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Prevalence of Non-Alcoholic Fatty Liver Disease in Women with Polycystic Ovary Syndrome and its Correlation with Metabolic Syndrome: A Single Centre Study

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in women. Women with PCOS have androgen excess as a defining feature. They also have increased insulin resistance and obesity, which are also risk factors for non-alcoholic fatty liver disease (NAFLD). However, published data regarding PCOS as independent risk factor for NAFLD remain controversial. To determine the prevalence of NAFLD and metabolic syndrome in patients with PCOS, and to verify if there is a correlation between NAFLD and metabolic syndrome in this population. **Material & Methods:** The prospective study was developed to determine the prevalence of NAFLD and MS in adult women with PCOS. Patients were admitted to the Bangladesh Institute of Research and Rehabilitation in Diabetes (BIRDEM), Dhaka, Bangladesh which treats patients with Diabetes Mellitus from all over the country Bangladesh. The study sessions were conducted from January 2020 to December 2020. **Results:** A total 213 patients were included and analyzed into two groups. Of these, 153 were diagnosed with PCOS, and 60 had other diagnoses. In the PCOS group, 36 (23.53%) patients had NAFLD, and 117 (76.47%) patients did not have NAFLD. From the control group, only two patients had NAFLD, and NAFLD was absent in 58 (96.67%) patients. In the control group, we found 16 (26.67%) patients with metabolic syndrome (NCEP/ATP III criteria) and 44 (73.33%) patients without metabolic syndrome (NCEP/ATP III criteria). From another perspective, describes the PCOS group, there are 68(44.44%) patients with metabolic syndrome (IDF criteria) and 85 (55.56%) patients without metabolic syndrome (IDF criteria). In the control group, we found 22 (36.67%) patients with metabolic syndrome (IDF criteria) and 38 (63.33%) patients without metabolic syndrome (IDF criteria). **Conclusions:** The mechanism of development of NAFLD in PCOS women is not fully known. Besides the progress in the diagnosis of NAFLD in PCOS, there is a lack of knowledge about mechanisms that lead to the development of NAFLD in PCOS. Future studies which would integrate epidemiological, clinical, and molecular investigations about NAFLD in PCOS will have a key role in the development of new diagnostic and therapeutic approaches of NAFLD in PCOS.

Keywords:- Polycystic ovary syndrome, Fatty liver, Metabolic syndrome X.

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INTRODUCTION

In women of childbearing age, Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders.[1] During the reproductive period, PCOS is estimated to affect approximately 6-10% of women with the classical definition of the syndrome as an endocrinological disease, and its prevalence increases to 18-20% when using the Rotterdam criteria.[2,3,4] Ultrasonography confirms that women with PCOS are characterized by ovulatory dysfunction, hyperandrogenism, and polycystic ovary morphology.[5] Hyperandrogenism usually manifests as hirsutism, acne, and alopecia, whereas ovulatory dysfunction manifests as oligomenorrhea, amenorrhea, and subfertility.[6,7] In addition to reproductive manifestations of PCOS, obesity and insulin resistance are present in this syndrome; It is considered that both have a leading role in the pathogenesis of PCOS.[6,8,9] Polycystic Ovary Syndrome (PCOS) is a multi-system reproductive metabolic disease that includes other health problems (Cardiovascular disease, Diabetes mellitus, and Cerebrovascular disease).[10,11,12,13] An additional disorder associated with insulin resistance is a nonalcoholic fatty liver disease (NAFLD) in the Western world which is one of the most common causes of chronic liver disease, with a prevalence of approximately 6.3-33% in the general population.[14,15,16] This disease represents a spectrum of disorders, including not only hepatic steatosis (fat accumulation in liver tissue without inflammation) but also steatohepatitis (accumulation of fat in liver tissue with inflammation and hepatocellular injury) with or without fibrosis, which may be liver cirrhosis and possibly hepatocellular carcinoma.[17,18] Although NAFLD is a growing health problem, the actual pathogenesis of NAFLD is unclear. However, it has been indicated that an unhealthy lifestyle, obesity, dyslipidemia, and ethnicity are risk factors for developing NAFLD, and like PCOS, insulin resistance has an essential role in the pathogenesis of NAFLD.[14,17,18] Interestingly, extrahepatic manifestations and endocrinopathies such as hypothyroidism, hypopituitarism, growth hormone deficiency, hypercortisolism, and early PCOS are associated with NAFLD.[19] NAFLD is strongly associated with obesity and insulin resistance as well as cardiovascular disease and diabetes mellitus type 2.[17,20,21] The occurrence of NAFLD is increased in women with PCOS, especially in women with high serum androgen levels, obesity, and insulin resistance; Thus, it is assumed that this multifactorial condition has one or more contact points rather than complete coexistence.[4] Therapeutic limitations due to the presence of NAFLD have multiple clinical consequences for the patient with PCOS, which clinicians encounter through clinical work. The most commonly used therapy for irregular uterine bleeding or amenorrhea in PCOS patients is a combination of oral contraceptives with antiandrogenic action, which can be used for a long time because they do not worsen metabolic parameters.[22] High ALT, which sometimes develops into NAFLD, is unfortunately a contraindication for contraceptives in situations requiring urgent and effective therapy. Correction of BMI, insulin resistance, and androgens, therapy with probiotics, and laboratory parameters improved PCOS and NAFLD. Considering how significant the health issues of NAFLD and

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PCOS are and their increased prevalence worldwide, this review aims to present the epidemiology, pathophysiology, diagnosis, and treatment of PCOS regarding the possible molecular basis of the development of NAFLD in PCOS women. This study aimed to determine the prevalence of NAFLD and metabolic syndrome in patients with PCOS and to verify whether there is a correlation between NAFLD and metabolic syndrome in this population.

MATERIAL AND METHODS

The prospective study was developed to determine the prevalence of NAFLD and MS in adult women with PCOS. Patients were admitted to the Bangladesh Institute of Research and Rehabilitation in Diabetes (BIRDEM), Dhaka, Bangladesh which treats patients with Diabetes Mellitus from all over the country Bangladesh. The study sessions were conducted from January 2020 to December 20210 during this period, 213 patients were included, among women with PCOS (n=153) and controls (n=60). The control group consisted of women who spontaneously sought medical care with symptoms of irregular menstrual cycles, infertility, hirsutism, acne, or problems trying to lose weight but did not have the criteria for PCOS.

Inclusion criteria:

- Women aged ≥18 years old
- Confirmed with the diagnosis of PCOS based on Androgen Excess Society Guidelines (12)
- Women who not using hormonal contraception for at least 3 months

Exclusion criteria:

- Previous history of chronic liver disease
- Suffering from conditions that can occur with known liver enzyme abnormalities
- Using medication that are risk factors for NAFLD such as corticosteroids, tamoxifen, amiodarone, diltiazem, protease inhibitors (ARVs)
- Using metformin for hirsutism because it may interfere with blood glucose levels
- Daily consumption of ethanol ≥20 grams
- Failure to agree to participate

All data were presented in a suitable table or graph according to their affinity. A description of each table and graph was given to understand them clearly. All statistical analysis was performed using the statistical package for social science (SPSS) program, and Windows. Continuous parameters were expressed as mean ±SD and categorical parameters as frequency and percentage. The significance of the results as determined by a value of $P<0.05$ was considered to be statistically significant.

RESULTS

This is a prospective case-control study; 213 patients were included and analyzed in two groups. Of these, 153 were diagnosed with PCOS, and 60 had other diagnoses. Patients were first divided into the PCOS group and control group. These groups were compared on various criteria such as age, weight, BMI, and waist circumference. We observed that patients with PCOS, even younger than the control group, showed higher weight, higher BMI, and larger waist circumference [Table 1]. Patients with PCOS showed worse levels of HDL compared to the control group. Furthermore, patients in the first group had a higher HOMA index than the second group, showing higher insulin levels [Table 2]. There was no significant difference between the analyzed groups regarding the prevalence of MS diagnosis (NCEP/ATP III and IDF criteria). Thus, it is

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understandable why these patients show a higher HOMA index and a higher prevalence of PCOS than patients without liver disease, regardless of the criteria used. PCOS and control groups were also compared regarding the prevalence of NAFLD; In the PCOS group, 36 (23.53%) patients had NAFLD, and 117 (76.47%) patients did not have NAFLD. From the control group, only two patients had NAFLD, and NAFLD was absent in 58 (96.67%) patients [Table 3]. Finally, PCOS patients were divided into two groups: PCOS with NAFLD and isolated PCOS. Both groups were compared according to the same clinical and laboratory criteria in [Table 1]. Under the PCOS group, there are 50 (32.68%) patients with metabolic syndrome (NCEP/ATP III criteria) and 103 (67.32%) patients without (NCEP/ATP III criteria). In the control group, we found 16 (26.67%) patients with metabolic syndrome (NCEP/ATP III criteria) and 44 (73.33%) patients without metabolic syndrome (NCEP/ATP III criteria) in [Table 4]. From another perspective, Table 5 describes the PCOS group, there are 68(44.44%) patients with metabolic syndrome (IDF criteria) and 85 (55.56%) patients without metabolic syndrome (IDF criteria). In the control group, we found 22 (36.67%) patients with metabolic syndrome (IDF criteria) and 38 (63.33%) patients without metabolic syndrome (IDF criteria).

Table 1: Clinical characteristics of the study population.

Variables	Group PCOS (n=153)	Control group (n=60)	P-value
Age (years) ± DP	26.8 ± 5	33.7 ± 7	0.01
Weight (kg) ± DP	74 ± 20	67.5 ± 13	0.03
BMI(kg/m2) ± DP	28.5 ± 6	26.1 ± 4	0.02
Waist circumference (cm) ± DP	91.6 ± 16	86.4 ± 12	0.05

Table 2: Oral glucose tolerance test of the study population.

Variables	Group PCOS (n=153)	Control group (n=60)	P-value
Oral glucose tolerance test	95.6 ± 8	97.6 ± 8	0.2
Blood glucose after 2 hours (mg/dL) ± DP	109.8 ± 28	107.3 ± 21	0.6
The area under the curve OGTT	1335.9 ± 216	1332.2 ± 169	0.7
Triglycerides (mg/dL) ± DP	103.3 ± 60	101.7 ± 41	0.8
HDL (mg/dL) ± DP	45.6 ± 11	49.9 ± 10	0.05
SBP (mmHg) ± DP	116 ± 13	114 ± 13	0.6
SBP (mmHg) ± DP	74 ± 12	72 ± 12	0.3
MAP (mmHg) ± DP	129.6 ± 15	128.7 ± 14	0.7
Insulin (µUI/mL) ± DP	12.2 ± 10	8 ± 7	0.02
HOMA ± DP	2.9 ± 2	2 ± 2	0.03

Table 3: Comparison of the prevalence of non-alcoholic fatty liver disease between patients with polycystic ovary syndrome group and control group.

NAFLD	PCOS group (n=153)		Control group (N=60)	
	N	%	N	%
Present	36	23.53	2	3.33
Absent	117	76.47	58	96.67

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Page no- 181-189 | Section- Research Article (Surgery)

Table 4: Metabolic syndrome (NCEP/ATP III criterion)

Variables	Group PCOS (n=153)		Control group (n=60)	
	N	%	N	%
Present	50	32.68	16	26.67
Absent	103	67.32	44	73.33

Table 5: Metabolic syndrome (IDF criteria)

Variables	Group PCOS (n=153)		Control group (n=60)	
	N	%	N	%
Present	68	44.44	22	36.67
Absent	85	55.56	38	63.33

DISCUSSION

Published studies on the association between PCOS and NAFLD are still few, and recently, they have evaluated populations with different lifestyles and genetic backgrounds from the Bangladeshi population. A study applied PCOS diagnostic criteria to 14 women with NAFLD, finding a prevalence of 71% in this population.[25] Our results correlate polycystic ovary syndrome with metabolic syndrome. It appears that patients with PCOS, although not presenting a higher incidence of MS, have hyperinsulinemia, are overweight, have increased waist circumference, and already begin to show lipoprotein changes. A common pathogenic mechanism of these two entities is insulin resistance, so it is expected that these women, if not monitored and treated, may develop MS and even NAFLD in the future. Once patients develop NAFLD, the worst score on MS defining criteria is expected. However, it should be remembered that NAFLD is already a cardiovascular risk factor, and the assistant physician should not, thus, wait for changes in glucose or lipids levels before beginning treatment. It is expected that physicians, especially gynecologists, look out not only for the reproductive and aesthetic effects but also for the metabolic and liver consequences of PCOS in particular. Further research will be important for future reference to answer whether it is valid to monitor all patients with PCOS for non-alcoholic fatty liver disease. Since insulin resistance has been recognized as a frequent and key feature in both NAFLD and PCOS, we sought to establish the frequency of NAFLD in PCOS patients.[6,7,24,25,26] Furthermore, half of these patients exhibited abnormal ALT levels, suggesting they may have NASH, a more severe form of NAFLD, although this remains to be proven. These findings are interesting since the women included in this study were young (mean age 24.6 years) and therefore eligible for early detection and treatment of potentially progressive liver disease.[1,19] Thus, the first implication of this study is that physicians that provide care for patients with PCOS must be aware of the need to evaluate NAFLD in this population. Published data on the co-existence of PCOS and NAFLD are limited to two retrospective studies and one case report.[15,16,27] The first published study was carried out by Seiji et al. and consisted of a retrospective chart review of PCOS patients attending an academic

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endocrinology clinic.[15] Histological examination of the liver found evidence of NASH with varying degrees of fibrosis. The authors focused the analysis on the latter group of biopsy-proven NASH and found that these patients had lower HDL and higher triglycerides, fasting insulin, and aminotransferase levels. Besides some methodological limitations [i.e., retrospective nature, referral bias, availability of complete data on all patients], this study indicates that severe liver disease may occur in PCOS. In the case of the recent report by Gambarin-Gelwan et al,[16] where a similar methodology to that of the present study was used, the authors found NAFLD in 55% of subjects with PCOS, a similar figure to the 41.5% found in our patients. It may be considered a relatively high frequency since the estimated prevalence of NAFLD in the general population ranges from 3% to 24%, with most estimates in the 6% to 14% range.[28] Although data regarding the prevalence of NAFLD in Chile are scarce, a recent epidemiological study designed to assess gallbladder disease in this country found ultrasonographic evidence of NAFLD in 22.5% of the population.[29] Interestingly, some studies indicate that Hispanic ethnicity, which is predominant in Chile, may increase susceptibility to NAFLD.[30,31] If this is the case, the high frequency of NAFLD seen in our patients with PCOS may be influenced by their Hispanic ancestry. Also similar to our study, Gambarin-Gelwan et al. found that steatosis was associated with a greater BMI and HOMA-IR, indicating that obesity and insulin resistance are major determinants of NAFLD in PCOS patients. Interestingly, a comparison of PCOS patients with a group of women without PCOS but of similar age and BMI showed that PCOS patients have higher HOMA-IR scores than their non-PCOS counterparts. Thus, PCOS patients seem to have more severe insulin resistance for a given BMI, likely contributing to a greater prevalence of NAFLD. It agrees with evidence suggesting that androgens and insulin resistance seem to have synergistic effects in PCOS patients.[32] Thus, the higher prevalence of NAFLD in patients with PCOS may be related to the fact that insulin resistance has a higher frequency and is more severe in PCOS patients. This study may also be related to the observed frequency of liver enzyme abnormalities (51%) in subjects with demonstrated hepatic steatosis by ultrasonography. This subgroup of patients may potentially have NASH, the more severe form of NAFLD, raising the possibility of an increased frequency of NASH in patients with PCOS since the reported frequency of NASH in NAFLD ranges from 20% to 30% of patients.[33] However, this remains speculative, and a liver biopsy would have been required to characterize this issue further. Although histological examination of the liver remains the most sensitive diagnostic tool in NAFLD, it was not considered in this study since deciding when to perform a liver biopsy in NAFLD is controversial and has to be made on an individual basis.[34,35] Interestingly, as mentioned earlier, in the report of Seiji et al,[15] all six women with abnormal liver enzymes who underwent liver biopsy had evidence of NASH and fibrosis despite their young age. Thus, severe insulin resistance and obesity may contribute to NASH in PCOS patients. However, further studies are needed to define better the role of liver biopsy in the diagnostic evaluation of these patients. Our study has both strengths and limitations. First, patients and

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Page no- 181-189 | Section- Research Article (Surgery)

controls were prospectively recruited, and all pertinent data were available at the time of analysis, including a serologic workup to exclude other causes of liver disease. Second, both diagnoses of PCOS and NAFLD were made on a homogeneous basis by the same group of physicians, which gives consistency to the clinical findings. Third, when recruited to the study, patients were not receiving any treatment like contraceptives, metformin, or other insulin sensitizers. Among the limitations are the relatively small number of patients and their exclusive Hispanic ethnicity. Both factors may preclude the applicability of findings to the general population. In conclusion, findings consistent with NAFLD are frequent in patients with PCOS, confirming a relevant clinical association. Abnormal aminotransferase levels were found in more than half of patients with NAFLD and PCOS, suggesting an increased frequency of NASH in patients with PCOS, likely related to more severe insulin resistance. Thus, women with PCOS should be screened for liver disease, given the potentially progressive nature of the disease and the possibility of early introduction of lifestyle changes that may improve NALFD (i.e., moderate exercise and weight loss).[27] In addition, some women may be candidates for specific drug treatment.[36] Further studies are needed to define the set of studies (including a liver biopsy or non-invasive markers of fibrosis) to be carried out in patients with PCOS and NAFLD, as well as the treatment strategy to be used in these patients.

Limitations of the study

The study was conducted in a single hospital with small sample size. So, the results may not represent the whole community.

CONCLUSIONS

Patients with PCOS have a higher prevalence of NAFLD than BMI-matched controls. IR and LAP are independently associated with NAFLD in this population. Given the high prevalence of NAFLD in patients with PCOS and its association with increased risk for T2DM and CVD, screening of women with PCOS for the presence of NAFLD appears reasonable, particularly in patients with abdominal obesity and elevated triglyceride levels. Interventional studies are also needed to evaluate whether targeting IR, obesity and elevated TG levels will also translate into beneficial effects on hepatic steatosis and its cardiometabolic sequelae in patients with PCOS.

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