Original Article

Polycystic Ovarian Syndrome

Study of Insulin Resistance and Glucose Transporter Protein 4 in Polycystic Ovarian Syndrome

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ABSTRACT

Objective: To evaluate the relationship of Glucose transporter protein 4 and insulin resistance in patients of polycystic ovarian syndrome of various age groups.

Study Design: Case control study

Place and Duration of Study: This study was conducted at the Department of Gynaecology, Jinnah Hospital, Lahore from November 2018 to April 2019.

Materials and Methods: This study included 58 polycystic ovarian syndrome women with age ranging between 18-45 years, subdivided into three age groups. Rotterdam's criteria were used to confirm the diagnosis of Polycystic ovarian syndrome.

Results: The interpretation of the results revealed significantly high level of serum insulin and insulin resistance in patients suffering from Polycystic Ovarian Disease. Glucose transporter protein-4 levels in patient group were not found to be statistically significantly different in comparison to control.

Conclusion: Insulin level in serum and insulin resistance is strongly associated with poly cystic ovarian syndrome. However, deranged glucose transporter protein- 4 is not always the case.

Key Words: Serum Insulin, Insulin resistance, Glucose Transporter Protein, Polycystic ovarian Syndrome

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a multifectorial, multigenic condition and its occurrence is increasing with time in our society.[1] A large number of environmental and genetic factors are associated with PCOS.[2] In addition, it's the commonest endocrine disorder and a well known causative factor for infertility caused by inovulation.[3]

Polycystic ovarian syndrome is well known to girls and women of reproductive age, who belong to every races and nationality. In developed countries PCOS is affecting 14% of women. Its more prevalent in developing countries like India, where 31% of the females between 20-40 years of age are effected.[4]

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Prevalence rate of 20.7% has been found amongst women of reproductive age in Pakistan.[5]

Commonest associated factor with PCOS is insulin resistance (IR). In one study IR is found to be present in nearly 70% of patients suffering from PSOC. High body mass index and hyperinsulinemia are also present along with IR.[6] Homeostatic Model Assessment (HOMA) is an effective arithmetic method for calculating insulin resistance. It is calculated from the product of serum insulin level and fasting blood glucose level (fasting blood glucose-level x serum insulin- level/22.5).[7]

Major insulin dependent transporter in tissue, Glucose Transporter 4(GLUT-4), plays a key role in regulation of body's glucose metabolism.GLUT-4 levels have been found to be decreased to a considerable level in insulin resistant patients of PCOS.[8] Secondary to resistance to human insulin, GLUT-4 do not travel effectively to cell surface and start to accumulate in membrane compartments inside the cell.[9] In PCOS effected women GLUT-4 decrease of 50 % causes similar decrease in adipocyte GLUT-4 translocation in spite of obesity and IR. [10]

MATERIALS AND METHODS

The present study included 58 PCOS affected women between 18-45 years of age. Patients were selected from Gynaecology Department of Jinnah Hospital, Lahore, Pakistan, both from outdoor and indoor

facility, in a time period of six months from 1st November 2018 to 30th April 2019. Rotterdam's criterion was applied to select polycystic ovarian syndrome patients. This criterion takes into consideration presence of hyperandrogenism, anovulation and ultrasonographic finding of polycystic ovaries. Women suffering from other endocrinological abnormalities including thyroid dysfunction, hyperprolactinaemia, Cushing's syndrome and tumours of endocrine origin were excluded from the study. Depending upon the age, individuals were categorized further into Patient and Control group having age between 18-24 year, Patient and Control group with age in between 25-35 years and Patient and Control group with age ranging between 36-45 years. SPSS 17 software was used for data analysis. Student t test and Pearson coefficient correlation was applied to express and compare various variables between control and patient group of all three age categories.

RESULTS

Table 1 enlists the mean value of variables along with significance levels. In present study, levels of BMI, Fasting blood sugar level, fasting insulin level and insulin resistance seems to increase with age i.e .lowest in patient age 18- 24 and highest in patient age 36-45 year old. Significant differences ($P<0.05$) were observed, in between Patient and Control group of all ages, for fasting serum insulin level, fasting serum glucose level and HOMA insulin resistance calculation However, GLUT-4 levels did not show a consistent increase with age increase and the difference was statistically not significant in all age groups in present study.

The blood glucose was more significantly altered in child bearing age to 119 mg% serum insulin, 33.83 IU/ml as compared to controls in the same age group the values of which were 94 mg% insulin, 3.3 IU/ml respectively. For young girls aged 18-24, glucose was 98 mg% and insulin was 9.31 IU/ml while the values for glucose and insulin in controls of this group were 79 mg% and 3.34 IU/ml respectively. For 36-45 years, the values were glucose 122 mg% and insulin, 42.40 IU/ml while for the controls they were 92 mg%, 3.31 IU/ml. Glucose insulin ratio was 3.44 in the child bearing age (25-35), while for controls it was 28.48. In young girls aged 18-24, it was 10.63, while the value for controls was 24.24. For ages 36-45, the glucose insulin ratio was 2.88 and for controls it was 27.86.

By looking at the table 2 of Pearson Coefficient Correlation, it can be observed that a significant negative correlation exist between parameters serum fasting insulin level and GLUT-4 only in patients of 18-24 years of age ($r = -0.51$). The only significant positive correlation can be seen between Glucose Insulin Ratio and GLUT-4 in patients of age group 36-45 years ($r = 0.6$).

Table No.1: BMI & Biochemical Parameters of PSOC Patients vs Control (age in yrs).

Variable	Patient Age 18-24 (n=15)	Control Age18-24 (n=20)	Patient Age 25-35 (n=39)	Control Age 25-35 (n= 20)	Patient Age 36-45 (n= 16)	Control Age 36-45 (n= 10)
Body Mass Index (kg/m^2)	26.86±0.86	23.60±1.94	29.77±4.39	28.60±1.12	32.63±4.22**	23.60±2.1
Blood glucose Fasting (mg/dl)	98.74±20.27*	80.1±8.4	119.16±14.94**	94.0±8.5	122.93±5.02**	92.0±8.5
Serum Insulin Fasting (µU/ml)	9.32±0.33**	3.6±2.5	23.83±15.83**	3.3 ± 2.6	42.4±6.87**	3.5±2.1
Glucose insulin ratio (GIR)	10.60	24.24	3.52	28.48	2.90	27.87
HOMA- IR	1.23±0.12**	0.43±0.06	4.46±2.7**	0.44 ± 0.6	5.56±1.1**	0.43 ± 0.6
GLUT-4 (arb. Units	5.01±4.43	4.28±2.43	4.77±4.08	4.22±0.54	6.37±5.89	4.28±2.43

*P<0.05= Significant **P<0.001= Highly significant

Table No. 2: Pearson correlation PSOC Patients VS Control

Coefficient of determination (r value) between variables	Age (years)		
	18-24	25-35	36-45
Body Mass Index and GLUT-4	0.06	0.09	-0.14
Fasting insulin & GLUT-4	-0.51	0.2	0.25
Glucose insulin ratio & GLUT-4	-0.34	0.18	0.62

DISCUSSION

Polycystic ovarian syndrome is a common well recognized condition in women with child bearing age.[11,12] The present study delineated that PCOS is commoner in patients belonging to age 25-35 years .Nevertheless, previous studies have reported that PCOS effects a vast range of women of reproductive age ranging from 15- 45 years.[13] It was noted in another study that PCOS is more prevalent in younger age group ranging between 18-24 years.[14]

In our present study it was noticed that fasting blood glucose levels and fasting serum insulin levels were not only significantly high amongst all age groups in comparison to control but these levels also increased consistently with age. It was also observed that insulin resistance increases with age being lowest in youngest age group and highest in oldest age group. It is consistent with previous studies in which 1/3 of the

PCOS patients under study had increased IR at mean age of 40 years.[15] It was observed in an invitro study that hormone levels and ovarian morphology changes as age advances. Possibility lies that metabolic abnormalities including insulin resistance worsen as age advances in patients of PCOS.[16]

Glucose transporter protein-4 was determined in all age groups, both in PCOS women and control, and it was found out that GLUT-4 was significantly low only in the child bearing age (25-35 years). GLUT-4 was 4.77 arbitrary units in this age group as compared to others as around 5-6 arbitrary units. Previous studies demonstrated the role of GLUT-4 in the muscles of the uterus for the transport of glucose as reported by Bryant et al.[17] The expression of GLUT-4 is seemed to be well maintained in menstrual cycle dependent way in the uterine endometrium.[18]

Since GLUT-4 is insulin dependent transporter level of insulin is also measured and compared with it.[19] The correlation of with GLUT-4with other parameters is positive for ages 25-35 years but non significant in our study. Previous studies demonstrated variation in insulin secretion.[20] It is a consistent finding in our study in comparison to previous literature that metabolic abnormalities may worsen with age in women having PCOS .[16]

CONCLUSION

Patients of all age groups with polycystic ovarian syndrome had significantly raised fasting blood glucose level, fasting serum insulin level and also significantly increased insulin resistance. And an upward trend has been noticed with increasing age. However GLUT -4 levels were not found to be raised significantly in any age group and also did not show a significant correlation pattern with other parameters in various age groups.

Author's Contribution:

Concept & Design of Study:	Roohi Jabbar
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Data Analysis:	Atif Zia, Sadia Amir, Sadia Naz
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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Ehrmann DA. Metabolic dysfunction in PCOS: relationship to obstructive sleep apnea. Steroids 2012; 77(4): 290–94.
2. Diamanti-Kandarakis E. Insulin resistance in PCOS. Endocrine 2006;30 (1): 13–7.
3. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 2013;6:1–13.
4. Majumdar A, Singh TA. Comparison of clinical features and health manifestations in lean vs. obese Indian women with polycystic ovarian syndrome. J Hum Reprod Sci 2009;2(1):12-7.
5. Arain F, Arif N, Halepota H. Frequency and outcome of treatment in polycystic ovaries related infertility. Pak J Med Sci 2015;31(3):694–9.
6. Shaw LJ, Bairey-Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. J Clin Endocrinol Metab 2008;93, 1276–84.
7. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. Indian J Endocrinol Metab 2015;19(1):160–64.
8. Chen YH, Heneidi S, Lee JM, Layman LC, Stepp DW, Gamboa GM, et al. miRNA-93 inhibits GLUT-4 and is overexpressed in adipose tissue of polycystic ovary syndrome patients and women with insulin resistance. Diabetes 2013;62(7): 2278-86.
9. Stoval DW, Baily AP, Pastore LM. Assessment of Insulin Resistance and Impaired Glucose Tolerance in Lean Women with Polycystic Ovary Syndrome. J Women's Health (Larchmt) 2011; 20(1): 37–43.
10. Kim JY, Song H, Kim H, Kang HJ, Jun JH, Hong SR, et al. Transcriptional profiling with a pathway-oriented analysis identifies dysregulated molecular phenotypes in the endometrium of patients with polycystic ovary syndrome. J Clin Endocrinol Metab 2009; 94: 1416–26.
11. Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 2000;85:2434–8.
12. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89: 2745–9.
13. Kumarapeli V, Seneviratne RA, Wijeyaratne CN, Yapa RM, Dodampahala SH. A simple screening approach for assessing community prevalence and phenotypes of polycystic ovary syndrome in semi-urban population in Srilanka. Am J Epidemiol 2008;168: 321–7.
14. Li R, Zhang Q, Yang D, Li S, Lu S, Wu X, et al. Prevalence of polycystic ovary syndrome in

women in China: A large community based study. Hum Reprod 2013; 28: 2562–9.
15. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002; 287: 356–9.
16. Alsamarai S, Adams JM, Murphy MK, et al. Criteria for polycystic ovarian morphology in polycystic ovary syndrome as a function of age. J Clin Endocrinol Metab 2009; 94: 4961–70.
17. Bryant NJ, Govers R, James DE. Regulated transport of the glucose transporter GLUT-4. Nat Rev Mol Cell Biol 2002;3:267–77.
18. Mioni RB, Mozzanega M, Granzotto A, et al. Insulin receptor and glucose transporters mRNA expression throughout the menstrual cycle in human endometrium: a physiological and cyclical condition of tissue insulin resistance. Gynecol Endocrinol 2012; 28: 1014–8.
19. Frolova AI, Moley KH. Glucose transporters in the uterus: an analysis of tissue distribution and proposed physiological roles. Reproduction 2011; 142: 211–20.
20. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997; 18: 774–800.