ORIGINAL ARTICLE

INCIDENCE OF NON-ALCOHOLIC HEPATIC FATTY INFILTRATION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT: OBJECTIVE: To evaluate the prevalence of non-alcoholic fatty infiltration in women with PCOS. **MATERIALS AND METHODS:** A prospective study in which 162 women with Polycystic ovarian syndrome (PCOS) and 165 healthy controls who were age and weight matched were included. Anthropometric parameters evaluation, biochemical and hormonal investigations were done in all the patients with PCOS and controls. Insulin resistance was calculated by Homeostasis model assessment (HOMA). Per abdominal sonography and biochemical investigations were used to determine the presence of hepatic steatosis. Other causes for liver disease were also excluded. **RESULTS:** Women with PCOS had a higher prevalence of hepatic steatosis (68% vs 26%, P =0.001), MS (37% vs. 6%, P <0.01) and elevated transaminases (32% vs. 8%, P **=**0.03) than controls. All patients with PCOS and controls with Metabolic Syndrome (MS) had presence of hepatic steatosis. **CONCLUSION:** Non-alcoholic fatty infiltration is significantly seen in women with PCOS in combination with other metabolic derangements. Liver disease should be excluded by various investigations at an earlier age in women with PCOS, particularly those who have an evidence of MS.
KEYWORDS: Insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, polycystic ovary syndrome.

INTRODUCTION: Polycystic ovary syndrome (PCOS) is one of the common endocrine diseases of reproductive age group women affecting nearly 10% of the population.[1, 2] It is associated with significant morbidity in terms of both reproductive and metabolic abnormalities. Women with PCOS demonstrate multiple metabolic derangements that lead to increased cardiovascular risk. Insulin resistance has been demonstrated in both obese and non-obese women with PCOS.[3] Insulin resistance possibly plays central role in the pathogenesis of PCOS. Nonalcoholic hepatic fatty infiltration is often called as hepatic manifestation of metabolic syndrome (MS) and is characterized by the accumulation of fat in the liver in the absence of excessive alcohol consumption. Non-alcoholic hepatic fatty infiltration demonstrates a spectrum of histological changes extending from benign simple steatosis to steatohepatitis, progressive fibrosis and cirrhosis.[4,5] Natural history of non-alcoholic hepatic fatty infiltration is not clear. But its recognition is important since it has potential to evolve into end-stage liver disease and its association with cardiovascular risk factors.[6, 7] Both non-alcoholic hepatic fatty infiltration and central obesity[8, 9, 10, 11] are associated with PCOS given that insulin resistance is the common feature, both disorders can be linked with MS. Association of Non-alcoholic hepatic fatty infiltration and PCOS was first reported by Brown et al.[12]

Many studies have demonstrated high prevalence of PCOS in Indian population [13] having higher fasting insulin levels.[14,15] Recently there is increasing incidence of MS in general population and in young women with PCOS. We intended to do this study to identify the factors that are associated with Non-alcoholic hepatic fatty infiltration in this subset of patients. Abdominal sonography was performed in patients with PCOS along biochemical testing in order to assess the presence of non-alcoholic fatty infiltration and its association with various metabolic and hormonal factors.

MATERIALS AND METHODS: The study was a prospective study conducted for a period of one year from 01/07/13 to 30/06/14 in MVJ Medical college and research hospital. All female patients with clinical and sonological diagnosis of PCOS were included in the study. Rotterdam criteria were used for sonological diagnosis of PCOS. Total PCOS patients included were 162 and controls were 165. All the participants were included in the study after obtaining written informed consent. Included controls were age and weight-matched with normal menstrual cycles with no clinical evidence of hyperandrogenism and with normal ovarian morphology in pelvic ultrasonography.

Inclusion criteria: Polycystic ovaries on ultrasound-Features include:

- presence of 10-12 or more follicles
- individual follicles are generally similar in size and measure 2-9 mm in diameter
- peripheral distribution of follicles - this can give a "string of pearls" appearance
- background ovarian enlargement (volume greater than 10 cc [7])
- central stromal brightness +/- prominence

Oligomenorrhea/oligo-ovulation
Clinical hyperandrogenism

Exclusion criteria:

Inherited disorders of insulin resistance
Type 2 diabetes mellitus, hypertension
Hyperprolactinemia
Untreated hypothyroidism
Congenital adrenal hyperplasia, with an androgen-secreting adrenal/ovarian tumor
Cushing's syndrome

Those taking corticosteroids, antiepileptic or antipsychotic drugs, insulin sensitizers, hormonal contraceptives, anti-tuberculosis drugs in past three months.

Currently pregnant.

Patients with alcohol consumption >20 gm/day

History of chronic viral hepatitis, hemochromatosis, autoimmune hepatitis, drug-toxin-induced liver injury, chronic liver disease.

Clinical examination, biochemical evaluation and abdomino pelvic ultrasonographic assessment were done for all patients and controls. During clinical examination, anthropometric

measurements (weight, height, hip and waist circumference) and blood pressure were recorded. Biochemical investigations include routine hematological profile, creatinine, urea, fasting glucose and insulin, serum ceruloplasmin, ferritin, lipid profile, aspartate aminotransferase (AST) and alanine aminotransferases (ALT), γ-glutamyltransaminase (γ-GT), total and direct bilirubin, alkaline phosphatase (ALP), hepatitis B surface antigen, anti-hepatitis C antibodies and antinuclear antibodies. Also included was hormonal assay to evaluate the serum levels of thyroxin, prolactin, dehydroepiandrosterone sulfate, total testosterone, follicle stimulating hormone, luteinizing hormone, and 17-hydroxy progesterone. Homeostasis model assessment (HOMA) method for insulin resistance was calculated by the formula: Fasting serum insulin (micro units/ml) × fasting serum glucose (mill moles per liter)/22.5.

Sonography was done by the radiologist who was blinded for subject's medical history and diagnosis. Machine used was General Electric voluson 730 with a 3.5 Hz convex-array probe. Hepatic fatty infiltration was defined as diffuse increase in fine echoes in liver parenchyma with or without impaired visualization of intrahepatic vessels and the diaphragm.[16]

The following parameters were used to diagnose metabolic syndrome(MS) in patients with PCOS and controls (i) waist circumference ≥88 cm (ii) serum triglyceride ≥150 mg/dl (iii) HDL cholesterol <50 mg/dl (iv) serum fasting glucose >100 mg/dl (v) blood pressure ≥130/85 mmHg according to NCEP/ATP III, 2001criteria.[17]

STATISTICAL ANALYSIS: Statistical package used for all statistical analysis was Social Sciences (SPSS version 13.0, Inc., Chicago, IL, USA). The values of continuous variables were presented as mean±SD and of categorical variables as absolute number and percentages. Differences in variables between groups (patients with PCOS and controls) and subgroups were tested with Mann-Whitney "U" test and χ^2 test as appropriate. Univariate regression analysis was used to evaluate the effect of age, BMI, waist circumference, HOMA-IR, lipid and hormonal parameters along with PCOS diagnosis in all the subjects on the presence of hepatic steatosis. Multivariate analysis was performed for each of the independent variables that were significantly related to hepatic steatosis by univariate regression analysis. AP <0.05 was considered statistically significant.

RESULTS: Table 1 demonstrates the clinical and laboratory parameters of patients with PCOS and age and weight-matched healthy controls. Higher central adiposity indicated by higher waist-hip ratio. Higher levels of total testosterone, fasting insulin, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transaminase (γ-GT) were seen in the women with PCOS. They also had lower HDL levels than the controls. 114/162 women with PCOS were found to be insulin resistant which was defined as value >75th percentile of HOMA-IR of controls, was >1.6.

Table 1: Clinical, biochemical and hormonal characteristics of polycystic ovary syndrome patients and controls.

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Variable	PCOS group(n=162)	Control (n=165)	P Value
Age in years	27.5+/-6.5	27.9+/-7.5	0.38
BMI(Kg/m2)	27.6+/-5.6	26.9+/-6.9	0.47
Waist-hip ratio	0.88+/-0.13	0.78+/-0.09	0.01
Fasting glucose(mg/dl)	93+/-12.2	80+/-10.7	0.001
Fasting insulin(mu/ml)	11.6+/-6.2	7.7+/-3.6	0.02
HOMA-IR	3.3+/-1.8	1.7+/-0.77	0.01
Total testosterone(nmol/L)	2.9+/-0.8	1.7+/-0.6	0.01
Dehydroepiandrosterone sulphate(micro mol/L)	8.33+/-3.8	6.94+/-2.9	0.41
Total cholesterol(mg/dl)	187+/-26.4	178+/-30.8	0.5
LDL cholesterol(mg/dl)	96.8+/-23	88.8+/-18.6	0.4
HDL cholesterol(mg/dl)	42.8+/-6.8	52.6+/-7.4	0.03
Triglycerides(mg/dl)	136.4+/-24	126+/19	0.12
ALT(U/L)	53+/-12	36+/-8.4	0.01
AST(U/L)	44+/-15.5	32+/-14	0.04
Gamma GT(U/L)	43+/-10.8	27+/-13.5	0.01
Hepatic steatosis	106(66%)	38(26%)	0.01
metabolic syndrome	59(36%)	13(8%)	0.001

PCOS=Polycystic ovary syndrome; ALT=Alanine aminotransferases; AST=aspartate aminotransferase; gamma GT=gamma-glutamyltransaminase; HOMA=Homeostasis model assessment

Hepatic steatosis was detected in 106/162 patients with PCOS and in 38/165 controls.

High transaminase levels (>45U/L) were detected in 51/162 women with PCOS and in 12/165 controls. Elevated transaminases were present in 60/108 patients and 36/126 controls of all women with hepatic steatosis (n = 150) whereas hepatic steatosis was detected in all women who had elevated transaminases. Hepatic fatty infiltration was seen in all patients and controls who had MS.

Table 2 demonstrates patients with PCOS who had hepatic steatosis had a greater waist-hip ratio, higher fasting glucose and insulin and lower HDL levels and also had high testosterone and HOMA-IR values than controls. Patients with PCOS who had elevated transaminases had higher BMI, HOMA-IR and fasting insulin levels than PCOS patients with normal transaminases.

Table 2: Clinical, biochemical and hormonal characteristics of polycystic ovary syndrome patients and controls with and without hepatic steatosis				
	PCOS with hepatic steatosis	PCOS without hepatic steatosis	Controls with hepatic steatosis	Controls without hepatic steatosis
Age in years	27.5+/-6.2	26.8+/-7.5	27.2+/-7	27.4+/-6.8
BMI(Kg/m2)	27.2+/-5.4	26.8+/-6.7	32.6+/-6.5	23.6+/-6
Waist-hip ratio	0.87+/-0.11	0.77+/-0.09	0.84+/-0.09	0.76+/-0.07
Fasting glucose(mg/dl)	94+/-12.2	81+/-10.7	86+/-9.9	85+/-10.2
Fasting insulin(mu/ml)	11.4+/-6.2	7.6+/-3.5	10.4+/-4.3	5.7+/-3.5
HOMA-IR	3.2+/-1.7	1.6+/-0.76	3.15+/-2.72	1.85+/-0.64
Total testosterone(nmol/L)	2.9+/-0.7	1.6+/-0.6	1.34+/-0.53	1.26+/-0.6
LDL cholesterol(mg/dl)	105+/-10.1	88+/-18.6	100.5+/-9.3	85+/-8.8
HDL cholesterol(mg/dl)	42.6+/-6.7	52+/-7.4	45.6+/-6.3	52.1+/-5.7
Triglycerides(mg/dl)	146+/-19.6	130+/16.6	134+/-15.3	121+/-12.3
ALT(U/L)	56+/-12.3	34+/-12	46+/-13.4	32+/-10.9
AST(U/L)	44+/-15.3	30+/-14	41+/-13	27+/-12.6
Gamma GT(U/L)	42+/-8.6	24+/-4.2	37.7+/-11.5	18.9+/-7.8
metabolic syndrome	51(141)	6(33)	12(66)	0(0)
Results for continuous variables are expressed as mean +/- SD and for binary variables as percentages in parentheses. P<0.001 and P<0.05 for PCOS with hepatic steatosis vs. PCOS non hepatic steatosis; P<0.001 and P<0.05 for PCOS with hepatic steatosis vs. control with hepatic steatosis; P<0.001 and f P<0.05 for control with hepatic steatosis vs. control without hepatic steatosis; HOMA; Homeostasis model assessment				

PCOS patients with hepatic steatosis were significantly older, had higher BMI, waist-hip ratio, fasting insulin, HOMA-IR, LDL, ALT and AST than PCOS patients without hepatic steatosis. Patients with PCOS who had elevated transaminases had higher BMI, waist-hip ratio, fasting insulin, HOMA-IR and lower HDL levels than those with normal transaminases.

The controls with hepatic steatosis were older, had higher BMI, waist-hip ratio, HOMA-IR, fasting insulin and glucose, triglycerides and LDL cholesterol. They also had high amino transaminase and γ-GT levels and non-significantly lower HDL levels.

In Univariate regression analysis age, BMI, waist-hip ratio, HOMA-IR, HDL and PCOS diagnosis were the factors significantly related to the presence of hepatic steatosis.

Table 3: Multivariate regression model showed only HOMA-IR, HDL and PCOS diagnosis remained significantly related to the hepatic steatosis after adjustment for age, BMI and waist-hip ratio.

Table 3: Multivariant logistic regression analysis for hepatic steatosis as dependent variable (n=109)			
Variable	OR	95%CI	P value
HOMA-IR	2.36	(1.76-3.92)	0.01
HDL cholesterol	1.6	(1.08-1.92)	0.04
PCOS status	4.58	(2.36-14.68)	0.003
Adjusted for age, BMI, waist-hip ratio value <0.05 considered significant,			
PCOS=Polycystic ovary syndrome; HOMA=Homeostasis model assessment			

Table 3: Multivariate logistic regression analysis for hepatic steatosis as dependent variable (n=109).

DISCUSSION: There is significant increase in the prevalence of fatty liver in general population of India and has been shown to be similar to the estimates reported from the western countries. PCOS is the most common endocrinopathy affecting women of reproductive age. Women with PCOS are at substantial risk for developing metabolic abnormalities such as glucose intolerance, dyslipidemia and MS.[18, 19] Many studies have proved that the prevalence of MS in women with PCOS appears to be significantly higher than the one estimated in their age-matched counterparts from the general population. High degree association of PCOS and MS has been documented in Brazilian, Chinese, Korean, Indian and in multiracial PCOS populations.[20, 21, 22, 23, 24] Increasing evidence suggests that PCOS is also associated with certain nontraditional markers of cardiovascular risk, such as low grade inflammation, oxidative stress, endothelial dysfunction and arterial stiffness. More recently, a link between PCOS and Non-alcoholic hepatic fatty infiltration has been demonstrated.[12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 26, 27, 28, 29, 30] The prevalence of Non-alcoholic hepatic fatty infiltration in women with PCOS may be as high as 40-55%,[24, 25] whereas a recent study found that the majority of women with Non-alcoholic hepatic fatty infiltration had evidence of PCOS.[17] Like PCOS, Non-alcoholic hepatic fatty infiltration has a strong association with insulin resistance, MS and obesity. Non-alcoholic hepatic fatty infiltration is also a powerful independent predictor of cardiovascular disease. There is strong association between non-alcoholic fatty infiltration and PCOS consistent with the central role of insulin resistance in the pathogenesis of both conditions. Presence of PCOS with non-alcoholic fatty infiltration has been diagnosed by aspartate AST elevation and/or ultrasound in most of the studies. Conversely, 10 of 14 (71%) female patients in childbearing years with histologically diagnosed non-alcoholic fatty infiltration also had revealed PCOS,[17] indicating a close relationship between these two entities.

In our study increased prevalence of hepatic steatosic, elevated liver transaminase and MS was observed in women with PCOS compared to their age and weight-matched healthy counterparts indicating that Non-alcoholic hepatic fatty infiltration is relatively common in these patients. The factors that might have contributed to the increased prevalence are increased central adiposity, insulin resistance, dyslipidemia and higher levels of testosterone. In our study, subgroup analysis between PCOS patients with and without hepatic steatosis as well as controls with and without hepatic steatosis showed that age, obesity waist-hip ratio, insulin resistance and dyslipidemia were the factors associated with the presence of hepatic steatosis, as described by in other studies.

All women with PCOS and controls who had MS were also detected to have hepatic steatosis. This finding is in agreement with data that confers Non-alcoholic hepatic fatty infiltration to be considered as a feature of MS, a cluster of cardiovascular risk factors known to predict long-term cardiovascular events, and may be seen as an additional marker of cardiometabolic risk. One study has linked long-term risk of adverse cardiovascular outcomes with Non-alcoholic hepatic fatty infiltration.

Many studies observed that insulin resistance, a hallmark of MS is observed in 50-80% of women with PCOS and patients with non-alcoholic fatty infiltration. In most studies, the

prevalence of both PCOS and Non-alcoholic hepatic fatty infiltration increases proportionally to the degree of insulin resistance. Non-alcoholic hepatic fatty infiltration is considered as the hepatic manifestation of MS since it worsens insulin resistance, predicts emergence of metabolic complications and increases the risk of cardiovascular events.[30] Similarly, it seems appropriate to consider PCOS as the ovarian manifestation of MS. Both these conditions can coexist and may respond to similar therapeutic strategies. Natural history studies have shown its potential to cause serious liver damage in form of cirrhosis and hepatocellular carcinoma and ultimately increased liver related morbidity and mortality.[31, 32] The recognition of insulin resistance as an underlying pathogenesis of steatosis contributed to the identification of cause which is amenable to treatment. So, screening for liver injury in patients with metabolic risk factors should be mandatory.

The limitation of the study was use of ultrasonography and not the liver biopsy which is thought to be the gold standard for diagnosis of non-alcoholic fatty infiltration. We also suggests further studies to establish the hepatic fatty infiltration as the additional sonographic marker along with the ovarian findings for sonographic diagnosis of PCOS.

CONCLUSIONS: Our study demonstrated that Non-alcoholic hepatic fatty infiltration is significantly common in patients with PCOS in combination with other metabolic abnormalities. Non-alcoholic hepatic fatty infiltration and PCOS are the independent manifestations of MS and indicates the increased risk for future cardiovascular events. So, early detection of Non-alcoholic hepatic fatty infiltration in PCOS is important to undertake early intervention.[33]

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