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Non-Alcoholic Fatty Liver Disease in Infertile Women with Polycystic Ovarian Syndrome: A Prospective Series

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Abstract

Objective: The aim of this study is to investigate the presence of non-alcoholic fatty liver disease (NAFLD) in women with PCOS.

Material and methods: A prospective study of 31 women with PCOS was observed at the Reproductive Endocrine and Infertility Medicine Department (REIMD) at Women's Specialized Hospital, King Fahad Medical City (KFMC) from April 2010 to August 2011.

Results: Nineteen of the 31 women (61.3%) had NAFLD, and 12 (38.7%) did not. A positive correlation was found between BMI and the number of affected patients in the PCOS subgroup with NAFLD (r^2 = 0.744). Patients with NAFLD had higher serum low density lipoprotein cholesterol, and testosterone levels than patients without.

Conclusion: Non-alcoholic fatty liver disease is a major risk factor for metabolic syndrome. Screening by abdominal ultrasound to assess hepatic statuses was suggested for women with PCOS.

Summary: PCOS affects 4% to 12% of reproductive aged women. They are predisposed to obesity and insulin resistance, and NAFLD.

Keywords

Polycystic ovarian syndrome, Nonalcoholic fatty liver disease, Obesity, Insulin resistance, Metabolic syndrome, Infertility

Introduction

PCOS is explained by Vassilatou [1] as a metabolic and reproductive disorder based on the role of insulin resistance in the pathophysiology. Polycystic ovary syndrome (PCOS) is present in 4% to 12% of reproductive age women [2] and is the most common cause of oligo-ovulatory infertility [3]. Polycystic ovarian syndrome is characterized by ovarian dysfunction with hyper androgenism and polycystic ovary morphology. Clinical features of PCOS include oligomenorrhea or amenorrhea, infertility or first-trimester miscarriage, obesity, hirsutism, acne, acanthosis nigricans, and male pattern alopecia. Patients with PCOS are at increased risk for type 2 diabetes and cardiovascular events. Insulin resistance is often found in these patients [4].

Patients with non-alcoholic fatty liver disease (NAFLD) are characterized by excessive fat accumulation in the liver and no evidence of viral, autoimmune, genetic, or alcoholic liver disease [5]. Ultrasound documented NAFLD is observed in 15 to 30% of the general population [6]. The severity of NAFLD can range from simple steatosis not requiring treatment to steatohepatitis, advanced fibrosis and cirrhosis [7]. NAFLD is a manifestation of metabolic syndrome, a disorder characterized by abnormal energy utilization and storage, and is associated with an increased risk of heart disease, diabetes, and stroke. The prevalence of NAFLD increases with age and is far more common among obese subjects [7]. Insulin resistance is a central pathologic feature of both NAFLD and metabolic syndrome. Diabetes and obesity are among the leading causes of NAFLD. The presence of NAFLD in association with PCOS obese patients is raised and might grow up to 70 percent. NAFLD, free

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androgens and IR existence are found to be greater in obese patients having PCOS as compared to obese patients, BMI-matched controls, which suggest that PCOS and its related features are crucial for the NAFLD instead of obesity [8]. This has also been supported by Vassilatou [1], who highlighted it as a most common cause of chronic liver disease prevailing in the West. Furthermore, the researchers indicated that it comprises a range of liver damage from end-stage liver disease to fatty liver infiltration. According to the study [1], there has been an increase in the prevalence of NAFLD reported among patients having PCOS. Obesity, specifically insulin resistance and central adiposity are highlighted as the main factors associated with the prevalence of NAFLD in PCOS patients. According to the research, excess of androgen, which is related to insulin resistance and is considered to be a main part of PCOS, might serve as a contributing factor in developing NAFLD [1].

Recent studies suggest that there is a strong relationship between PCOS and metabolic syndrome or NAFLD; a recognized component of metabolic syndrome [9,10]. Vassilatou, et al. and [11] conducted a research to examine the presence of NAFLD and evaluate factors that are related with the issue in patients with PCOS. The researchers included 57 premenopausal patients with PCOS having same weight from the age group of 60, with a history of minimal or no consumption of alcohol. The researchers evaluated NAFLD using biochemical testing and abdominal ultrasonography [11], excluding the factors affecting secondary liver disease. The researchers concluded that NAFLD is commonly found in PCOS patients. They further concluded that metabolic abnormalities in addition to increase in androgen bioavailability might be implicated. They suggested liver evaluation in patients with PCOS [11]. The study focused on determining the existence of metabolic syndrome and NAFLD with patients suffering from PCOS [12]. Furthermore, they attempted to verify whether there is a correlation between metabolic syndrome and NAFLD in PCOS patients. They conducted the study from April 2008-January 2009. The researchers included 131 patients and diagnosed 101 with PCOS and used 30 participants as the control group [12]. The researchers concluded that around 25 percent of the PCOS patients had NAFLD. Furthermore, they concluded that metabolic syndrome was present between 44.6% and 32.7% amongst PCOS patients. Metabolic syndrome was found to be highly prevalent in the sub-group PCOS + NAFLD patients, who had a higher BMI, higher glucose levels and were more obese [12]. In this study, we aimed to evaluate sub fertile women with PCOS to characterize the diagnosis of NAFLD in these patients. Although, evaluation of NAFLD and metabolic syndrome is a routine, understanding its prevalence in the Saudi Arabian population is important due to difference in lifestyle and genetic backgrounds from the populations observed in previous studies. This will help in providing insights to the issue of NAFLD prevailing in the Saudi population and will be beneficial in increasing the knowledge base of the literature related to NAFLD and PCOS patients.

Materials and Methods

A prospective study of fifty-nine consecutive infertile women with PCOS attending the Reproductive Endocrine and Infertility Medicine Department (REIMD) at Women's Specialized Hospital, King Fahad Medical City (KFMC), from April 2010 to August 2011 was performed. Physicians diagnosed PCOS according to the revised 2003 Rotterdam criteria [4].

The revised 2003 Rotterdam criteria call for the diagnosis of PCOS when two out of three diagnostic criteria are present [4]. These criteria are oligo- and/or anovulation, clinical and/or biochemical signs of hyper-androgenism, and polycystic ovaries. Patients with PCOS were screened as recommended to exclude hypothyroidism, hyperprolactinemia, late onset congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome [4,5]. They were evaluated by history, physical examination, and blood testing. Clinical assessment included patient age, weight, height, and BMI. Serum fasting blood glucose, insulin, HDL, LDL, cholesterol, AST, ALT, prolactin, TSH, testosterone, dehydro-epiandrosterone sulfate (DHEAS), and 17-OH progesterone levels, and a low dose dexamethasone suppression test were also evaluated. Patients with elevated low dose dexamethasone suppression test results underwent a 24-hour urine collection for assessment of free urinary cortisol.

NAFLD was diagnosed by abdominal ultrasound after the exclusion of alcohol intake, use of oral contraceptives, history of chronic viral hepatitis, autoimmune liver disease, other chronic liver diseases, history of type 2 diabetes mellitus and medication use causing hepatotoxicity or elevations of liver enzymes [9]. NAFLD was diagnosed by the presence of hepatic steatosis on imaging once other causes have been ruled out [10].

Informed consent was obtained from all patients. This study was approved by the IRB of KFMC prior to starting (IRB # 10-028, 04/04/2010).

Statistical Analysis

MS Excel 2010 and SPSS 22.0 software were used for data analysis. Categorical variables were expressed as frequencies and percentages and were analyzed using Chi-square tests. Metric data was presented as the mean ± standard deviation and analyzed using independent sample t-tests. The Spearman's correlation method was used for association measurements. All statistical tests were 2-tailed. The hypotheses were tested based on the p-value, where p less than 0.05 were considered statistically significant.

Table 1: Demographic data.

	All patients	PCOS without NAFLD	PCOS with NAFLD	P value
Age (years)	28.4 ± 3.93	28.9 ± 4.4	28.2 ± 1.8	0.600
Height (cm)	155.1 ± 4.34	155.1 ± 5.4	155.5 ± 3.7	0.980
Weight (kg)	77.1 ± 13.5	71.8 ± 8.0	80.6 ± 15.4	0.081
BMI (kg/m²)	32.3 ± 5.11	29.8 ± 2.8	33.5 ± 6.2	0.064
SBP (mmHg)	118.6 ± 10.6	115.3 ± 15.3	121.0 ± 6.1	0.210
DBP (mmHg)	68.3 ± 6.85	64.5 ± 7.0	71.3 ± 5.9	**0.010**
Duration of Infertility (years)	4.74 ± 2.91	3.9 ± 2.7	4.3 ± 2.3	0.640
Patients with parity	12	7 (58.3%)	5 (26.3%)	0.075
Patients with abortions	7	3 (25.0%)	4 (21.1%)	0.790

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

Table 2: BMI.

BMI (kg/m²)	All patients†	PCOS without NAFLD‡	PCOS with NAFLD‡
		N (%)	N (%)
≤ 24.9 (normal)	1/2 (50%)	1 (8.3%)	1 (5.5%)
25.0-30.0	3/7 (0.429)	4 (33.3%)	3 (16.7%)
30.1-32.0	2/7 (0.286)	5 (41.7%)	2 (11.1%)
32.1-34.9	6/7 (0.857)	1 (8.3%)	6 (33.3%)
32.1-34.9	6/7 (0.857)	1 (8.3%)	6 (33.3%)
Total	30	12/30 (40.0%)	18/30 (60.0%)
Correlation coefficient (r^2)	0.4	0.026	0.744

* = BMI not available for 1 patient; † = data presented as proportion of patients in BMI category with NAFLD; ‡ = data presented as proportion of patients in NAFLD subgroup in that BMI category.

Results

Thirty-one out of the 59 women with PCOS in this study had attended the REIMD over a 17-month period, who were evaluated for NAFLD by abdominal ultrasound imaging. Twenty-seven women, who did not undergo hepatic ultrasound testing, were excluded.

Patients' demographics were demonstrated in table 1. Hyperandrogenism was identified in 17 patients (12 clinical, 1 biochemical, and 4 both), while fourteen patients had no signs of hyperandrogenism. The identified causes of infertility in 31 study patients and their spouses were an ovulation (74.2%; n = 23), combined male and female factors (16.1%; n = 5), tubal factors (6.5%; n = 2), and multiple factors (16.1%; n = 5). Women were divided into sub groups based on the presence of a normal hepatic US or hepatic steatosis on US (NAFLD) (Table 1). However, there was no difference in the infertility factors of the two groups.

Twelve of the 31 (38.7%) women did not have NAFLD (Group 1) and 19 (61.3%) had NAFLD (Group 2). PCOS patients in the two groups had similar age, height, systolic blood pressure, duration of infertility, number of abortions, and causes of infertility. It was observed that patients with NAFLD had a higher diastolic blood pressure than non-NAFLD patients. Furthermore, the finding of more women without NAFLD having children than women with NAFLD was of borderline significance.

The greater weight and BMI of our NAFLD patients, compared to non-NAFLD patients, approached statistical significance. A weak correlation was found between BMI and the number of patients affected with NAFLD in that BMI category (r^2 = 0. 401) (Table 2). There was no correlation found between BMI and the number of patients with that BMI in the PCOS subgroup without NAFLD (r^2 = 0.0263). However, a positive correlation was found between BMI and the number of patients with that BMI in the PCOS subgroup with NAFLD (r^2 = 0.7437).

Moreover, the two groups of PCOS patients had similar serum albumin, AST, ALT, serum bilirubin, fasting blood sugar, serum insulin, luteinizing hormone (LH), follicle stimulating hormone (FSH), 17-OH progesterone, and DHEAS levels (Table 3). It was also observed that patients with NAFLD had higher serum testosterone levels as compared to patients without NAFLD. The results also demonstrated that 21.4% of women had elevated serum testosterone values, and 71.4% had elevated DHEAS values.

With the exception of one patient in each PCOS group, all women had elevated ALT levels. Only one patient, who was without NAFLD, had elevated AST levels. Patients with NAFLD had higher serum cholesterol and serum LDL levels than patients without NAFLD. Elevated cholesterol levels were observed in 7 patients with NAFLD and in one patient without NAFLD. Elevated LDL levels were observed in 6 NAFLD patients and in 3 patients without NAFLD. Furthermore, patients with NAFLD had a trend toward a lower HDL than patients without NAFLD.

Two patients were treated for Type II diabetes using metformin in the group without NAFLD and three in the group with NAFLD. It was highlighted that four patients in the NAFLD group and 3 in the group without

Table 3a: Laboratory testing.

Lab parameters	Non-NAFLD		NAFLD		p value
	mean ± SD	'n'	mean ± SD	'n'	
Serum albumin	51 ± 40.8	10	33.9 ± 9.9	14	0.143
AST	26.3 ± 23.3	4	14.5 ± 6.8	4	0.371
ALT	32.4 ± 8.5	11	29.3 ± 9.5	15	0.4
Total bilirubin	8.7 ± 11.0	10	7.1 ± 4.4	14	0.621
HDL	3.0 ± 3.3	11	**1.3 ± 0.6**	14	0.066
LDL	2.6 ± 0.5	9	3.4 ± 0.8	14	0.014
Cholesterol	4.4 ± 0.7	9	5.2 ± 0.8	14	0.023
FBS	5.1 ± 0.3	8	5.1 ± 0.5	17	0.892
Serum insulin	86.7 ± 50.1	7	120.2 ± 71.8	14	0.285
LH	10.1 ± 8.2	11	7.4 ± 4.4	16	0.273
FSH	6.1 ± 2.5	11	5.3 ± 1.7	17	0.283
17-OH Progesterone	3.5 ± 2.2	8	5 ± 3.2	15	0.266
Testosterone	1.3 + 0.7	8	1.7 + 0.5	6	0.042
DHEAS	9.1 ± 11.9	8	11.2 ± 20.7	13	0.797

Table 3b: Laboratory testing reported as binary outcome.

		Non-NAFLD	NAFLD	p value
		n (n%)	n (n%)	
Serum albumin	Normal	9 (90.0%)	14 (100.0%)	0.417
	Deranged	1 (10.0%)	0 (0.0%)	
AST	Normal	3 (75.0%)	4 (100.0%)	0.5
	Deranged	1 (25.0%)	0 (0.0%)	
ALT	Normal	1 (9.1%)	2 (13.3%)	0.619
	Deranged	10 (90.9%)	13 (86.7%)	
Total bilirubin	Normal	9 (90.0%)	13 (92.9%)	0.67
	Deranged	1 (10.0%)	1 (7.1%)	
HDL	Normal	7 (63.6%)	10 (71.4%)	0.504
	Deranged	4 (36.4%)	4 (28.6%)	
LDL	Normal	8 (72.7%)	8 (57.1%)	0.352
	Deranged	3 (27.3%)	**6 (42.9%)**	
Cholesterol	Normal	7 (77.8%)	6 (42.9%)	0.111
	Deranged	2 (22.2%)	**8 (57.1%)**	
Insulin	Normal	4 (57.1%)	10 (71.4%)	0.428
	Deranged	3 (42.9%)	4 (28.6%)	
LH	Normal	7 (63.6%)	10 (62.5%)	0.637
	Deranged	4 (36.4%)	6 (37.5%)	
FSH	Normal	8 (72.7%)	11 (64.7%)	0.493
	Deranged	3 (27.3%)	6 (35.3%)	
17-OH Progesterone	Normal	8 (100.0%)	14 (93.3%)	0.652
	Deranged	0 (0.0%)	1 (6.7%)	
Testosterone	Normal	7 (87.5%)	4 (66.7%)	0.385
	Deranged	1 (12.5%)	2 (33.3%)	
DHEAS	Normal	4 (50.0%)	3 (23.1%)	0.213
	Deranged	4 (50.0%)	10 (76.9%)	

NAFLD had elevated serum insulin values. Two of these insulin elevations occurred in diabetic patients taking metformin. All patients evaluated had normal fasting blood sugar values.

Metabolic syndrome has been characterized by the presence of at least three factors out of five, these include: abdominal obesity, elevated triglycerides, reduced HDL level, hypertension, and impaired fasting glucose levels [13], although, there is a lack of a standard definition [14]. Twenty-five patients were evaluated to have an abnormality in metabolic syndrome related factors, including 18 with only one abnormality (16 with obese BMI and two with low HDL levels), six with 2 abnormalities (obese BMI plus low HDL [n = 2] or Type II diabetes [n = 4]), and one with 3 (obese BMI plus increased triglyceride plus Type II diabetes). These metabolic abnormalities were distributed similarly in patients with and without NAFLD. A patient who suffered from metabolic syndrome was also found to have NAFLD.

Discussion

PCOS is the most common endocrine disorder in women, with a prevalence of 6-15% [15], and metabolic syndrome is a well-recognized finding in women with PCOS. Different phenotypes of PCOS are associated

with different risks for metabolic syndrome. Hyperandrogenic ovulatory women with polycystic ovaries are more likely to have mild insulin resistance and mild ovarian dysfunction, a rate that is significantly less than that found in women with an ovulatory PCOS [16]. The analysis showed that women with PCOS, hyperandrogenemia, and oligomenorrhea have the greatest risk for metabolic syndrome [15-17]. Furthermore, the analysis highlighted that women with PCOS had a significantly higher BMI than women not affected by PCOS (30.7 ± 8.9 kg/m^2 versus 24.7 ± 5.4 kg/m^2) [18].

Patients in our group with NAFLD had a greater BMI and weight than those without NAFLD, though the result was not statistically significant. A weak correlation was observed between higher BMI and prevalence of NAFLD; however, the correlation became stronger when patients without NAFLD were removed from the evaluation (Table 2). Together, these findings suggest an association between higher weight or BMI and NAFLD in women with PCOS.

Only, 21.4% of women with PCOS who were evaluated had elevated serum testosterone levels. However, women with PCOS and NAFLD in our group had significantly higher testosterone values than those without NAFLD. In addition, 71.4% of women who were evaluated had elevated DHEAS levels.

NAFLD has been diagnosed in 7% to 16.6% of adults in Saudi Arabia [19,20]. In one report, 80.3% of Saudi patients with NAFLD had normal ALT levels [21]. In contrast, almost all women with PCOS we examined had mild elevations of liver enzymes. Previous work has suggested that Saudi patients with NAFLD and elevated ALT levels were younger, had lower fasting blood sugar, and lower cholesterol levels than patients with a normal ALT [21]. No such differences were observed in our patients with PCOS. PCOS patients we examined with NAFLD did have significantly higher cholesterol and lower LDL levels than those without NAFLD, a finding not previously reported.

NAFLD in the general population is frequently associated with obesity, increased BMI, type II diabetes mellitus, dyslipidemia, and metabolic syndrome [7,10]. Some ethnic groups are particularly at risk for NAFLD [22]. Ninety percent of individuals with NAFLD have at least one risk factor for metabolic syndrome and a third are characterized as having metabolic syndrome [13]. Almost all the patients we evaluated had one risk factor, an elevated BMI. The number of women with Type II diabetes was small and similar in our patients with and without NAFLD.

About 50 to 70% of women with PCOS have insulin resistance and increased insulin levels [15]. Increased insulin levels have been shown to stimulate androgen production in the ovaries and suppress sex hormone-binding globulin levels [23]. Insulin resistance is most common and severe in women diagnosed using the NIH PCOS criteria. We found no difference in the serum insulin levels of our NAFLD and non-NAFLD groups. Insulin levels in our patients were comparable to normal values reported in the literature [24]. The cellular and molecular mechanisms of insulin resistance in women with PCOS are different from those found in patients with obesity and Type 2 diabetes [15]. All women with PCOS have marked decreases in skeletal muscle sensitivity to insulin, compared to women without PCOS, and hepatic insulin resistance is found only in obese women with PCOS. Together, these findings may explain the similar frequency of insulin abnormalities in the two PCOS study groups we evaluated and the high incidence of NAFD in PCOS patients.

Some patients with NAFLD are not obese, but are still at increased risk for cardiovascular disease and diabetes. Between 12 and 16.4% of NAFLD patients in the general population have a normal BMI [7,19,25], although the mean BMI of these patients has been reported to be higher than that of unselected healthy controls with normal BMIs [7]. BMI does not appear to correlate with fasting glucose, HDL, LDL, or cholesterol levels, or the frequency of diabetes, arterial hypertension, metabolic syndrome, steatohepatitis, or advanced hepatic fibrosis in NAFLD patients reported in the literature [13,25]. These findings suggest that "metabolically obese" NAFLD patients with a normal BMI should be evaluated for metabolic syndrome and associated co-morbidities [22].

NAFLD patients with a normal BMI commonly have elevated serum insulin levels and insulin resistance whether or not they have other metabolic disorders [7]. NAFLD patients with a normal BMI have been reported to have significantly less fasting hyperinsulinemia, insulin resistance, diabetes, and metabolic syndrome than obese NAFLD patients, and a greater BMI than lean healthy controls [25]. Similar correlative studies of women with PCOS are lacking. We found no association between increased insulin values, diabetes, or metabolic syndrome and NAFLD in the small number of patients we evaluated.

As many as 89% of NAFLD patients in the general population with a normal BMI have been reported to have elevations in at least one serum lipid concentration [25]. These patients have been reported to have fewer comorbidities and characteristics of metabolic syndrome, and higher ALT and AST levels, than patients with an elevated BMI [7]. Only two of the patients we evaluated had a normal BMI, one without NAFLD had elevated ALT levels and one with NAFLD had increased ALT and cholesterol levels. Together, these findings suggest women with PCOS and normal BMI may still be at risk for NAFLD and other metabolic problems.

There were several limitations to this study. Not all lab values were available for all patients. The number of

patients in this study was small and they were treated at a single hospital infertility center. This cohort may not be representative of all PCOS patients. Our cohort may have been too small to detect some risk factors or associations with statistical significance. The use of different PCOS diagnostic criteria in the literature affects the ability to compare reported studies. The higher incidence of insulin resistance and higher BMI found in patients diagnosed using the 1990 NIH criteria suggests NAFLD will be found in these patients more frequently than in patients we evaluated using the revised 2003 Rotterdam criteria.

PCOS is a common disease requiring significant use of healthcare resources. The health care costs attributed to PCOS in the United States exceeded 4 billion dollars in 2005 [17]. NAFLD is commonly found in women with PCOS, and may be an early sign of metabolic syndrome. Collaborative national or international studies are needed to define health care risks of PCOS patients, using different PCOS definitions in a better way.

Conclusions

NAFLD diagnosed by US was common in patients with PCOS, as per the examination. Patients with NAFLD had higher LDL and cholesterol levels than patients without NAFLD. Women with NAFLD had a trend toward lower HDL, higher weight and BMI, and more difficulty achieving childbirth than patients without NAFLD. PCOS patients with and without NAFLD shared characteristics of metabolic syndrome. Screening for NAFLD and metabolic syndrome in both lean and obese women with PCOS is recommended. Larger studies of women with PCOS are needed to validate this study.

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