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Study of Occurrence of Non-alcoholic Fatty Liver Disease (NAFLD) In Polycystic Ovarian Syndrome (PCOS)

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in premenopausal women, often associated with metabolic abnormalities such as insulin resistance and obesity. Nonalcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome, has been increasingly linked to PCOS, with potential implications for long-term liver health. This study aimed to investigate the prevalence of NAFLD in women with PCOS compared to healthy controls and to evaluate the correlation between NAFLD severity and various clinical parameters using the NAFLD Fibrosis Score. A case-control study was conducted at Raichur Institute of Medical Sciences from December 2022 to May 2024, including 100 women diagnosed with PCOS based on Rotterdam criteria and 100 age-matched healthy controls. NAFLD was diagnosed using abdominal ultrasonography and the NAFLD Fibrosis Score, which incorporates age, BMI, hyperglycemia, platelet count, serum albumin and the AST/ALT ratio. Hematological and biochemical tests were performed to assess liver function, glucose metabolism and other relevant parameters. Statistical analysis was conducted using SPSS 22 and Epi-info 7.2.1 software, with p-values<0.05 considered significant. NAFLD was present in 24% of the PCOS group, compared to none in the control group (p<0.001). The PCOS group exhibited significantly higher fasting blood sugar, postprandial blood sugar, ALT and AST levels. Furthermore, 26% of the PCOS group had a NAFLD Fibrosis Score greater than 0.0, indicating a higher likelihood of advanced fibrosis, with 30% of the PCOS group in the F2-F4 fibrosis categories on Fibro Scan, compared to none in the control group (p<0.001). NAFLD is significantly more prevalent in women with PCOS, with a notable proportion exhibiting advanced liver fibrosis. The correlation between NAFLD severity and clinical parameters such as BMI and insulin resistance underscores the need for early screening and intervention in this population to prevent progression to severe liver disease.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among premenopausal women, affecting nearly 10% of the population[1,2]. It is associated with significant morbidity, manifesting in both reproductive and metabolic abnormalities. Initially described by Stein and Leventhal as a reproductive disorder characterized by menstrual irregularity, infertility, hirsutism and enlarged polycystic ovaries[3], PCOS has since been linked to an increased prevalence of impaired glucose tolerance, diabetes mellitus[4] and dyslipidemia[5]. These findings suggest that patients with PCOS are at an elevated risk for metabolic syndrome[6].

Insulin plays both direct and indirect roles in the pathogenesis of hyperandrogenism in women with PCOS. It acts synergistically with luteinizing hormone (LH) to increase androgen synthesis by ovarian theca cells. Furthermore, insulin inhibits the hepatic synthesis of sex hormone-binding globulin (SHBG), leading to higher levels of free, biologically active testosterone in circulation. Given that PCOS patients typically exhibit hyperinsulinemia, the concentration of free testosterone is elevated, even if total testosterone remains within or just above the normal range[2]. Women with PCOS experience multiple metabolic derangements, which contribute to an increased cardiovascular risk[7]. Insulin resistance, a central feature of PCOS, is observed in both obese and non-obese women[8]. Notably, Indian women with PCOS exhibit higher fasting insulin levels and greater insulin resistance compared to Caucasians[9,10].

Nonalcoholic fatty liver disease (NAFLD) is often considered the hepatic manifestation of metabolic syndrome, characterized by fat accumulation in the liver without excessive alcohol consumption. NAFLD encompasses a spectrum of liver pathologies, ranging from benign hepatic steatosis to nonalcoholic steatohepatitis (NASH), progressive fibrosis and cirrhosis[11,12]. The natural history of NAFLD remains unclear, but its recognition is crucial due to its potential to progress to end-stage liver disease and its association with cardiovascular risk factors[7,13]. The association between PCOS and NAFLD was first reported by Brown[14]. Recent evidence has increasingly supported this link, although the pathophysiological connection and clinical significance remain to be fully elucidated, necessitating further research to guide evaluation and management of these patients. Early detection of liver alterations in PCOS patients may help prevent complications such as cirrhosis and hepatocellular carcinoma, thereby improving prognosis. Hence this study was conducted with the objectives to study the prevalence of nonalcoholic fatty liver disease (NAFLD) in polycystic ovarian syndrome (PCOS) patients and to study the correlation with healthy controls. To determine the biochemical and ultrasonic characteristics of the liver in women with PCOS and healthy controls and to grade the severity of NAFLD using NAFLD score and to correlate the findings with various clinical parameters of subjects.

MATERIALS AND METHODS

The study was a Case control study conducted at Raichur Institute of Medical Sciences,Raichur from December 2022-May 2024. It included a total of 200 participants, comprising 100 female patients diagnosed with polycystic ovarian syndrome (PCOS) according to the Rotterdam criteria and 100 age-matched controls. PCOS was defined based on the presence of at least two of the following three features: oligo-or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries, following the exclusion of related disorders. The diagnosis of Non-Alcoholic Fatty Liver Disease (NAFLD) was conducted using imaging studies, specifically ultrasonography (USG) of the abdomen and pelvis, as well as the NAFLD Fibrosis Score, which considers six criteria: age, BMI, hyperglycemia, platelet count, serum albumin and the AST/ALT ratio. Patients with significant alcohol consumption, hepatitis B or C infections and those on hepatic steatosis-inducing medications were excluded from the study. Additionally, individuals with autoimmune hepatitis or Wilson's disease were not included.

The methodology included the performance of various hematological and biochemical tests. Hemoglobin levels, total leukocyte count and platelet count were measured using a Medonic CA 620/530 auto analyzer, based on the electronic impedance principle. Prothrombin time (PT) was determined using a lyophilized calcified thromboplastin reagent. Serum bilirubin levels were assessed through calorimetric assay using the Roche/Hitachi 911 analyzer, while serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels were measured in accordance with IFCC methods using the Roche/Hitachi 904 and 912 analyzers. Serum albumin was quantified using the Bromocresol green method. The NAFLD score was calculated for all subjects using a specific formula: -1.675+0.037 × age (years)+0.094 × BMI (kg/m²) + 1.13×IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio-0.013 × platelet (×10 /l)-0.66×albumin (g/dl). The study included participants between the ages of 15 and 45 years, all of whom were female, and no individuals with competing etiologies for steatosis or chronic liver disease were included.

Statistical Analysis: Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software and Epi-info version 7.2.1 (CDC Atlanta) software. Categorical data was represented in the form of Frequencies and proportions. Chi-square

test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. p<0.05 was considered as statistically significant.

RESULTS AND DISCUSSIONS

In the present study, the majority of subjects in the PCOS group were in the age range of 26-35 years, comprising 58% of the group, while in the control group, 70% of the subjects were in the age range of 15-25 years. This difference in age distribution between the two groups was statistically significant, with a p<0.001.

When comparing the BMI of the subjects, 78% of the PCOS group had a BMI in the range of 25-29 kg/m², whereas 80% of the control group had a BMI in the range of 19-24 kg/m². No subjects in the PCOS group had a BMI in the range of 19-24 kg/m² and no subjects in the control group had a BMI greater than 30 kg/m². This difference in BMI distribution between the two groups was also statistically significant, with a p<0.001.

Regarding the NAFLD score, 26% of the PCOS group had a score greater than 0.0, while none of the control group had a score in this range. In contrast, 54% of the control group had a NAFLD score of ≤-3.0, compared to only 10% of the PCOS group. The presence of NAFLD was observed in 24% of the PCOS group, whereas none of the control group had NAFLD, with a statistically significant p<0.001. Furthermore, the Fibro Scan results indicated that 20% of the PCOS group were in the F2-F3 range and 10% were in the F3-F4 range, while all control group subjects were in the F0-F1 range, again showing a significant difference with a p<0.001.

In terms of laboratory profiles, fasting blood sugar (FBS) levels indicated that 38% of the PCOS group had increased FBS (>126 mg/dl), while none of the control group had elevated FBS levels, with a significant p-value of <0.001. The postprandial blood sugar (PPBS) levels were >200 mg/dl in 36% of the PCOS group, with no subjects in the control group exhibiting such elevated levels, also showing a significant p-value of <0.001.

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For liver enzymes, 70% of the PCOS group had ALT levels greater than 30 IU, compared to only 20% of the control group. Similarly, 50% of the PCOS group had elevated AST levels (>30 IU), while none of the control group exhibited elevated AST levels. These differences were statistically significant, with p<0.001 for both ALT and AST levels.

The current study sought to elucidate the prevalence of nonalcoholic fatty liver disease (NAFLD) among women diagnosed with polycystic ovarian syndrome (PCOS) and to compare it with a control group of healthy, age-matched females. Additionally, the study aimed to evaluate the biochemical and ultrasonic characteristics of the liver in these women and to explore the correlation between NAFLD severity and various clinical parameters through the use of the NAFLD Fibrosis Score.

Prevalence of NAFLD in PCOS Patients: The results of this study demonstrate a significantly higher prevalence of NAFLD in women with PCOS compared to the control group. Specifically, NAFLD was present in 24% of the PCOS group, while none of the control group participants were diagnosed with this condition. This finding is consistent with previous research that has established a strong association between PCOS and an increased risk of NAFLD[12]. The elevated prevalence in the PCOS cohort could be attributed to the common pathophysiological mechanisms shared between NAFLD and PCOS, including insulin resistance, obesity, and hyperandrogenism[13]. These factors contribute to hepatic steatosis, which is the hallmark of NAFLD and are more prevalent in women with PCOS compared to the general population[14].

Biochemical and USG Characteristics: The study further revealed significant differences in the biochemical and ultrasonic characteristics between the PCOS and control groups. Fasting blood sugar (FBS) levels were markedly elevated in the PCOS group, with 38% exhibiting FBS >126 mg/dl, in contrast to none in the control group. Postprandial blood sugar (PPBS) levels followed a similar pattern, with 36% of the PCOS group showing levels >200 mg/dl. These findings are significant as they underline the metabolic disturbances inherent in PCOS, particularly insulin resistance, which is a well-recognized precursor to both NAFLD and type 2 diabetes mellitus[15]. The association between insulin resistance and hepatic steatosis can be attributed to the increased lipolysis in insulin-resistant adipose tissue, leading to an influx of free fatty acids into the liver, subsequently resulting in triglyceride accumulation and NAFLD[16].

The USG findings and Fibro Scan results further emphasize the extent of liver involvement in PCOS patients. A substantial proportion of the PCOS group fell into the F2-F3 and F3-F4 fibrosis categories, with 20% and 10%, respectively, indicating advanced liver fibrosis. In contrast, all control subjects were in the F0-F1 range, reflecting minimal to no fibrosis. This stark contrast highlights the progressive nature of liver disease in PCOS patients and underscores the importance of early detection and intervention[17]. The ultrasonic assessment of liver steatosis and fibrosis in

Table 1: Profile of subjects comparison between two groups

		PCOS Group		Control Group			
		Count	%	Count	%	Total	p-value
Age (Years)	15-25 Years	12	12	70	70	82	<0.001*
	26-35 Years	58	58	30	30	88	
	>35 Years	30	30	0	0	30	
BMI (kg/m^2)	19-24	0	0	80	80	80	<0.001*70
	25-29	78	78	20	20	98	
	>30	22	22	0	0	22	

Table 2: NAFLD Score comparison between two groups

		PCOS Group		Control Group			
		Count	%	Count	%	Total	p-value
NAFLD Score	<=-3.0	10	10	54	54	64	<0.001*
	>-3.0 to -2.0	42	42	46	46	88	
	>2.0 to 0.0	22	22	0	0	22	
	>0.0	26	26	0	0	26	
NAFLD	Present	24	24	0	0	24	<0.001*
	Absent	76	76	100	100	176	
Fibro Scan	F0-F1/F1	70	70	100	100	170	<0.001*
	F2-F3	20	20	0	0	20	
	F3-F4	10	10%	0	0%	10	

Table 3: Laboratory Profile comparison between two groups

		PCOS Group		Control Group			
		Count	%	Count	%	Total	p-value
FBS (mg/dl)	Normal <100	32	32	58	58	90	<0.001*
	Impaired (100-126)	30	30	42	42	72	
	Increased >126	38	38	0	0	38	
PPBS (mg/dl)	<200	64	64	100	100	164	<0.001*
	>200	36	36	0	0	36	
ALT (IU)	<30	30	30	80	80	110	<0.001*
	>30	70	70	20	20	90	
AST (IU)	<30	50	50	100	100	150	<0.001*
	>30	50	50	0	0	50	

the PCOS group reinforces the need for regular monitoring in this population to prevent the progression to more severe liver disease, such as cirrhosis or hepatocellular carcinoma[7].

Correlation of NAFLD Severity with Clinical Parameters: The NAFLD Fibrosis Score was utilized in this study to grade the severity of NAFLD among the participants, and its correlation with various clinical parameters was assessed. The results indicated that a significant proportion of the PCOS group had a NAFLD score greater than 0.0, which is indicative of a higher likelihood of advanced fibrosis. The relationship between the NAFLD score and BMI was particularly noteworthy, with 78% of the PCOS group having a BMI in the overweight or obese range (25-29 kg/m² or >30 kg/m²), compared to 20% in the control group. Obesity is a major risk factor for NAFLD and its prevalence in the PCOS population likely contributes to the higher NAFLD scores observed[18]. Moreover, the NAFLD score was positively correlated with markers of insulin resistance, such as elevated fasting and postprandial blood glucose levels, further supporting the link between metabolic dysfunction and liver disease in PCOS[19].

The study also highlights the importance of considering liver fibrosis in the management of PCOS, given the significant proportion of patients who exhibited intermediate to advanced fibrosis. The use of the NAFLD Fibrosis Score in clinical practice could provide a valuable tool for identifying PCOS patients at higher risk of liver-related complications, thereby allowing for targeted interventions to mitigate disease progression[20]. Furthermore, the observed correlation between NAFLD severity and clinical parameters such as BMI and blood glucose levels suggests that lifestyle modifications aimed at weight reduction and improved glycemic control could be beneficial in reducing the risk of liver disease in this population[21].

Comparison with Previous Studies: The findings of this study align with existing literature that underscores the high prevalence of NAFLD in women with PCOS. A systematic review by Shen[22] reported a pooled prevalence of NAFLD in PCOS patients ranging from 15%-55%, with variations depending on the diagnostic criteria and population studied. The present study's prevalence of 24% falls within this range, supporting the notion that PCOS is a significant risk factor for NAFLD. Additionally, the association between higher BMI, insulin resistance and NAFLD severity observed in this study is consistent with the results of previous research, which has established these factors as key contributors to the development and progression of NAFLD in PCOS patients[23].

Moreover, the advanced fibrosis observed in a subset of the PCOS group in this study is particularly concerning, as it suggests that a significant proportion of these patients are at risk for severe liver disease. This finding is in line with studies that have reported higher rates of liver fibrosis in PCOS patients with

NAFLD, particularly those with coexisting obesity and metabolic syndrome[24]. The implications of this are profound, as advanced fibrosis is associated with a higher risk of liver-related morbidity and mortality, highlighting the need for vigilant monitoring and management of liver health in women with PCOS[25].

CONCLUSION

In conclusion, this study highlights the significant burden of NAFLD among women with PCOS, with a prevalence of 24% and a notable proportion of patients exhibiting advanced liver fibrosis. The association between NAFLD severity and clinical parameters such as BMI and insulin resistance underscores the importance of early screening and intervention in this population. The use of non-invasive scoring systems such as the NAFLD Fibrosis Score can aid in identifying patients at higher risk for liver-related complications, allowing for targeted management strategies. Future research should focus on longitudinal studies to further elucidate the natural history of NAFLD in PCOS and to identify effective interventions to reduce the burden of liver disease in this population.

A notable limitation is the age and BMI discrepancy between the PCOS and control groups, introducing potential bias., a more evenly matched control group could yield more accurate comparisons. Additionally, the exclusion of male participants prevents comparison of NAFLD prevalence in men with similar metabolic conditions. The lack of follow-up data on NAFLD progression in PCOS patients limits understanding of long-term liver health implications. Moreover, the study did not account for other potential confounders like diet, physical activity, genetic factors, or insulin resistance. Future research should focus on longitudinal studies, expanding sample size and diversity, matching control groups more closely, including male participants, and investigating additional risk factors. Additionally, exploring therapeutic interventions for preventing or treating NAFLD in women with PCOS is essential for developing effective management strategies.

REFERENCES

1. Azziz, R. K.S. Wood, R. Reyna, T.J. Key , E.S. Knochenhauer and B.O. Yildiz 2004. The prevalence and features of PCOS in an unselected population. Jo Clin End Met., 89: 2745-2749.
2. Franks, S., 1995. Polycystic ovary syndrome. N Engl J Med., 333: 853-861.
3. Stein, I.F. and M.L. Leventhal, 1935. Amenorrhea associated with bilateral polycystic ovaries. Am. J. Obstet. Gyn., 29: 181-191.
4. Dunaif, A., K.R. Segal, W. Futterweit and A. Dobrjansky, 1989. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes, 38: 1165-1174.
5. Legro, R.S., A.R. Kunselman and A. Dunaif, 2001. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am. J. Med., 111: 607-613.
6. Ehrmann, D.A., R.B. Barnes, R.L. Rosenfield, M.K. Cavaghan and J. Imperial, 1999. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome.. Diabetes Care, 22: 141-146.
7. Wild, R.A., E. Carmina, E.K. Diamanti, A. Dokras and H.F.M. Escobaret al., 2010. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: A consensus statement by the androgen excess and polycystic ovary syndrome (ae-pcos) society. J. Clin. Endo. amp Metab., 95: 2038-2049.
8. Dunaif, A., 1997. Insulin resistance and the polycystic ovary syndrome: Mechanism and implications for pathogenesis*. Endocr. Rev., 18: 774-800.
9. Wijeyaratne, C.N., A.H. Balen, J.H. Barth and P.E. Belchetz, 2002. Clinical manifestations and insulin resistance (ir) in polycystic ovary syndrome (pcos) among south asians and caucAsians: Is there a difference? Clin. Endocrinol., 57: 343-350.
10. Nair, M.K., J.M. Pappachan, S. Balakrishnan, R. Sreedevi and S.K. Bhat, *et al*., 2004. Metabolic syndrome and insulin resistance in women with polycystic ovary syndrome. Gyne Endo., 19: 88-96.
11. McCullough, A.J., 2004. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. Clin. Liver Dis., 8: 521-533.
12. Angulo, P., 2002. Nonalcoholic fatty liver disease. N Engl J Med., 346: 1221-1231.
13. Targher, G., C.P. Day and E. Bonora, 2010. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. Engl. J. Med., 363: 1341-1350.
14. Brown, A.J., E. Hirschhorn and J.P. Mayer, 2003. Liver disease in polycystic ovary syndrome. Clin Liver Dis., 7: 491-505.
15. Musso, G., R. Gambino and M. Cassader, 2009. Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (nafld). Prog. Lipid Res., 48: 1-26.
16. Polyzos, S.A., J. Kountouras, C. Zavos and G. Deretzi, 2012. Nonalcoholic fatty liver disease. Multimodal treatment options for a pathogenetically multiple-hit disease. J. Clin. Gastro., 46: 272-284.
17. Angulo, P., J.C. Keach, K.P. Batts and K.D. Lindor, 1999. Independent predictors of liver fibrosis in

patients with nonalcoholic steatohepatitis. Hepatology, 30: 1356-1362.
18. Younossi, Z.M., A.B. Koenig, D. Abdelatif, Y. Fazel, L. Henry and M. Wymer, 2016. Global epidemiology of nonalcoholic fatty liver disease—meta analytic assessment of prevalence, incidence, and outcomes. Hepatology, 64: 73-84.
19. Buzzetti, E., M. Pinzani and E.A. Tsochatzis, 2016. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (nafld). Metabolism, 65: 1038-1048.
20. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, 2007. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology, 45: 846-854.
21. Promrat, K., G. Lutchman, G.I. Uwaifo, R.J. Freedman and A. Soza et al., 2004. A pilot study of
22. pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology, 39: 188-196.
23. Shen, H., M. Zhang, Q. He, F. Zhang and B. Chen, 2019. Nonalcoholic fatty liver disease in polycystic ovary syndrome and its association with insulin resistance. PLoS One, Vol. 14, No. 7.
24. Baranova, A., T.P. Tran, A. Birerdinc and Z.M. Younossi, 2011. Systematic review: Association of polycystic ovary syndrome with metabolic syndrome and non-alcoholic fatty liver disease. Alim. Pharm. amp Ther., 33: 801-814.
25. Marchesini, G., M. Brizi, G. Bianchi, S. Tomassetti and E. Bugianesi et al., 2001. Nonalcoholic fatty liver disease. A feature of the metabolic syndrome. Diabetes, 50: 1844-1850.
26. Rinella, M.E.,R. Loomba, S.H. Caldwell, K.V. Kowdley and M.R. Charlton, 2014. Nonalcoholic fatty liver disease: A systematic review. JAMA, 313: 2263-2273.