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Association of Polycystic Ovary Syndrome with Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease

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Abstract: ***Objective: the aim of this study was to determine if there is an association between metabolic syndrome and nonalcoholic fatty liver disease in Polycystic Ovarian Syndrome (PCOS). Setting: This study was done in a private Clinic and a private Pathology Lab in district Shivpuri (M.P.) Method: This is a retrospective study of 33 PCOS patients with mean BMI 33.39 kg/m^2 from 1st January 2013 to 31st December 2018. Clinical history, height, weight, BP, WC and different laboratory values like AST, ALT, AST:ALT ratio, lipid profile values, fasting glucose, fasting insulin and OGTT 2 hr glucose and other were obtained to diagnose the metabolic syndrome and NAFLD. Fatty liver was diagnosed by abdominal ultrasound following exclusion of alcohol consumption, viral, or autoimmune liver disease. Results: Thirty three PCOS patients (mean body mass index [BMI]: 33.39 kg/m^2) were included. 26 (78.78 %) of 33 PCOS patients had NAFLD, the presence of NAFLD was associated with greater body mass index (BMI), lower fasting high density lipoprotein (HDL) and greater prevalence of impaired fasting glucose and impaired glucose tolerance. Metabolic syndrome was found in 23 (69.69%) of 33 PCOS patients and both metabolic syndrome and NAFLD was found in 24 (72.72%) patients. 18 (69.23%) of the 26 NAFLD patients also had abnormal Alanine aminotransferase. Conclusion: The prevalence of metabolic syndrome was also high in obese PCOS patients. Excess weight may lead to insulin resistance, which in turn may play a part in the development of NAFLD disease. Both NAFLD and metabolic syndrome were frequent in patients with PCOS confirming a relevant clinical association between these three conditions.***

Keywords: Nonalcoholic fatty liver disease, polycystic ovary syndrome, insulin resistance, hyperandrogenism, obesity.

1. Introduction

Polycystic ovarian syndrome (PCOS) is one of the most widespread endocrine disorders in women of the reproductive age group of 12-45 years [1,2]. Polycystic ovarian disease (PCOD) is the full blown syndrome of hyperandrogenic polycystic ovarian syndrome (PCOS), presenting with typical somatic features of hyperandrogenism which includes hirutism, obesity menstrual irregularity and anovulation (Stein and Leventhal 1935), Yen 1980).[3]

PCOS is a multi system endocrinopathy involving women from menarche to menopause. In essence PCOS is a complex metabolic, endocrinopathy and reproductive disorder that results in production of androgens and is associated with insulin resistance. It is a harbinger of a lifelong condition that can lead to serious sequel such as diabetes mellitus, hyperlipidemia, endometrial cancer, central obesity and sleep apnea. It has a prevalence of 5%-10% of female population in developed countries 3.7%-22.5% prevalence rate have been reported in India with almost 1/3rd o adolescents being diagnosed with PCOS.**[4]**

Nearly a third of woman (30-35%) with PCOS have impaired glucose tolerance and 8-10.5 have type 2 diabetes mellitus. A family history of diabetes, age and adiposity contribute the risk.[5].

There is atherogenic dylipidemia with elevated low density lipoprotein (LDL), cholesterol and triglycerides and lower high density lipoprotein (HDL) level than women who are not affected by this condition. [6].

Metabolic syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is comprised of a combination risk factor for coronary heart disease, as well for diabetes, fatty liver, and several cancers. [7]

PCOS and metabolic syndrome share the same pathophysiological mechanism. Insulin resistance and compensatory hyper insulinemia is the key pathogenic event in both conditions. Metabolic syndrome is a collection of cardiovascular disease risk factors associated with insulin resistance, dyslipidemia, hypertension and central obesity. [8]

Women with menstrual dysfunction and hyperandrogenism are more insulin resistant than those with hyperandrogenism. [9,10].

The NCEP ATP III definition is one of the most widely used criteria of metabolic syndrome. It incorporates the key features of hyperglycemia/insulin resistance, visceral obesity, atherogenic dyslipedemia and hypertension.

According to National Cholesterol Education Program (NCEP) Adult treatment Panel (ATP) III definition, participant having ≥3 of the following 5 criteria were defined as having metabolic syndrome. Metabolic syndrome is present if three or more of the following five criteria are met: (1). Waist circumference (WC) >102 cms (men) >88 cms (women), (2). Systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure(DBP) ≥ 85 mmHg , (3). fasting triglyceride (TG) level over 150 mg/dl fasting (4). High density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) (5). fasting plasma glucose (FPG) ≥ 110 mg/dl [11]

Recent studies have demonstrated an association between PCOS and another metabolic complication nonalcoholic fatty liver disease (NAFLD). (NAFLD) occurs as a result of abnormal lipid handling by liver, which sensitizes the liver to injury and inflammation. NAFLD is more common PCOS because of insulin resistance and hyperandrogenemia.

Metabolic syndromes have 4 to 11 times higher risk for future NAFLD.

Panel markers for the identification of NAFLD are the presence of metabolic syndrome and T2DM, fasting serum insulin, serum AST and the AST/ ALT ratio.

2. Methods

This is a retrospective study of 33 PCOS patients with mean BMI 33.39 kg/m^2 from 1st January 2013 to 31st December 2018. PCOS patients were diagnosed according to Rotterdam 2003 [b,] (ESHERE/ ASRM) the European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine criteria. Data were collected from the medical records of the patients including clinical history, height, weight, blood pressure, waist circumference and Modified Ferriman-Gallway score for hirsutisim. Laboratory values were obtained like, Fasting Glucose level, fasting insulin level, Amino transference level AST, ALT level, AST/ALT Ratio, Total cholesterol, HDL, LDL and Triglyceride level. Abdominal ultrasonography was used to determine the presence of NAFLD. Ovarian ultrasound completed trans abdominally or trans vaginally. (Polycystic ovarian morphology was seen.) The other laboratory data were also collected e.g. Luteinizing hormone (LH), Follicle stimulating Hormone (FSH), Prolactin, thyroid stimulating Hormone (TSH) and Testosterone.

Exclusion criteria

1) Before diagnosing NAFLD history of alcohol consumption, Viral or Autoimmune liver disease were excluded.
2) Use of medication that influence glucose or lipid metabolism or blood pressure.
3) Pregnancy
4) Patients under treatment for PCOS.

All the data was analyzed using IBM SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare tables. Data is expressed as number and percentage.

3. Results

The most common age group of PCOS patients was 26-35 years (45.45%). Most women were Housewife (75.75%), who viewed their socio economic standing as satisfactory (63.63%) had no children (52.52%), had most common BMI 30-35 (72.72%) kg/m^2, and had been diagnose with PCOS 1 to 5 years before (48.48%). Waist hip ratio was >0.8 in (78.78%), and modified FG Score was 15.15% in patient having abnormal hair growth. The baseline characteristics and socio demographic data of the study population are shown in **Table 1.**

Table 1: Participants Characteristics and sociademographic data

Age	Under 25 Year Old	21.21	7
	26-35 years	45.45	15
	Over 35 year old	33.33	11
Professionally activity	Working Professionally	24.24	8
	Not Working (Housewives)	75.75	25
Socio economic standing	Unsatisfactory	36.36	12
	Satisfactory	63.63	21
Having Children	No Children	52.42	17
	One Child	32.42	10
	Two or more children	15.15	5
Time from PCOS diagnosis	Up to 1 year	12.12	4
	1-5 year	48.48	16
	6-10 years	39.39	13
BMI kg/m^2	25-30	12.12	4
	30-35	72.72	24
	35-40	15.15	5
Waist hip Ratio	>0.8	78.78	26
Modified Ferriman – Gallway score	>8	15.15	5

Data is expressed as percentage and number.

In our study the mean duration of PCOD symptom was 8 ± 2.6 years the majority of women was presented with menstrual problems (Only menstrual problem + menstrual + infertility problem) 72.72% followed by fertility problem (Infertility problem + infertility + menstrual problem) 48.48% and problems 9% with hyper androgenism. **(Figure 1)**

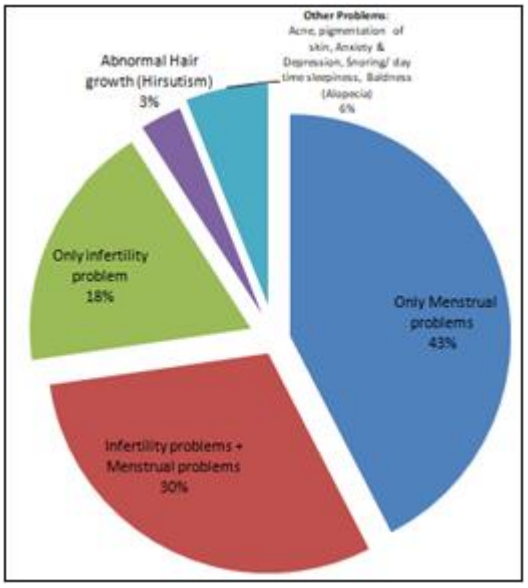

Figure 1: Chief complaints of the patient attending the private clinic

Thirty-three PCOS patients (**mean body mass index [BMI]: 33.39 kg/m^2)** were included. 26 (78.78 %) of 33 PCOS patients had NAFLD, the presence of NAFLD was associated with greater body mass index (BMI), lower fasting high density lipoprotein (HDL) and greater prevalence of impaired fasting glucose and impaired glucose tolerance. Metabolic syndrome was found in 23 (69.69%) of 33 PCOS patients and both metabolic syndrome and NAFLD was found in 24 (72.72%) patients. **Table 2**

Table 2: Association of PCOS with metabolic syndrome and nonalcoholic fatty liver disease NAFLD

PCOS patients (mean body mass index [BMI]: 33.39 kg/m2) with Metabolic Syndrome		
*Laboratory Characteristics of the Study Population of **MS***	69.69%	23
1) BMI >30 (kg/m^2)		
2) Waist circumference > 88 cms		
3) Systolic BP ≥ 130 mmHg		
4) Diastolic BP ≥ 85 mmHg		
5) Fasting Plasma Glucose ml/dl ≥ 110 mg/dl		
6) Fasting triglyceride (TG) ≥150 mg/dl		
7) Fasting high density lipoprotein (HDL) < 50 mg/dl		
8) OGTT- 2 hr glucose (140 to 199 mg/dl)		
9) Higher Fasting Insulin		
PCOS patients with NAFLD	78.78%	26
PCOS patients with NAFLD & Metabolic syndrome	72.72%	24

Data is expressed as no. of patients and percentage.

In our study 18 (69.23%) of NAFLD patients also had abnormal aminotransferase. **(Table: 3)**

Table 3: Showing NAFLD with Abnormal liver Chemistry

NAFLD	*Liver Chemistry*	*Aminotrnasferase*	*Percentage*	*Number*
Increased hepatic brightness or hyperechogenicity in USG (Fatty liver) 78.78% (n=26)	Patient with Abnormal liver Chemistry	Higher Alanine aminotransferase **(ALT)**	69.23%	18
	Patient with normal liver Chemistry having fatty liver		30.76%	8

ALT level were also significantly higher in subject with metabolic syndrome.

In our study the presence of fatty liver was associated with greater median BMI. The prevalence and severity of steatosis in relation to BMI are shown in **figure 2**

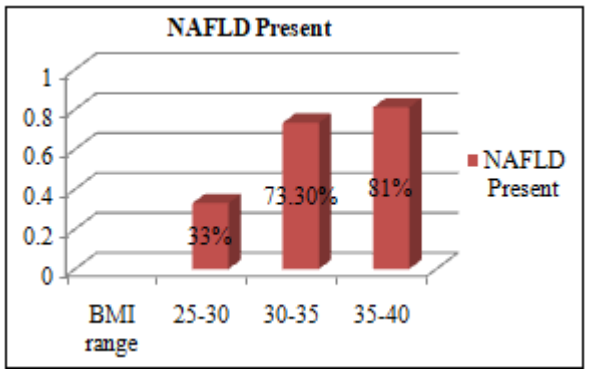

Figure 2: Prevalence and Severity of NAFLD according to BMI Group

4. Discussion

The most common age group in PCOS patient was found to be 26-35 years (45.45%) which is an agreement done by Judy Griffin McCook where author reported most cases of PCOD aged 26-35 years (43.20%) [12]

In our study the mean duration of PCOD symptom was 8 ± 2.6 years the majority of women was presented with menstrual problems (Only menstrual problem + menstrual & infertility problem) 72.72% followed by fertility problem (Infertility problem + infertility & menstrual problem) 48.48% and problems with hyperandrogenism 9% . In a similar study of 282 women JPW Chung, et al reported the mean duration of PCOD symptom was 8.6 ± 5.4 years. The majority if the women presented with menstrual problems, (82.1%, n=215), followed by fertility problems (17.6%, n=46), and problems with hyperandrogenis (0.4%, n= 1).

In our study obesity and insulin resistance are associated with higher prevalence of NAFLD. This study is consistent with previous work in the field in which insulin resistance and obesity appear to be important associated factors with NAFLD. [13,14,15]. In one other study 11% of overweight and 63% of obese girls with PCOS had metabolic syndrome [16] which was comparable to our study.

In our study total 33 cases were of PCOS **(mean BMI 33.39)** (78.78%) had fatty liver, the presence of fatty liver was associated with greater body mass index (BMI), lower fasting high density lipoprotein (HDL) and greater prevalence of impaired fasting glucose and impaired glucose tolerance. Metabolic syndrome was found in 23 (69.69%) patients and both metabolic syndrome and fatty liver was found in 24 (72.72%) patients. These finding are comparable with other studies. In one study Insulin resistance, a hallmark of metabolic syndrome is observed in 50-80% of women with PCOD syndrome and patient with nonalcoholic fatty liver disease· [17] in another study prevalence of NAFLD in obese cohorts of PCOS is estimated to be between 60%-90%. [18] and a recently published study of 14 NAFLD female patients of reproductive age group (22-25) revealed that 71% (10/14) of these patients match the 2003 Rotterdam criteria for PCOS. [19]

In study of Elaine Barfield MD1 showed that 15.4% (6 of 39) of patients had elevated Alanine aminotransferase levels, suggestive of nonalcoholic steatohepatitis and 43.6% (17 of 39) of patients qualified as having metabolic syndrome. Finally 10.2% (4 of 39) of patients were found to have both liver dysfunction and metabolic syndrome. [20] Our finding was different because of PCOS patients (mean body mass index [BMI]: 33.39 kg/m2) study cohort.

In 2005 Schwimmer et al [21] found a 30% risk of Alanine aminotransferase (ALT) elevation (>35 U/L) amongst a cohort of PCOS patients attending a fertility clinic was comparable to our study but in our study 18 (69.23%) of 26 NAFLD patients had abnormal aminotransferase which is also comparable to Cristian Cerda study in which 64% of NAFLD had abnormal aminotransferase in PCOS patients. [22]

In most studies, the prevalence of both polycystic ovary syndrome and non alcoholic fatty liver disease rises proportionally to the degree of insulin resistance and increase in the mass of adipose tissue.

5. Conclusion

In our study we found both NAFLD and metabolic syndrome were frequent in patients with PCOS confirming a relevant clinical association between these three conditions.

Obesity and insulin resistance are considered as the main factors related to NAFLD in PCOS.

Limited data imply that advanced stage of liver disease is possibility more frequent in obese PCOS patients with NAFLD. PCOS patients, particularly obese patients with the metabolic syndrome, should be screened for NAFLD. Long-term follow up studies are needed to clarify clinical implications, appropriate diagnostic evaluation and optimal treatment for PCOS patients with and metabolic syndrome.

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