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Hyperandrogenism leads to alteration of liver enzymes in Poly Cystic Ovarian Syndrome in the background of Insulin Resistance: a cross sectional study

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ABSTRACT: Polycystic ovary syndrome (PCOS), is a rapidly growing endocrinal disorder, affecting women of reproductive age group. Insulin resistance and metabolic syndromes are associated PCOS which is thought to have a key role in its pathogenesis and progression of Non Alcoholic fatty liver disease (NAFLD).Present study is aiming to ascertain possible association between Liver enzymes with free testosterone and insulin resistance: two important diagnostic markers for PCOS; further trying to elucidate if any of the above enzyme might correlating better with free testosterone level in the back ground of insulin resistance among drug- naive diagnosed PCOS cases. An observational case control study was performed among 102 patients attending Gynaecology OPD aged between 16 to 40 years.Their Fasting Insulin, glucose, ALT, AST, GGT, ALP, free testosterone were measured, IR was calculated by the HOMA-IR calculator. Sonography was done to assess cystic changes. Using unpaired student's t- test it has been found that there is significant differences between the mean values of ALT, AST, GGT, IR, free testosterone in control and PCOS group. Further grouping was done using the cut-off value of Insulin Resistance (1.95) among cases. Significant differences is found between the mean values of ALT, GGT & free testosterone level among two groups.By Pearson correlation test it is found that there is significant positive concordance between liver enzymes ALT, GGT and free Testosterone level among cases having insulin resistance ≥ **1.95.**By linear regression analysis it has been observed that with Higher GGT values stronger positive correlation found with free testosterone than ALT among cases having insulin resistance ≥ **1.95**(significance at the level p value<0.01).To conclude though both ALT & GGT have positive concordance withhyperandrogenism; GGT among all the liver enzymes are most strongly associated with hyperandrogenism in insulin resistant background.

Keywords: Polycystic ovarian syndrome, Hyperanddrogenism, Insulin resistance, Non alcoholic fatty liver disease

I. INTRODUCTION

Polycystic ovary syndrome (PCOS), is a rapidly growing non-communicable endocrinal disorder, affecting up to 8-12% of women of reproductive age group .[1,2] PCOS is characterized by menstrual and hormonal irregularities resulting in anovulation, hirsutism, obesity and hyperandrogenism[3]. As the long term consequence it may lead to infertility & premature menopause. A number of studies successfully establish the fact that insulin resistance & hyperandrogenism are most common endocrinal irragularities. Currently, a number of guidelines like the NIH consensus criteria [4], the Rotterdam criteria [5] and most recently the clinical practice guideline from The Endocrine Society [6]. Despite some differences, all criteria establish this fact. [3-6]. Hyperandrogenism is characterised by elevated level of serum testosterone seen in the patients of PCOD than other women of reproductive age group [6].

Non-alcoholic fatty liver disease (NAFLD) is the most common type of liver disease among the broad disease spectrum which includes nonalcoholic fatty liver, nonalcoholic steatohepatitis (NASH), liver cirrhosis and hepato-cellular carcinoma, in adults and children worldwide.[7-9] Here also, Insulin resistance is the key pathogenic factor for the metabolic

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derangement of NAFLD.[10] Considering that insulin resistance is a common feature of both NAFLD and PCOS, it would not be surprising that both entities might coexist in a given patient. Recent reports support those women with PCOS having higher prevalence of NAFLD than women without PCOS [11–12]. Generally, in the liver function test Alanine Transaminases (ALT) levels are higher than Aspartate Transaminases (AST) levels in most instances of NAFLD disease spectrum[7,13]. But, In some recent studies, It has been observed that Gamma-Glutamyl-Transferase (GGT), is also elevated in persons having NAFLD[14,15] frequently associated with insulin resistance and higher BMI[16].

But still there is a lacuna of concrete data which can establish the association between PCOD & NFALD in our native population

II. AIMS & OBJECTIVES:

In light of the above understanding, we started our present study is aiming to ascertain possible association between Liver enzymes with free testosterone and insulin resistance: two important diagnostic markers for PCOS; further trying to elucidate if any of the above enzyme might correlating better with free testosterone level in the back ground of insulin resistance among drug- naive diagnosed PCOS cases from urban population.

III. MATERIALS & METHODS:

This observational case control study with was undertaken in the Department of Biochemistry in collaboration with the Department of Obstetrics & Gynaecology, North Bengal Medical College and Hospital, Darjeeling, West Bengal, during the period from July 2016 to June 2017. Total no of 102 non pregnant women coming in the OPD with menstrual irregularities among reproductive age group (16 to 45 years) were included in the study. Women having history of any known endocrinal disorder like Cushing's syndrome, congenital adrenal hyperplasia, thyroid disease, diabetes & women having any history of acute & chronic liver disease, any history of alcoholism, smoking & contraceptive intake were excluded from the study.

Almost 6 ml of blood samples were collected from all women after 8 to 10 hours of fasting, providing proper explanation and taking consents. Blood was collected aseptically in disposable syringes. 2ml of blood immediately transferred into a fluoride containg vial & rest blood was transferred into plain vial to get clotted sample. After that the sample of plain vial was centrifuged in 2500 rpm for 5 minutes. The serum was separated and was kept in aliquots and stored in minus twenty degree Centigrade (-20°C) refrigerator.

For all the subject, thorough physical examinations including anthropometry was performed.

Among laboratory investigations Fasting blood sugar(FBS) , fasting insulin, liver enzymes like alanine aminotransferase(ALT), aspartate amino transferase (AST) , gamma glutamyl transferase(GGT) ,free testosterone were measured. FBS, ALT, AST, GGT were assayed in automated analyser. Fasting insulin and free testosterone were assayed by ELISA method. Insulin resistance calculated by HOMA- IR calculator.

Polycystic changes were diagnosed by Ultrasonography.

Quality assurance of the parameters under study was maintained by internal and external quality assurance.

The data obtained were analysed for by SPSS 22 software and MS-Excel. Results obtained were arranged in tabular and graphical forms as requi

IV. RESULT & ANALYSIS:

The study population consisted of 102 patients attending Gynaecology OPD aged between 16 to 45 years.

The participants were divided into two study groups as follows:

case: women with newly diagnosed PCOS (n=50) and **control:** (n=52).

Using unpaired student's t- test it has been found that there is significant differences between the mean values of ALT, AST, GGT, IR, free testosterone in control and case group. Difference is significant at the ($p < 0.01$) level (vide table-1)**.**

Parameters	Control (52) Mean ±SD	Case (50) Mean ± SD	t value	P value
ALT (IU/ lt)	25.36±1.64	49.56±2.81	-7.5	<0.001**
AST (IU/ lt)	25.59±1.26	34.95±2.65	-3.219	<0.001**
GGT (IU/ lt)	10.036± 0.48	32.26± 1.7	-12.82	<0.001**
ALP (IU/lt)	72.14 ± 2.97	73.21 ± 2.52	-2.06	0.052
Free Testosterone(pg/ml)	2.22±0.14	6.16 ±0.1	-12.59	<0.001**

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IR (HOMA-IR)	1.32± 0.08	2.91± 0.15	-9.35	<0.001**

** Difference is significant at the ($p < 0.01$) level.

Table-1: Comparison of the mean values of Liver enzymes (ALT, AST, GGT, ALP) & markers of PCOS (IR & free testosterone) between control and case group (unpaired Student's t test).

While progressing to further analysis we can exclude ALP as there are no significant differences between the mean values of ALP between case and control groups.

Cut off value of Insulin resistance in this study population is determined by ROC (Receiver Operating Characteristic) curve. Area under the curve is 0.961 which is nearer to 1 (vide figure-1). So the accuracy of the test is very good. The cut off value of IR in the present study population is determined to be 1.95 (p value < 0.001).

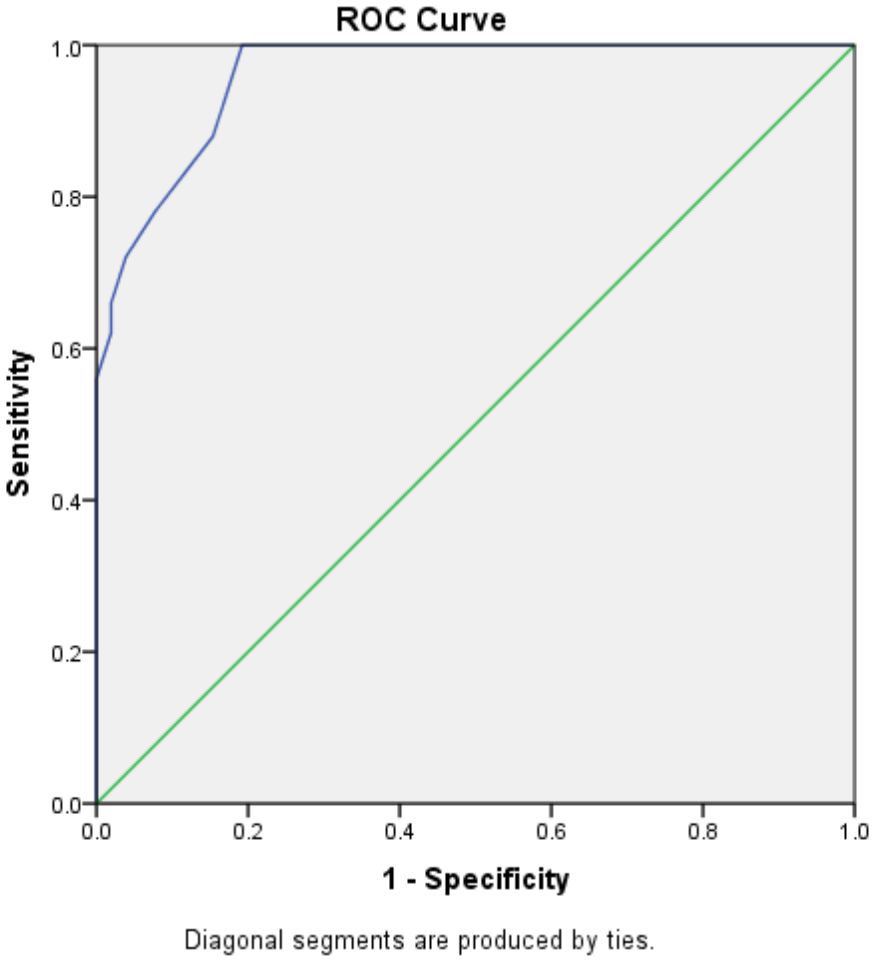

Figure-1: ROC curve for determination of cut off value of Insulin Resistance.

Further grouping was done using the cut-off value of Insulin Resistance (1.95) among cases. Significant differences are found between the mean values of ALT, GGT & free testosterone level among two groups. (i.e. cases without Insulin Resistance and cases who have Insulin Resistance more than the Cut-Off). Difference is significant at the ($p < 0.05$) level. But there is no significant difference found between the mean values of AST among two groups. (Vide table-2).

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Parameters	Cases with IR ≥ 1.95 (32) Mean ±SD	Cases with IR<1.95 (18) Mean ± SD	t value	P value
ALT (IU/ lt)	51.02± 20.59	38.83±8.59	1.42	0.02*
AST(IU/ lt)	36.23±19.43	25.57± 9.55	1.31	0.05
GGT(IU/ lt)	33.89± 11.88	20.31± 0.20	9.51	0.008**
Free Testosterone(pg/ml)	6.27±0.69	5.3±0.45	3.3	0.002**

* Difference is significant at the ($p < 0.05$) level.
** Difference is significant at the ($p < 0.01$) level.

Table-2: Comparison of the mean values of Liver enzymes (ALT, AST, GGT) & free Testosterone between groups (Cases with IR ≥ 1.95) & (Cases with IR<1.95) (unpaired Student's t test)

By Pearson correlation test it is found that there is significant positive concordance between liver enzymes ALT, GGT and free Testosterone level among cases having insulin resistance ≥ 1.95. Difference is significant at the ($p < 0.05$) level.

But when significance is brought down to $p < 0.01$ level only GGT is found to have strong positive correlation with free testosterone level.(vide table-3, figure-2, figure-3)

		ALT	AST	GGT
Free Testosterone	**Pearson Correlation coefficient (r)**	0. 317*	0.140	0.675**
	Significance (p) 2- tailed	0.025	0.286	<0.001

* Correlation is significant at the ($p < 0.05$) level.
**. Correlation is significant at the ($p < 0.01$) level.

Table-3: Showing correlation between free Testosterone & Liver enzymes (ALT, AST, GGT) among case shaving insulin resistance ≥ 1.95.

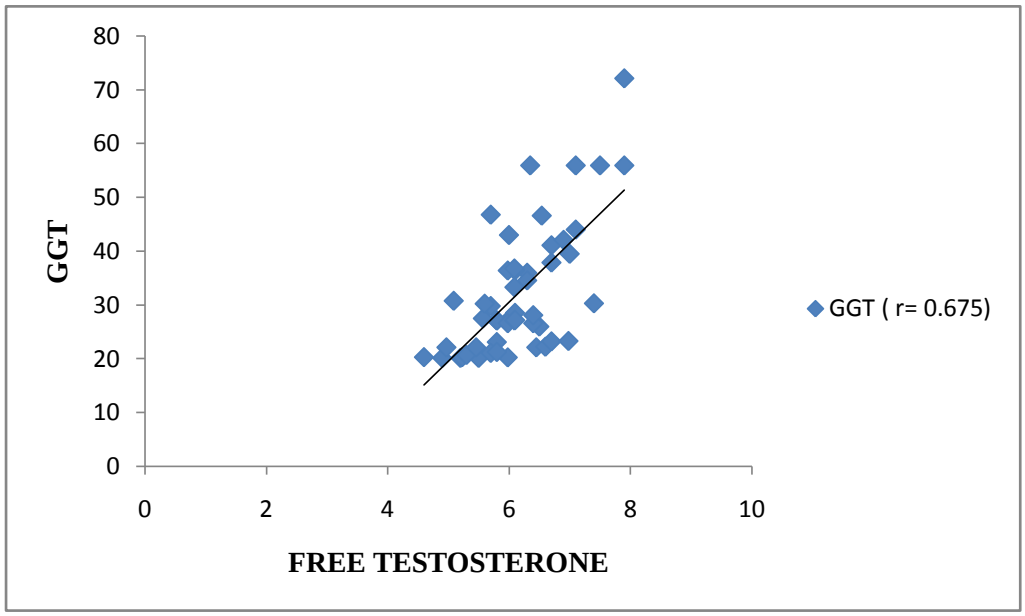

Figure no- 2: Showing Correlation between GGT and free Testosterone.

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Figure no- 3: Showing Correlation between ALT and free Testosterone.

Having ALT and GGT positively correlating with free Testosterone in presence of insulin resistance≥ **1.95**, further linear Regression analysis has been performed to ascertain which one of them predicts better increase in free testosterone level in this scenario. By linear regression analysis it has been observed that with Higher GGT values stronger positive correlation found with free testosterone than ALT among cases having insulin resistance ≥ **1.95**. While standardized beta coefficient for GGT is 0.620 (p value < 0.001), beta coefficient for ALT is only 0.022.(vide table-4).

Parameters	**Standardized Coefficients Beta**	**T value**	**Significance (two tailed)**
ALT in presence of IR (≥ 1.95) (n=32)	.022	0.165	0.870
GGT in presence of IR (≥ 1.95) (n= 32)	.620	**4.71**	**<0.001****

** Correlation is significant at the (p< 0.01) level (2-tailed).

Table-4: Showing Beta coefficient of ALT & GGT for predictability of increase in free testosterone level among drug- naive diagnosed PCOS cases (IR≥ 1.95) by linear regression model.

V. DISCUSSION:

Polycystic ovary syndrome is among the most common endocrine diseases in women, affecting up to 10% of women of reproductive age. The primary pathophysiological defect is unknown, and not fully understood, resistance of insulin, androgen excess and impaired gonadotropin dynamic play a role in the development of this disease [17]. Levels of the sex hormones progesterone and estrogen are out of balance in condition of PCOS, this can cause problems with women's menstrual cycle, fertility, leads to growth of ovarian cysts (benign masses on the ovaries). [18]. PCOS is not only a gynecological condition, but also a syndrome comprehensive with a variety of metabolic disorders associated commonly with PCOS [19, 20].

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Prevalence of NAFLD is increasing in adolescents and young population nowadays and is now increasingly recognized as a major cause of liver-related morbidity and mortality. Studies introduced that NAFLD may progress to cirrhosis, liver failure, and hepatocellular carcinoma. It has been shown that NAFLD is strongly associated to the features of metabolic syndrome. Insulin resistance is the key pathogenic factor in both NAFLD and metabolic syndrome. Both peripheral and hepatic insulin resistance is present in patients with NAFLD, irrespective of the coexistence of impaired glucose tolerance or obesity. NAFLD is often diagnosed after the finding of mildly abnormal LFTs.It happens to be the most common cause of elevated Transaminases other than viral and alcoholic hepatitis[7-9]. It has also been found that GGT is elevated in persons having NAFLD frequently associated with insulin resistance and higher BMI[16].

This study was conducted among 102 individuals between 18-40 years age attending gynaecology opd. The participants were divided into two groups; cases: **case:** women with newly diagnosed drug naïve PCOS (n=50) and **control:** healthy, eumenorrheic, nonhirsute control women(n=52).

In the present study it has been observed that cases having higher values of ALT, AST, GGT, free Testosterone & IR than the healthy individuals (IR- 2.91 ± 0.15 vs 1.32 ± 0.08)].The difference between the two groups is significant at the level of p value < 0.01. But there is no significant difference between the mean values of ALP between two groups which implies that ALP is not affected in PCOS patients. A good number of study were conducted in the recent past and their finding is unison.A Faisal, A Nasser, AZ Zyiton etal. stated in their study that Risk factors of elevated ALT, AST & GGT associated ultrasonic diagnosed NAFLD in PCOS patients were the metabolic-related factors such as high BMI,high fasting glucose, and dyslipidemia. These results were similar to that studied by C Cerda et al.[12].

Now when it becomes evident that PCOS affects liver to a variable extent and that is reflected through elevated liver enzymes ALT, AST & GGT we tried to establish this affection in the light of Insulin Resistance. Many studies have already shown that insulin resistance is the common etiological factor in both PCOS & NAFLD [21].

First cut off value of Insulin Resistance is determined by ROC curve and it is found to be 1.95 with P value <0.001.Further analysis was done among the drug naive PCOS patients. We divided the cases into two groups i.e. cases with Insulin Resistance <1.95 and cases who have Insulin Resistance >/= 1.95. By unpaired students t test it has been found that PCOS patients having IR >/= 1.95 showed higher level of ALT, GGT, free Testosterone than patients having IR below the cut-off. [(ALT- 51.02± 20.59 vs 38.83 ± 8.59 IU/lt), (GGT- 33.89 ± 11.88 vs 20.31 ± 0.20 IU/lt), (free Testosterone - 6.27±0.69 vs 5.3 ±0.45 pg/ml). difference is significant at level (p <0.05). No significant difference is found in case of AST level between aforesaid groups. Though TL Setz, ND Holland et.al concluded in their study that abnormal values of both the aminotransferases are very commonin women with PCOS. From our findings of t test statistics it is very much evident that insulin resistant drug naive PCOS patients have abnormally high liver enzymes specially ALT & GGT which also supports the possibility of NAFLD in them. Though there is not enough study directly supporting elevated GGT level in drug naive insulin resistant PCOS but A very few studies are found to directly or indirectly support the finding of the present study. R. Haring, H. Wallaschofski et al. in 2009 found in their study that GGT is frequentlyelevated in NAFLD and may also be a marker of increased mortality [14]. S. Akila, R. Deepti et al also concluded in their study in 2014 that NAFLD with MetS (Insulin Resistant condition) had increased serum GGT level [22]. As insulin resistance also contributes to PCOS we can state that serum GGT level can be elevated in insulin resistant PCOS patients.

Further statistical analysis has been done to find out is there any Enzyme better correlating with free testosterone level in the back ground of insulin resistance among drug- naive diagnosed PCOS cases and an interesting finding came into the light. Let's explore that in further discussion.

When Pearson correlation test performed it was found that there is significant positive concordance between liver enzymes ALT, GGT and free Testosterone level among cases having insulin resistance ≥ 1.95. Difference is significant at the (p < 0.05) level. The correlation coefficient (i.e. r) is found to be higher in case of GGT than ALT. The finding implies that GGT has more positive concordance with free testosterone level than ALT in the scenario of insulin resistance among drug naïve PCOS cases.

Having ALT and GGT positively correlating with free Testosterone level in presence of insulin resistance, further linear Regression analysis has been performed to ascertain which one of them predicts better about increase in free testosterone level in this scenario. While standardized beta coefficient for GGT is 0.620 (p

value < 0.001), beta coefficient for ALT is only 0.022. So it can be derived that with higher GGT values stronger predictability was found with increase in free testosterone level than ALT among PCOS cases having insulin resistance > 1.95.

Hyperandrogenism has not only been reported to beassociated with the polycystic ovary morphology but has also been reported to have a strong association with the presence of metabolic syndrome, dyslipidemia, and insulin resistance, independent of obesity, in women with PCOS . Several previous study already suggested androgens were speculated to have a harmful effect on liver function. [23, 24, 25]. The prevalence of elevated ALT in women with PCOS varies among different studies, from 21%to 39% owing to different ALT cutoff level and selected population [21].

Our present study also goes in agreement with above statement. But there is another interesting finding came into light that though ALT & GGT both are positively correlated with free testosterone in insulin resistant drug naive PCOS patients; GGT has found to have better concordance than ALT. This is a very new finding, there is not enough study supporting this finding. As oxidative stress is very high in both the condition PCOS and NAFLD and is directly proportional to the degree of Insulin Resistance, GGT being intracellular defence against oxidative stress often found to be chronically elevated in

NAFLD. Increased GGT level not only reflects the hepatic oxidative stress but also its association with insulin resistance (22). So we can say that GGT is rightly associated with free Testosterone level (an important biomarker for PCOS) in drug naïve insulin resistant PCOS patients though the population-based vivid evaluation is highly recommended.

VI. CONCLUSION:

In conclusion, the findings of our study are consistent with the hypothesis. Not only a good positive correlationfound between Liver enzymes ALT and GGT (markers of NAFLD) with free testosterone level (independent marker of PCOS) among drug naïve PCOS patients in insulin resistant background but also an interesting finding was established that GGT among all the liver enzymes are most strongly associated with hyperandrogenism in insulin resistant background. Such observations add an extra edge to the pathophysiological understanding of NAFLD in PCOS patients.

Because NAFLD is high prevalent in PCOS patients, early screening and liver evaluation in those patients is very important. As NASH is a risk factor for the development of cirrhosis, and occasionally HCC, the high prevalence of NAFD in young women having PCOS is of concern.

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