Hyper prolactinemia, Diabetes mellitus, Coronary heart disease, on medication known to alter insulin hemodynamic, Ovulation index, OCPs and anti-obesity drugs within three months were excluded from study.

Approval was obtained from the ethical committee of the institution. A written informed consent was obtained from all subjects prior to the performance of any study related procedure.

A detailed history was taken with special reference to age, parity, habitat, socioeconomic status, education, and personal habits such as nutrition and exercise.

Special focus was on menstrual pattern such as oligomenorrhoea (interval between menstrual periods ≥ 35 days amenorrhoea(absence of vaginal bleeding for at least six months), clinical hyperandrogenism (a Ferriman-gallwey score ≥6) and/or biochemical hyperandrogenism (total testosterone (TT) ≥ 58ng/dl (2nmol/l)) to test for PCOS.

History of obesity, palpitations, hypertension, cardiovascular risk factors, and impaired glucose tolerance was taken. The patients were also asked about history of diabetes-mellitus, thyroid disorder, congenital adrenal hyperplasia and adrenal tumours. A thorough clinical examination including general condition, built, height, weight, body mass index, waist/hip ratio, feature of hirsutism (increased facial hair, acne), thyroid gland examination, breast examination for galactorrhoea was done. In married women per speculum examination was done for inspecting vagina and cervix and bimanual per vaginum examination was also done. Clinical and hormonal assessments was done at baseline and repeated after 12 weeks of treatment.

RESULT –

66 cases were divided into three groups. Each group had 22 patients. Group 1received NAC,600 mg three times a day,Group 2 Metformin hydrochloride 500 mg two times a day for one week, then three times a day for rest of study and Group 3 Vit-D3 60,000 IU weekly and Calcium 1500mg daily. Carbohydrate metabolic parameters were measured before treatment and after 12 weeks of treatment.

Table 1 Fasting Plasma glucose (Pre-treatment and post treatment)

FBS (mg/dl)	Group 1				Group 2				Group 3			
	Pre treatment		Post treatment		Pre treatment		Post treatment		Pre treatment		Post treatment	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<110	17	77.27	21	95.45	18	81.81	21	95.45	17	77.27	20	90.90
110-126	3	13.63	1	4.54	3	13.63	1	4.54	3	13.63	2	9.09
>126	2	9.09	0	0	1	45.45	0	0	2	9.09	0	0
Total	22	100	22	100	22	100	22	100	22	100	22	100
Mean±SD	99.45.±13.66		87.77±8.585		99.40±11.15		93.09±7.315		97.95±14.89		93.31±10.39	

Before treatment, Group 1 had 17 women (77.27%) with <110 FBS, 3 women (13.63%) in 110 to 126 FBS and 2 women (9.09 %) with >126 FBS. Group 2 had 18 women (81.81 %) with <110 FBS, 3 women (13.63%) in 110 to 126 FBS and 1 woman with >126 FBS. Group 3 had 17 women (77.27 %) with <110 FBS, 3 women (13.63 %) in 110 to 126 FBS and 2 women (9.09 %) with >126 FBS.

Post treatment, Group 1 had 21 women (95.45 %) with <110 FBS, 1 women (4.54 %) in 110 to 126 FBS and zero women with >126 FBS. Group 2 had 21 women (95.45 %) with <110 FBS, 1 woman (4.54 %) in 110 to 126 FBS and no woman with >126 FBS. Group 3 had 20 women (90.90 %) with <110 FBS, 2 women (9.09 %) in 110 to 126 FBS and nowoman with >126 FBS.

Table 2 Effect on Fasting Plasma Glucose

Groups	Pre treatment	Post treatment	Paired test p value
Group 1	99.45.±13.66	87.77±8.585	0.0001
Group 2	98.68±10.021	92.86±6.951	0.0028
Group 3	97.95±14.89	93.31±10.39	0.0002
Anova test p value	0.929	0.1135	

After 3 months of treatment, Fasting Plasma Glucose decreased significantly in all the three groups.(Group 1 p=0.0001 ,Group 2 p=0.0028, Group 3 p=0.0002). However, the difference in mean value between three groups before treatment and post treatment remained statistically insignificant (p=0.929 and p=0.1135respectively)

Table 3 Serum Fasting Insulin Level (pre Tt and post Tt)

Serum Fasting Insulin Level (µU/ml)	Group 1				Group 2				Group 3			
	Pre Tt		Post Tt		Pre Tt		Post Tt		Pre Tt		Post Tt	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
2 to 20	12	54.54	20	90.90	8	36.36	18	81.81	6	27.27	16	72.72
>20	10	45.45	2	9.09	14	63.63	4	18.18	16	72.72	6	27.27
Total	22	100	22	100	21	100	22	0	22	100	22	100
Mean±SD	17.88 ± 5.39		10.72 ± 5.27		19.60 ± 6.31		13.87 ± 5.72		20.94 ± 4.81		16.31 ± 4.77	

Before treatment in Group 1, 12 cases (54.54 %) had the level of serum fasting insulin between 2-20 µU/ml and 10cases (45.45 %) the level of serum fasting Insulin>20 µU/ml with a mean of 17.88 ± 5.39µU/ml. In Group 2, 8 cases (36.36 %) had the serum fasting insulin 2-20 µU/ml and 14 cases (63.63 %) serum fasting I nsulin > 20 µU/ml with the mean of19.60 ± 6.31µU/ml. In Group 3, serum fasting insulin 2-20 µU/ml was observed in 6 cases (27.27 %) and 16cases(72.72 %) had serum fasting insulin >20 µU/ml with the mean of 20.94 ±4.81 µU/ml.
After treatment in Group 1, 20 cases (90.09 %)had the s. fasting insulin 2-20 µU/ml and only 2 case (9.09 %) had the s.insulin >20 µU/ml with the mean of 10.72 ± 5.27 µU.ml. In Group 2, 18 cases (81.81%) had serum fasting insulin 2-20 µU/ml and only 4 cases (18.18%) had s.insulin > 20 µU/ml with the mean of 13.87 ± 5.72µU/ml .In Group 3,16 cases (72.72%) had s. fasting insulin 2-20µU/mland 6 cases (27.27 %) had s insulin > 20 µU/ml with mean value of 16.31 ± 4.77 µU/ml.

Table 4 Effect on Serum Fasting Insulin Level

Groups	Pre Tt	Post Tt	Paired test p value
Group 1	17.88 ± 5.39	10.72 ± 5.27	0.0001
Group 2	19.60 ± 6.31	13.87 ± 5.72	0.0001
Group 3	20.94 ± 4.81	16.31 ± 4.77	0.0001
ANOVA test p value	0.1854	0.0040	

After 3 months of treatment, s. fasting insulin decreased significantly in all the three groups. (p=0.0001). The difference in mean value between three groups before treatment was statistically insignificant (p=0.1854). However, post treatment, significant difference between three groups was observed (p<0.0040). The difference between Group 1 and Group 2 was found to be statistically significant (p< 0.0083). However greater reduction in serum fasting insulin was observed in Group 1.The difference in mean value between Group 1 and Group 3 was statistically significant (p<0.0001).The difference between Group 2 and Group 3 was statistically insignificant (p<0.0598).

Table 5 Fasting glucose/Fasting insulin ratio(Pretreatment and post treatment)

Fasting glucose/ Fasting insulin ratio	Group 1				Group 2				Group 3			
	Pre treatment		Post treatment		Pre treatment		Post treatment		Pre treatment		Post treatment	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
2.4 to 4.5	11	50	5	22.72	10	45.4	4	18.18	10	45.45	6	27.27
> 4.5	11	50	17	77.27	12	54.5	18	81.81	12	54.54	16	72.72
Total	22	100	22	100	22	100	22	100	22	100	22	100
Mean±SD	**4.63±1.26**		**6.21±2.13**		**4.71±1.03**		**6.71±1.98**		**4.68±1.13**		**6.01±1.68**	

Before treatment in Group 1, 11 women (50%) had the ratio between 2.4 to 4.5 and 11 women (50%) had the ratio >4.5. Group 2 had 10 women (45.4%) with the ratio between 2.4 to 4.5 and 12 women (54.5%) with ratio >4.5. Group 3 had 10 women (45.4%) with the ratio between 2.4 to 4.5 and 12 women (54.5%) with the ratio >4.5.

Post treatment, in Group 1, 5 women (22.72%) had the ratio between 2.4 to 4.5 and 17 women (77.27 %) had the ratio >4.5. Group 2 had 4 women (18.18 %) with the ratio between 2.4 to 4.5 and 18 women (81.81%) with ratio >4.5. Group 3 had 6 women (27.27%) with the ratio between 2.4 to 4.5 and 16 women (72.72%) with the ratio >4.5

Table 6 Effect on Fasting glucose/Fasting insulin ratio

Groups	Pre Tt	Post Tt	Paired test p value
Group 1	4.63±1.26	6.21±2.13	0.001
Group 2	4.71±1.03	6.71±1.98	0.001
Group 3	4.68±1.13	6.01±1.68	0.004
Anova test p value	0.2254	0.0035	

After 3 months of treatment, s. fasting insulin decreased significantly in all the three groups. (p=0.0001). The difference in mean value between three groups before treatment was statistically insignificant

(p=0.2254). However post treatment, significant difference between three groups was observed (p=0.0035).

DISCUSSION - N- Acetyl Cystein is not found in the diet, but is available as a nutritional supplement. Whereas the mechanisms of NAC are only beginning to be understood, it is likely that NAC is exerting benefits beyond being a precursor to the antioxidant, glutathione, modulating glutaminergic, and inflammatory pathways. Side effects of NAC includes nausea, vomiting, and diarrhea or constipation. Rarely it can cause rashes, fever, headache, drowsiness, low blood pressure. Symptomatic treatment is required for the treatment of these side effects.

Metformin, (molecular formula $C_4H_{11}N_5$) is an oral antidiabetic drug in the biguanide class. It is an insulin sensitizer and works by suppressing glucose production by the liver.

Antidiabetic therapy has been proposed as a treatment for polycystic ovary syndrome (PCOS), a condition frequently associated with insulin resistance, since the late 1980s. The use of metformin in PCOS was first reported in 1994, in a small study conducted at the University of the Andes, Venezuela. Treatment with metformin might indeed decrease the risk of developing diabetes and heart disease in women with PCOS. The most logical candidates for treatmen with metformin are women with impaired glucose tolerance or diabetes, those with obvious evidence of severe insulin resistance and women having other features of metabolic syndrome such as central obesity, hypertension and dyslipidemia.

The beneficial effects of metformin are based on alleviation of insulin excess acting upon ovary and through direct ovarian effects. Insulin was shown to directly stimulate several steroidogenic enzymes in the ovary, such as CYP17, 3β-HSD and StAR protein. By improving insulin sensitivity, metformin reduces CYP17 activity.

Metformin is currently used as an antihyperglycemic agent. It is accepted that the main effect of this drug is to decrease hepatic glucose production through a mild inhibition of the mitochondrial respiratory-chain complex . As a consequence, the resulting transient decrease in cellular energy status promotes activation of AMPK, a well-known cellular energetic sensor. Consequently, metformin-induced AMPK activation is believed to promote transcriptional inhibition of hepatic gluconeogenic program. Additionally, AMPK-dependent mechanisms linked to the action of metformin on hepatic lipid metabolism are also proposed, notably for explaining its beneficial effect on hepatic steatosis and insulin resistance, leading to the normalization of blood glucose levels.

Currently Vitamin-D deficiency has also been implicated as the cause of insulin resistance and the development of PCOS. 1-25hydroxy vitamin D is positively correlated with insulin sensitivity and negatively with beta cell function. Vitamin D is thought to play a role in the pathogenesis of type 2 diabetes by affecting insulin metabolism. Vitamin D3 enhances insulin action by enhancing insulin synthesis & release, increased insulin receptor expression and/ or suppression of proinflammatory cytokines that are believed to mediate insulin resistance.

CONCLUSION-

Thus from the above study we conclude that -

1. Greater reduction in serum fasting insulin was observed in group receiving N-Acetyl cysteine (10.72±5.27 from 17.88±5.39) as compared to group receiving Metformin and Vitamin D3 with Calcium (13.87±5.72 from 19.60 ± 6.31 and 16.31±4.77 from 20.94 ± 4.81respectively).
2. After 3 months of treatment a significant difference in fasting plasma glucose/ fasting insulin ratio between three groups was observed (p=0.0035).
3. The difference in mean value of fasting plasma glucose/ fasting insulin ratio between Group 1 and Group 2 was insignificant. ($p>0.05$) and between Group 2 and Group 3 ($p<0.05$) as well as in Group 1 and Group 3 ($p<0.01$) was significant.

Highly significant changes brought by a 12 week course of treatment with NAC suggested that, longer treatment with N-acetyl cysteine may result in more desirable outcomes, such as more effective control of clinical symptoms of PCOS,and carbohydrate parameters with lesser side effects than metformin .

Vitamin D deficiency is the basic pathophysiology for PCOS, hence Vitamin D3 with Calcium supplementation can be tried in the management of PCOS to improve insulin sensitivity. Beneficial effects of Vitamin D3 support a future therapeutic role in women with PCOS.

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