

Relation Between Non-Alcoholic Fatty Pancreas and Clinical and Biochemical Parameters in Women with Polycystic Ovary Syndrome: A Multi-Centric Study

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Background: Polycystic ovary syndrome (PCOS) is the most common endocrinological disease affecting women in the reproductive age. Non-alcoholic fatty pancreas disease (NAFPD) can promote many aspects of pancreatic dysfunction. The present study aimed to determine the prevalence of NAFPD and to identify its association with clinical and biochemical parameters in PCOS patients.

Methods: The present study included 150 patients with PCOS and 150 age-matched healthy controls. All patients were submitted to careful history taking and thorough clinical examination. Performed laboratory investigations included fasting and postprandial blood glucose, lipid profile, liver function tests, serum prolactin and total testosterone. Fatty pancreas was diagnosed using abdominal ultrasound.

Results: Among PCOS women, NAFPD was diagnosed in 57 women (38.0%) in contrast to 18 women (12.0%) in the control group ($p < 0.001$). Patients with NAFPD were significantly older [median (IQR): 38.0 (35.0–43.0) versus 29.0 (25.5–33.0) years, $p = 0.001$] with higher BMI [median (IQR): 31.5 (29.1–34.7) versus 30.4 (28.6–32.4) kg/m^2 , 0.042]. Moreover, they had significantly higher frequency of metabolic syndrome (84.2% versus 54.8%, $p = 0.001$), insulin resistance (68.4% versus 26.9%, $p < 0.001$) and severe NAFLD (22.8% versus 2.2%, $p < 0.001$). NAFPD patients had significantly lower sex hormone binding globulin (SHBG) [median (IQR): 36.0 (30.8–40.7) versus 38.1 (35.15–42.7), $p = 0.002$] and significantly higher free androgen index (FAI) [median (IQR): 4.08 (3.3–4.92) versus 3.47 (3.12–4.05), $p < 0.001$].

Conclusion: NAFPD is prevalent PCOS. It is related to metabolic syndrome, insulin resistance, dyslipidemia and hyperandrogenism.

Keywords: polycystic ovary, non-alcoholic fatty pancreas, free androgen index

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinological disease affecting women in the reproductive age. The condition is cardinaly manifested by oligo/ovulation, hyperandrogenism and polycystic ovaries.¹ PCOS is associated with a wide range of clinical manifestations affecting multiple body systems. The metabolic consequences related to PCOS range from insulin resistance to metabolic syndrome, diabetes mellitus and non-alcoholic fatty liver disease (NAFLD).² Hyperandrogenism in particular plays an essential role in the development of metabolic derangement in those patients.³ These effects may be exacerbated by the associated obesity and chronic low-grade inflammation.^{4,5}

The association between PCOS and NAFLD is well documented. It's thought that development of NAFLD in PCOS patients is mediated through reduction of hepatic sex hormone-binding globulin and enhanced apoptotic processes.⁶ In contrast to the liver, fat accumulation in the pancreas is a less-studied condition. It entails a spectrum of pathological states ranging from fatty replacement to non-alcoholic fatty pancreas disease (NAFPD).⁷ NAFPD can promote many aspects of pancreatic dysfunction including insulin resistance, β -cell dysfunction, pancreatitis and pancreatic cancer in affected patients.^{8,9}

Unfortunately, the clinical consequences and interrelations between NAFPD and different clinical conditions are not well studied.¹⁰ Interestingly, recent experimental research revealed that PCOS rat models had significant reduction of pancreatic β -cell mass.¹¹ The present study aimed to determine the prevalence of NAFPD and to identify its association with the clinical and biochemical parameters in PCOS patients.

Patients and Methods

The present cross-sectional study was conducted at Al-Azhar, October 6 and Minia University Hospitals, Egypt. The study protocol was approved by the local ethical committee and informed consent was obtained from all participants. The study included 150 patients with PCOS. Diagnosis was established if at least two of the three 2003 Rotterdam criteria were fulfilled. These criteria included: 1) Chronic ovulatory dysfunction 2) Biochemical and/or clinical evidence of hyperandrogenism and 3) Ultrasound evidence of polycystic ovaries.¹² In addition, there were 150 age-matched healthy controls.

Chronic ovulatory dysfunction was diagnosed in the presence oligomenorrhea (menstrual cycles of 35–90 days) or amenorrhea (absence of menses >90 days). In patients with regular cycles, anovulation was documented by ultrasound and/or mid-luteal phase serum progesterone in two consecutive cycles. Biochemical hyperandrogenism was identified in the presence of total testosterone ≥ 0.73 ng/mL and/or a free androgen index (FAI) ≥ 4.5 ¹³ while clinical hyperandrogenism included hirsutism diagnosed based on a standardized scoring system,¹⁴ acne, or androgenic alopecia.¹⁵ Patients were excluded from the study if they had associated malignancies, liver cirrhosis or autoimmune diseases eg, systemic lupus erythematosus.

All patients were submitted to careful history taking and thorough clinical examination. Performed laboratory investigations included assessment of fasting and postprandial blood glucose, lipid profile, liver function tests, serum prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), sex hormone binding globulin (SHBG) and total testosterone.

In the present study, we defined metabolic syndrome (MetS) according to the Joint Interim Statement criteria.¹⁶ These criteria included elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure and elevated fasting glucose. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the equation: $\text{HOMA-IR} = \text{fasting glycemia (mg/dL)} \times \text{fasting insulinemia (\mu UI/mL)} / 405$.¹⁷ Fatty pancreas was diagnosed using abdominal ultrasound if there is increased echogenicity of the pancreas over the liver or renal cortex.¹⁸ Depending on the echogenicity of the hepatic parenchyma, non-alcoholic fatty liver disease (NAFLD) was classified into three grades: mild, moderate, and severe.¹⁹

Data obtained from the present study were presented as median and interquartile range (IQR) or number and percent. Numerical data were compared using Mann–Whitney *U*-test while categorical data were compared using chi-square test. Correlation analysis was achieved using Spearman correlation coefficient. Binary logistic regression analysis was used to identify predictors of outcome. All statistical computations were processed using SPSS 25.0 with *p* value < 0.05 considered statistically significant.

Results

The present study included 150 women with PCOS and 150 age-matched healthy controls. Among PCOS women, NAFPD was diagnosed in 57 women (38.0%) in contrast to 18 women (12.0%) in the control group (*p* < 0.001). Comparison between patients NAFPD and patients without NAFPD revealed that the former group are significantly older [median (IQR): 38.0 years (35.0–43.0) versus 29.0 years (25.5–33.0), *p* = 0.001] with higher BMI [median (IQR): 31.5 kg/m² (29.1–34.7) versus 30.4 kg/m² (28.6–32.4), 0.042], higher fasting blood glucose (FBG) levels [median (IQR): 94.0 mg/dl (85.0–104.5) versus 90.0 mg/dl (82.0–95.0), *p* = 0.012] and higher total cholesterol levels [median (IQR): 193.0 mg/dl (172.8–233.0) versus 172.0 mg/dl (163.0–224.0), *p* = 0.013]. Also, patients with NAFPD had significantly higher frequency of metabolic syndrome (84.2% versus 54.8%, *p* = 0.001), insulin resistance (68.4% versus 26.9%, *p* < 0.001) and severe NAFLD (10.5% versus 2.2%, *p* < 0.001) (Table 1).

Table 1 Clinical and Metabolic Findings in the Studied Patients (n = 150)

	All Patients N=150	NAFPD +ve n=57	NAFPD -ve n=93	p-value
Age (years) median (IQR)	32.0 (28.0–36.0)	38.0 (35.0–43.0)	29.0 (25.5–33.0)	0.001
BMI (kg/m ²) median (IQR)	30.8 (28.9–32.8)	31.5 (29.1–34.7)	30.4 (28.6–32.4)	0.042
Associated morbidities n (%)				
Diabetes	14 (9.3)	8 (14.0)	6 (6.5)	0.12
Hypertension	47 (31.3)	21 (36.8)	26 (28.0)	0.26
Laboratory parameters median (IQR)				
Hb (gm/dL)	12.6 (11.8–13.2)	12.2 (11.6–12.9)	12.8 (12.0–13.3)	0.25
Albumin (gm/dL)	4.4 (4.1–4.7)	4.3 (4.0–4.6)	4.4 (4.2–4.7)	0.17
Bilirubin (mg/dL)	0.8 (0.8–1.0)	0.9 (0.8–1.0)	0.8 (0.7–0.9)	0.31
AST (U/L)	27.5 (22.0–32.0)	28.0 (22.0–40.0)	27.0 (22.0–32.0)	0.18
ALT (U/L)	30.0 (26.0–38.0)	30.0 (27.0–44.0)	31.0 (26.0–35.0)	0.19
FBG (mg/dL)	90.0 (83.8–100.0)	94.0 (85.0–104.5)	90.0 (82.0–95.0)	0.012
Cholesterol (mg/dL)	175.0 (165.1–208)	193.0 (172.8–233.0)	172.0 (163.0–224.0)	0.013
Triglycerides (mg/dL)	137.0 (111.0–180.0)	171.0 (149.2–190.0)	155.0 (83.0–182.0)	0.009
LDL (mg/dL)	108.0 (92.9–127.0)	115.0 (103.0–142.0)	114.0 (94.0–135.6)	0.17
HDL (mg/dL)	37.4 (36.0–39.5)	36.7 (35.1–39.0)	38.0 (36.0–41.0)	0.015
Creatinine (mg/dL)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	0.86
Metabolic conditions n (%)				
MetS	99 (66.0)	48 (84.2)	51 (54.8)	0.001
IR	64 (42.7)	39 (68.4)	25 (26.9)	<0.001
NAFLD	77 (51.3)	32 (56.1)	45 (48.4)	0.36
NAFLD grades				
Mild	30 (20.0)	4 (7.0)	26 (28.0)	<0.001
Moderate	39 (26.0)	22 (38.6)	17 (18.3)	
Severe	8 (5.3)	6 (10.5)	2 (2.2)	

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; FBG, Fasting blood glucose; Hb, Hemoglobin; HDL, High-density lipoprotein; IR, Insulin resistance; LDL, Low-density lipoprotein; MetS, Metabolic syndrome; NAFLD, Non-alcoholic fatty liver disease; NAFPD, Non-alcoholic fatty pancreas disease.

Regarding the gynecological parameters, it was shown that NAFPD patients had significantly higher testosterone levels [median (IQR): 1.44 ng/mL (1.28–1.65) versus 1.39 ng/mL (1.19–1.53), $p = 0.018$], lower LH levels [median (IQR): 9.61 U/L (8.34–10.74) versus 10.53 U/L (9.56–11.52), $p < 0.001$], lower SHBG [median (IQR): 36.0 nmol/L (30.8–40.7) versus 38.1 nmol/L (35.15–42.7), $p = 0.002$] and higher FAI [median (IQR): 4.08 (3.3–4.92) versus 3.47 (3.12–4.05), $p < 0.001$] (Table 2, Figure 1).

Correlation analysis showed a significant direct correlation between FAI and patients age ($r = 0.24$, $p = 0.003$) (Table 3). It was also noted that patient with MetS had significantly higher FAI than patients without MetS [median

Table 2 Gynecological Parameters in the Studied Patients

	All Patients N=150	NAFPD +ve n=57	NAFPD -ve n=93	p-value
PCOS criteria n (%)				
PCO + HA + MI	27 (18.0)	10 (17.5)	17 (18.3)	0.15
PCO + HA	49 (30.0)	23 (40.4)	26 (28.0)	
PCO + MI	22 (17.3)	4 (7.0)	18 (19.4)	
HA + MI	52 (34.7)	20 (35.1)	32 (34.4)	
Laboratory parameters median (IQR)				
Testosterone (ng/mL)	1.4 (1.22–1.54)	1.44 (1.28–1.65)	1.39 (1.19–1.53)	0.018
FSH (U/L)	4.74 (4.15–5.4)	4.7 (4.18–5.5)	4.77 (4.14–5.36)	0.84
LH (U/L)	10.04 (9.15–11.34)	9.61 (8.34–10.74)	10.53 (9.56–11.52)	<0.001
LH/FSH	2.17 (1.77–2.49)	2.09 (1.57–2.4)	2.24 (1.87–2.6)	0.012
Prolactin (ng/mL)	15.82 (14.1–17.12)	16.12 (14.2–17.6)	15.46 (14.05–16.8)	0.16
SHBG (nmol/L)	37.6 (33.7–41.8)	36.0 (30.8–40.7)	38.1 (35.15–42.7)	0.002
FAI	3.59 (3.19–4.35)	4.08 (3.3–4.92)	3.47 (3.12–4.05)	<0.001

Abbreviations: FAI, Free androgen index; FSH, Follicle stimulating hormone; HA, Hyperandrogenism; LH, Luteinizing hormone; MI, Menstrual irregularities; PCO, Polycystic ovary; SHBG, Sex hormone binding globulin.

(IQR): 3.68 (3.22–4.5) versus 3.47 (3.07–3.98), $p = 0.023$] (Figure 2) and patients with IR had significantly higher FAI when compared with patients without IR [median (IQR): 3.97 (3.22–4.58) versus 3.49 (3.15–4.13), $p = 0.037$] (Figure 3).

Multivariate logistic regression analysis identified patients' age [OR (95% CI): 1.72 (1.4–2.13), $p < 0.001$], FAI [OR (95% CI): 2.23 (1.12–4.46), $p = 0.023$] and IR [OR (95% CI): 4.68 (1.25–17.55), $p = 0.022$] as significant predictors of NAFPD in the studied patients (Table 4).

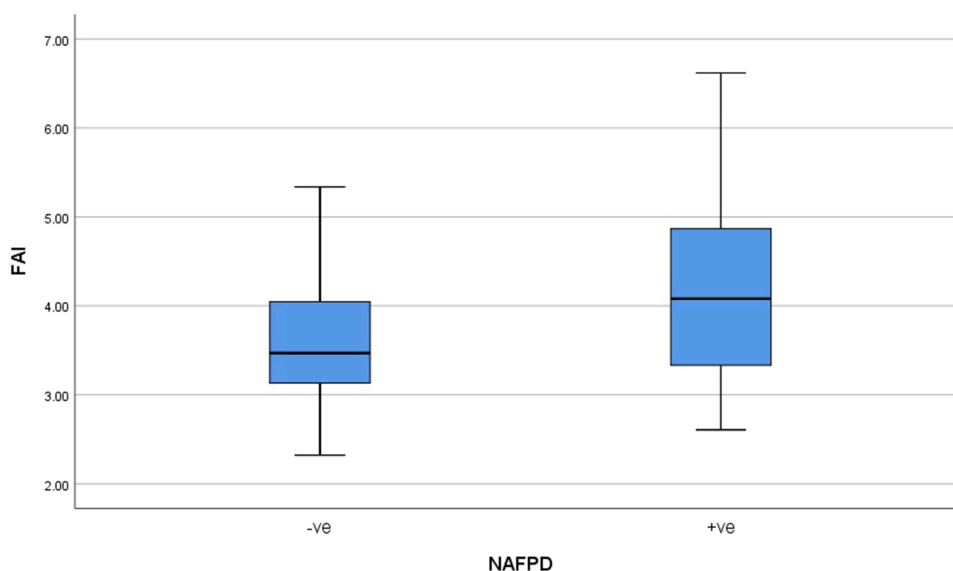
**Figure 1** FAI in patients with and without NAFPD.

Table 3 Correlation Between FAI and Clinical and Laboratory Data

	FAI	
	r	p
Age	0.24	0.003
BMI	0.067	0.42
Hb	-0.002	0.98
Albumin	-0.02	0.81
Bilirubin	0.062	0.45
AST	-0.041	0.62
ALT	-0.029	0.72
FBS	0.12	0.15
Cholesterol	0.078	0.34
Triglycerides	0.045	0.59
LDL	0.062	0.45
HDL	-0.15	0.066
Creatinine	-0.1	0.21
Testosterone	0.73	<0.001
FSH	-0.11	0.16
LH	-0.011	0.9
LH/FSH	0.059	0.47
Prolactin	-0.071	0.39
SHBG	-0.71	<0.001

Discussion

The recent years had witnessed increased clinical awareness of the relatively newly introduced entity of NAFPD. However, knowledge about the condition and its consequences remain limited and the methods of diagnosis are still non-standardized.^{9,20–22} Reportedly, NAFPD has been linked to pancreatic endocrine impairment,²³ increased epicardial adipose tissue and aortic intima-media thickness,²⁴ incident diabetes mellitus^{25,26} pancreatic adenocarcinoma²⁷ and acute pancreatitis.²⁸

In the present study, we identified NAFPD in 38.0% of PCOS patients which is significantly than the 12.0% of NAFPD cases detected in apparently healthy controls. It is remarkable that one study could diagnose NAFPD in 25.9% of patients referred to endosonography.²⁹ This discrepancy is probably attributed to the variable standards used for diagnosis of NAFPD in different studies.

In contrast to our results, a recent study conducted on adolescents found no relation between pancreatic fat and PCOS.³⁰ Conclusions of the latter study are very interesting if taken together with the present study finding that patients' age was independently associated with development of NAFPD in PCOS patients. Probably, the metabolic interactions between PCOS and NAFPD need longer time to be evident as seen in adult patients included in the current study.

In our work, PCOS patients with NAFPD has significantly higher frequency of MetS. This finding is supported by previous studies that documented a significant relation between NAFPD and MetS or its components. For example, Jaghutriz

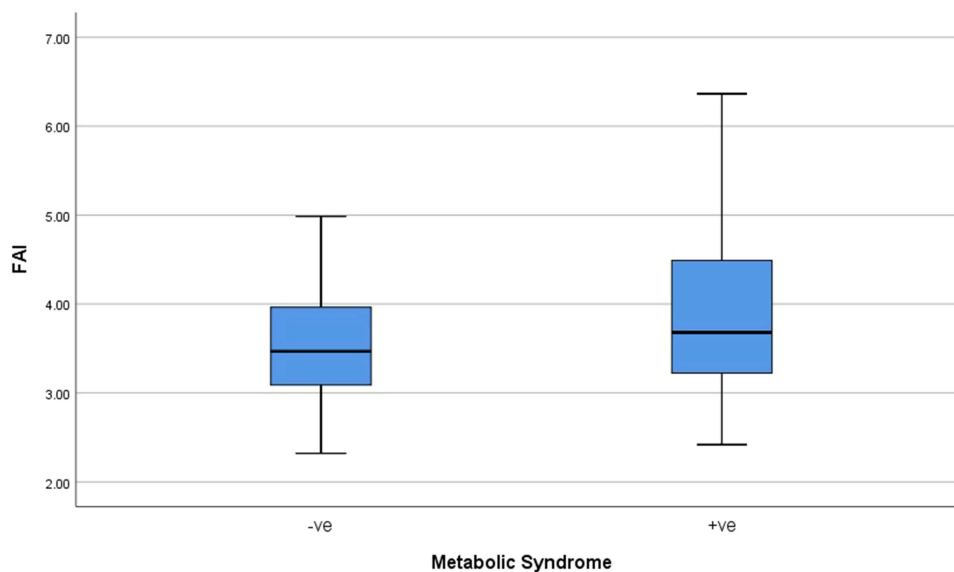


Figure 2 FAI in patients with and without metabolic syndrome.

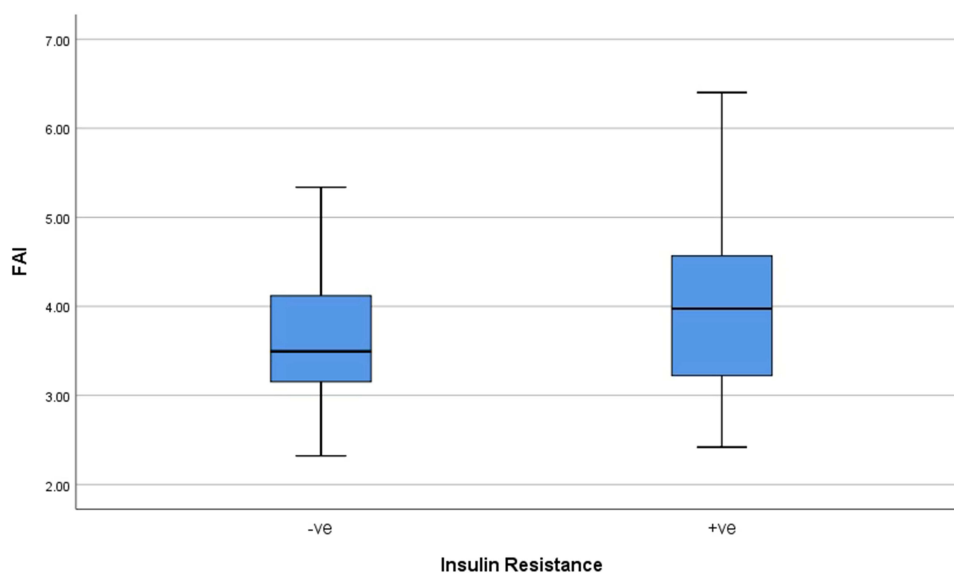


Figure 3 FAI in patients with and without insulin resistance.

et al³¹ who assessed the metabolomic characteristics of fatty pancreas in prediabetics identified as association between NAFLD and obesity. Also, Sotoudehmanesh et al²⁹ and Yu et al³² found an association between NAFLD and dyslipidemia. Furthermore, Chiyanka et al³⁴ reported a significant association between NAFLD and MetS in obese adolescents.

Moreover, the current study noted that most patients with NAFLD had radiologically documented severe form of NAFLD. The association between NAFLD and NAFLD was previously reported.³³ Notably, a computed tomographic study on patients with biopsy-proven NAFLD found a significant correlation between radiological hepatic and pancreatic fat masses.³⁵ It is also exciting to learn that IR is associated with the synergistic effects of both hepatic and pancreatic fat accumulation as shown by one study.³⁶

In the present study, patients with NAFLD had significantly higher FAI when compared with patients without and FAI was associated with NAFLD in multivariate regression analysis. The association between NAFLD and biochemical

Table 4 Predictors of NAFFD in the Studied Patients

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.67	1.4–1.98	<0.001	1.72	1.4–2.13	<0.001
BMI	1.14	1.03–1.26	0.009	1.18	0.97–1.43	0.093
FAI	2.48	1.58–3.88	<0.001	2.23	1.12–4.46	0.023
NAFLD	1.37	0.7–2.65	0.36	1.42	0.43–4.64	0.57
MetS	4.39	1.93–9.98	<0.001	1.14	0.3–4.35	0.85
IR	5.89	2.86–12.14	<0.001	4.68	1.25–17.55	0.022

hyperandrogenism in PCOS women is a novel finding. This association may be explained by the documented link between hyperandrogenism and the metabolic consequences of NAFFD namely metabolic syndrome, insulin resistance and dyslipidemia as shown by the present study. The relation between metabolic syndrome and hyperandrogenism in PCOS women was previously reported.³⁷ Also, Rasool et al³⁸ reported an association between insulin resistance and hyperandrogenism in PCOS women.

In conclusion, the present study found that NAFFD is prevalent in PCOS women as compared to healthy counterparts. It is related to older age, metabolic syndrome, insulin resistance and hyperandrogenism in those patients.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical and Consent

The study protocol was approved by the local ethical committee of October 6 University and informed consent was obtained from all participants in accordance with Helsinki Declaration.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in relation to this work.

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