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Cardiometabolic Risk Factors and Its Association with Hyperandrogenemia Among Sudanese Reproductive Women with Polycystic Ovary Syndrome

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Abstract

Background: Risk factors for cardiovascular disease (CVD) are more common and frequently occur among PCOS women. The objective of this study was to evaluate atherogenic index of plasma (AIP) as a predictor of CVD and its association with hyperandrogenemia among PCOS women.

***Methods and Results*:** This hospital-based study, conducted in Khartoum (Sudan) from October 2020 to September 2021, used a case-control design. The patients (n=150) were women with diagnosed PCOS, according to Rotterdam criteria. The controls were 150 infertile women who did not have PCOS. An ELISA reader (ASYS Expert Plus Microplate, Austria) was used to quantify serum insulin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and anti-Mullerian hormone (AMH) by indirect methods and total testosterone (TT) by competitive method during the follicular phase of the menstrual cycle. Serum samples of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG) were assayed on the Cobas c311 system (Roche Diagnostics GmbH, Germany). The triglyceride–glucose index (TyGI) and TyGI-BMI, as a marker for insulin resistance (IR), were calculated. The logarithmically converted ratio of the molar concentrations of TG to HDL-C was used to determine the AIP. Low CVD risk was defined as < 0.1, medium risk as 0.1– 0.24 and high risk as >0.24.

PCOS women had a significant increase in BMI, compared to non-PCOS (P<0.05). Moreover, 73.4% of PCOS women were overweight to obese. PCOS women were found to have significantly increased serum levels of TC, TG, and LDL-C, as well as significantly increased levels of HOMA-IR and AIP, and a significantly decreased level of HDL-C, compared with non-PCOS women. Overall, among PCOS women, 30.0% had high TC (≥200 mg/dL), 24.7% - high TG (≥150 mg/dL), 29.3% - high LDL-C (≥130 mg/dL), and 46.7% - lower HDL-C (<40 mg/dL). Moreover, 40.6% of PCOS women had medium-to-high CVD risk, and their mean AIP was >0.1. PCOS women with hyperandrogenemia showed significantly increased AIP and decreased HDL-C. Additionally, about 73% of PCOS women with hyperandrogenemia had lower HDL-C, and 29.9% had a high risk of CVD (AIP>0.24). A Spearman correlation revealed that PCOS women's TT correlates positively with TC, TG, TyGI, and AIP and inversely correlates with HDL-C. AIP positively correlates with TT, TC, TyGI, and TyGI-BMI index.

Conclusion: Our data revealed a significant occurrence of hyperandrogenemia, dyslipidemia, AIP, and obesity, all of which are considered risk factors for CVD in PCOS women. PCOS women should be screened, diagnosed, and treated early, which will almost certainly reduce the overall burden of CVD. **(International Journal of Biomedicine. 2023;13(4):261-268.)**

Keywords: PCOS • hyperandrogenemia • hyperlipidemia • atherogenic index of plasma

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Abbreviations

AIP, atherogenic index of plasma; **AMH**, anti-Mullerian hormone; **BMI**, body mass index; **CVD**, cardiovascular disease; **FPG**, fasting plasma glucose; **FSH**, follicle-stimulating hormone; **HDL-C**, high-density lipoprotein cholesterol; **IR**, insulin resistance; **LH**, luteinizing hormone; **LDL-C**, low-density lipoprotein cholesterol; **PCOS**, polycystic ovarian syndrome; **TT**, total testosterone; **TC**, total cholesterol; TG, triglycerides; **TyGI**, triglyceride–glucose index; **T2DM**, type 2 diabetes mellitus.

Introduction

Cardiovascular disease (CVD) is the main cause of death in women worldwide.[1] Risk factors for CVD are more common and frequently occur among PCOS women.[2,3] It is the most prevalent endocrine illness in women of reproductive age.[4] Cardiometabolic abnormalities, such as obesity, dyslipidemia, T2DM, hypertension, metabolic syndrome, and low-grade inflammation, have been linked to PCOS and have been shown to enhance the risk for CVD.[5-7]

Atherogenic hyperlipidemia, the joint occurrence of high fasting TG levels and low levels of HDL-C, is common among patients with metabolic disorders.[8,9] Single lipid indicators are thought to be less accurate predictors of CVD than comprehensive lipid ratios.[10] In this regard, Log10 of the ratio of the molar concentration of TG to HDL-C is used to establish the atherogenic index of plasma (AIP).[10] It possesses a solid and independent prognostic factor for CVD and has demonstrated a good association with LDL-C.[11]

Additionally, atherosclerosis and myocardial infarction have been strongly predicted by AIP.[12,13] TG/HDL-C ratio and fasting triglyceride–glucose index (TyGI) have been linked to CVD in previous research.[14,15] Moreover, some studies have shown that the TC/HDL-C ratio correlates with IR and CVD risk.[16,17]

Investigating CVD risk among PCOS women is important for the investigators as well as the treating doctors. There is no published information on CVD risk among PCOS in Sub-Saharan Africa, including Sudan. Contradictory views on the pattern of atherogenic lipid profile and anthropometric measurement in PCOS encouraged us to conduct the present study.

The objective of this study was to evaluate AIP as a predictor of CVD and its association with hyperandrogenemia among PCOS women.

Materials and Methods

This hospital-based study, conducted in Khartoum (Sudan) from October 2020 to September 2021, used a case-control design. The patients (n=150) were women with diagnosed PCOS, according to Rotterdam criteria. The controls were 150 infertile women who did not have PCOS.

Exclusion criteria were women suffering from CVD and diabetes, women using oral contraceptives, glucocorticoids, ovulation-inducing drugs, and estrogen and anti-androgen medications.

There were no published statistics on the prevalence of PCOS in Sudan when the study was conducted. The prevalence of PCOS in unspecified populations is 3%–10%.

The Sudanese Federal Ministry of Health in Khartoum approved the study protocol. All study participants provided thorough sociodemographic details and medical and gynecological history, including information on menstrual patterns, fertility, and hirsutism. Then, comprehensive general and pelvic exams were carried out.

Weight was measured twice using customary procedures. OMRON BF508l Body Fat Scales (China) were used following calibration. Weight was calculated with a precision of 0.1kg. After calibration, height was measured twice using a portable stadiometer (SECA-213 model, Germany). BMI was calculated and categorized as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2), based on WHO classification.[18]

Women were asked to return on days 2 through 5 following an unforeseen period or on a convenient day if they experienced amenorrhea. Between the hours of 8 and 9 in the morning, 5mL of venous blood was drawn. Hettich Centrifuge D-78532 (Tuttlingen, Germany) was used to centrifuge the blood, and the plasma was then collected and stored at -20°C until the test. An ELISA reader (ASYS Expert Plus Microplate, Austria) was used to quantify serum insulin, LH, FSH, and AMH by indirect methods and TT by competitive method during the follicular phase of the menstrual cycle. Serum samples of TC, TG, LDL-C, HDL-C, and FPG were assayed on the Cobas c311 system (Roche Diagnostics GmbH, Germany). Every time the methodologies employed in this investigation were tested for precision and accuracy, commercially prepared control sera were added to each batch for analysis. The logarithmically converted ratio of the molar concentrations of TG to HDL-C was used to determine the AIP. Low CVD risk was defined as <0.1, medium risk as 0.1– 0.24 and high risk as >0.24.[13] The TyGI and TyGI-BMI, as a marker for IR, were calculated. The TyGI was calculated using the following formula: ln (fasting TG [mg/dL]×FPG [mg/dL]/2).[19] TyGI-BMI, as a marker for IR, was calculated as ln [TG (mg/dl) × FBG (mg/dl)/2] × BMI (kg/m^2).[20] TT>109.5 ng/dL was the threshold for hyperandrogenism.[21]

Statistical analysis was performed using the statistical software package SPSS version 26.0 (SPSS Inc, Armonk, NY: IBM Corp). The normality of the distribution of continuous variables was tested by the one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean (standard deviation [SD]); non-normal variables were reported as median (Me) and interquartile range (IQR [Q1;Q3]). For data with normal distribution, inter-group comparisons were performed using Student's t-test. The Mann-Whitney U Test was used to compare the differences between the two independent groups (for nonparametric data). Group comparisons with respect to categorical variables are performed using chi-square test. Spearman's rank correlation coefficient (R) was calculated to measure the strength and direction of the relationship between two variables. Multiple linear regression was applied using several explanatory

variables to predict the outcome of a dependent variable (AIP). A probability value of $P<0.05$ was considered statistically significant.

Results

PCOS women had a significant increase in BMI, compared to non-PCOS ($P<0.05$). Moreover, 73.4% of PCOS women were overweight to obese. In addition, PCOS women revealed a significant increase in LH, LH/FSH ratio, AMH, and TT levels, and a significant decrease in FSH, compared to non-PCOS women; 70.0% of PCOS women had increased LH/FSH ratio (>1), and 58.7% had hyperandrogenemia (TT>109.5 ng/dL). About 52% of PCOS women had menstrual cycle irregularity (Table 1).

Table 1.
Baseline data of PCOS women and non-PCOS women.

Variable	PCOS (n = 150)	Non-PCOS (n = 150)	*P*- value
Age, year			
Mean ± SD	29.03 ± 6.0	28.5 ± 5.5	0.683
Me [Q1-Q3]	28.5 [25.0- 33.0]	28.5 [24.0- 32.0]	
BMI, kg/m^2			
Mean ± SD	28.6 ± 4.8	22.9 ± 1.3	0.000
Me [Q1-Q3]	28.4 [24.7- 31.6]	22.8 [22.2- 24.0]	
BMI classification			
Normal, n (%)	40 (26.7)	146 (97.3)	0.000
Overweight, n (%)	61 (40.7)	4 (2.7)	
Obese, n (%)	49 (32.7)	0 (0)	
LH, mIU/mL			
Mean ± SD	10.5 ± 6.2	4.4 ± 1.4	0.000
Me [Q1-Q3]	9.2 [5.6 - 14.7]	4.2 [3.3 - 5.2]	
FSH, mIU/mL			
Mean ± SD	6.6 ± 2.9	8.2 ± 2.2	0.000
Me [Q1-Q3]	6.4 [4.9 - 8.2]	8.1 [6.3 - 9.8]	
LH:FSH ratio			
Mean ± SD	1.88 ± 1.4	0.55 ± 0.12	0.000
Me [Q1-Q3]	1.39 [0.91 - 2.27]	0.55 [0.47 - 0.64]	
LH:FSH ratio			
≥ 1, n (%)	45 (30.0)	150 (100.0)	0.000
>1, n (%)	105 (70.0)	0 (0.0)	
TT, ng/dL			
Mean ± SD	214.1 ± 167.2	44.1 ± 28.4	0.000
Me [Q1-Q3]	163.0 [64.7 - 390.0]	39.4 [18.9 - 67.3]	
TT level			
≤109.5 (ng/dL), n (%)	62 (41.3)	148 (98.7)	0.000
>109.5 (ng/dL), n (%)	88 (58.7)	2 (1.3)	
AMH, ng/mL			
Mean ± SD	7.2 ± 3.3	2.3 ± 1.6	0.000
Me [Q1-Q3]	6.1 [5.0 - 7.72]	2.4 [1.6 – 3.0]	

Furthermore, PCOS women were found to have significantly increased serum levels of TC, TG, and LDL-C, as well as significantly increased levels of TyGI-BMI index, insulin, HOMA-IR, and AIP, and a significantly decreased level of HDL-C, compared with non-PCOS women. However, PCOS women revealed insignificant differences in TyGI and FPG when compared with non-PCOS women. Overall, among PCOS women, 30.0% had high TC (≥200 mg/dL), 24.7% - high TG (≥150 mg/dL), 29.3% - high LDL-C (≥130 mg/dL), and 46.7% - lower HDL-C (<40 mg/dL) (Table 2). Moreover, 40.6% of PCOS women had medium-to-high CVD risk, and their mean AIP was >0.1 (Table 2).

Table 2.

Classical and non-classical cardiometabolic risk factors among reproductive women with and without PCOS.

Variable	PCOS (n=150)	Non-PCOS (n=150	*P*-value
TC, mg/dL			
Mean ± SD	190.3 ± 36.8	148.4 ± 22.0	0.000
Me [Q1-Q3]	186.5 [163.7 - 222.0]	151.5[127.0 - 167.0]	
TC level			
≤200 (mg/dL), n (%)	96 (64.0)	149 (99.3)	0.000
>200 (mg/dL), n (%)	54 (30.0)	1.0 (0.67)	
TG, mg/dL			
Mean ± SD	119.6 ± 53.9	108.1 ± 38.1	0.034
Me [Q1-Q3]	105.0 [83.0 - 150.5]	99.0 [78.5 - 136.0]	
TG level			
≤150 (mg/dL), n (%)	113 (75.3)	121 (80.7)	0.265
>150 (mg/dL), n (%)	37 (24.7)	29 (19.3)	
LDL-C, mg/dL			
Mean ± SD	113.9 ± 30.0	84.7 ± 25.3	0.000
Me [Q1-Q3]	113.5 [92.2 - 135.0]	86.5 [66.0 - 104.2]	
LDL-C level			
≤130 (mg/dL), n (%)	106 (70.7)	147 (98.0)	0.000
>130 (mg/dL), n (%)	44 (29.3)	3 (2.0)	
HDL-C, mg/dL			
Mean ± SD	39.9 ± 4.7	47.4 ± 9.1	0.000
Me [Q1-Q3]	40.0 [37.0 - 43.0]	45.0 [40.0 - 53.0]	
HDL-C classification			
<40(mg/dL), n (%)	70 (46.7)	22 (14.7)	0.000
≥40 (mg/dL), n (%)	80 (53.3)	128 (85.3)	
FPG, mg/dL			
Mean ± SD	89.9 ± 12.5	89.7 ± 12.6	0.916
Me [Q1-Q3]	89.0 [81.5 - 97.0]	90.0 [79.0 - 96.2]	
Insulin, mIU/ml			
Mean ± SD	4.48 ± 3.6	0.71 ± 0.7	0.000
Me [Q1-Q3]	2.2 [1.2 - 8.7]	0.5 [0.3 - 0.8]	
HOMA-IR			
Mean ± SD	0.98 ± 0.7	0.15 ± 0.1	0.000
Me [Q1-Q3]	0.45 [0.27 - 1.74]	0.11 [0.06 - 0.17]	

Table 2 (continued).

Classical and non-classical cardiometabolic risk factors among reproductive women with and without PCOS.

Variable	PCOS (n=150)	Non-PCOS (n=150	*P*-value
TyGI			
Mean ± SD	4.5 ± 0.2	4.5 ± 0.2	1.000
Me [Q1-Q3]	4.56 [4.44 - 4.73]	4.53 [4.39 - 4.72]	
TyGI–BMI index			
Mean ± SD	131.8 ± 23.1	104.2 ± 7.3	0.000
Me [Q1-Q3]	130.7 [114.1 - 146.5]	104.4 [99.6 - 108.8]	
AIP			
Mean ± SD	0.08 ± 0.1	-0.022 ± 0.1	0.000
Me [Q1-Q3]	0.017 [-0.09 - 0.18]	-0.023 [-0.15 - 0.12]	
AIP classification			
Low risk, n (%)	89 (59.3)	109 (72.2)	0.000
Medium risk, n (%)	26 (17.3)	30 (20.0)	
High risk, n (%)	35 (23.3)	11 (7.3)	

PCOS women with hyperandrogenemia showed significantly increased AIP and decreased HDL-C, but insignificant differences in age, BMI, TC, TG, LDL-C, TyGI, TyGI-BMI index, and HOMA-IR (Table 3). Additionally, about 73% of PCOS women with hyperandrogenemia had lower HDL-C (<40 mg/dL), and 29.9% had a high risk of CVD (AIP>0.24) (Figure 1).

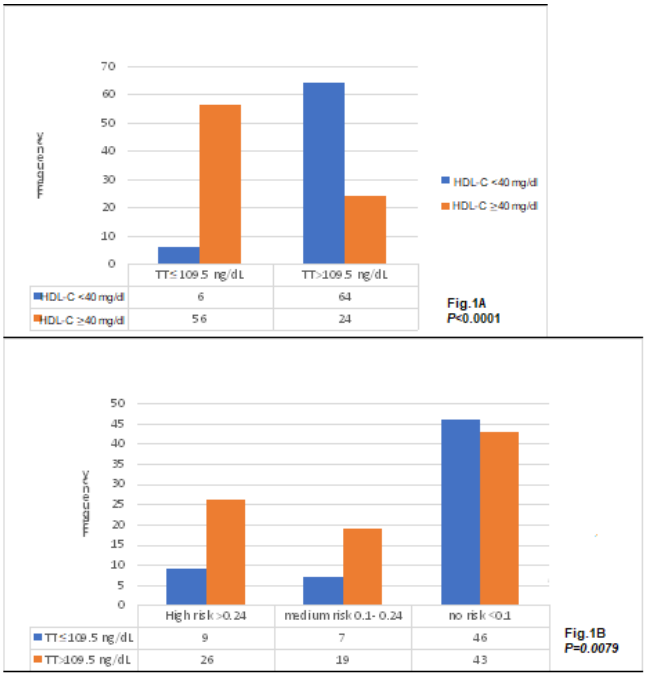

Figure 1.

(A) HDL-C level in association with TT level.

(B) Risk of CVD based on AIP in association with TT level.

Table 3.

Classical and non-classical cardiometabolic risk factors among reproductive women with PCOS based on hyperandrogenemia (cut-off > 109.5 ng/dL)

Variable	TT, ng/dL Mean ± SD		P-value
	≤ 109.5 (n= 62)	>109.5 (n= 88)	
Age, year	29.7 ± 4.9	28.4 ± 5.7	0.202
BMI, kg/m^2	29.0 ± 4.9	28.4 ± 4.7	0.431
TC, mg/dL	185.5 ± 35.5	193.7 ± 37.6	0.178
TG, mg/dl	110.0 ± 45.5	126.5 ± 58.5	0.067
LDL-C, mg/dl	111.5 ± 29.5	115.5 ± 30.4	0.413
HDL-C, mg/dl	43.3 ± 3.8	37.5 ± 3.5	0.000
TyGI	4.5 ± 0.1	4.6 ± 0.2	0.163
TyGI–BMI index	132.7 ± 22.8	131.3 ± 23.8	0.717
FPG, mg/dL	91.7 ± 3.7	88.6 ± 11.5	0.159
Insulin, mIU/ml	4.6 ± 3.7	4.3 ± 3.5	0.706
HOMA-IR	1.17 ± 0.5	1.24 ± 0.6	0.488
AIP	0.01 ± 0.1	0.13 ± 0.1	0.000

A Spearman correlation revealed that PCOS women's TT correlates positively with TC, TG, TyGI, and AIP and inversely correlates with HDL-C. AIP positively correlates with TT, TC, TyGI, and TyGI-BMI index (Table 4).

The multiple linear regression model determined the factors affecting the AIP level among PCOS women. The dependent variable entered in the model was AIP level, whereas age, BMI, LDL-C, TT, and TyGI were the independent variables. Findings revealed that AIP increased significantly with TT, LDL-C, and TyGI (Table 5).

Discussion

Some cardiometabolic risk factors were examined in the current study among Sudanese PCOS. It is thought that obesity, hyperlipidemia, IR, and hyperandrogenemia may be the root causes of this risk. PCOS women's BMI was noticeably greater than non-PCOS. Additionally, 32.7% of PCOS women were obese. Mohammed et al.[22] demonstrated that BMI was significantly higher among Sudanese women with PCOS. Obesity in 31.4% of cases was reported among infertile Jordanian women with PCOS.[23] A higher frequency (63.7%) of obesity was noted in PCOS women in California.[24] This difference may depend on race, ethnicity, location, and environmental factors.

In this study, we hypothesized that PCOS women would suffer from dyslipidemia/hyperlipidemia and AIP. The results of our study showed that low HDL-C was the most common type of dyslipidemia, which was in line with other studies' findings.[25,26]

Table 4.

Spearman correlation between serum TT, AIP and cardiometabolic risk factors among PCOS women.

TT										
Variables	Age	BMI	TC	TG	LDL-C	HDL-C	TyGI	TyGI-BMI	HOMA-IR	AIP
R	-0.103	-0.042	0.184	0.215	0.120	-0.647	0.166	0.012	-0.043	0.345
P-value	0.211	0.608	0.024	0.008	0.144	0.000	0.043	0.882	0.606	0.000
AIP										
	Age	BMI	TC	TG	LDL-C	HDL-C	TyGI	TyGI-BMI	HOMA-IR	TT
R	-0.137	0.005	0.480	0.963	0.331	-0.536	0.898	0.236	0.028	0.345
P-value	0.095	0.953	0.000	0.000	0.000	0.000	0.000	0.004	0.733	0.000

Table 5.

Multiple linear regression with AIP level being a dependent variable.

	Unstandardized coefficients		Standardized coefficients			95% CI	
	B	Std. error	Beta	T	Sig.	Lower bound	Upper bound
Age, years	-0.001	0.001	-0.026	-0.858	0.392	-0.003	0.001
BMI, kg/m^2	-0.001	0.001	-0.036	-1.225	0.223	-0.004	0.001
LDL-C, mg/dL	0.000	0.000	0.076	2.473	0.015	0.000	0.001
TT, ng/dL	0.021	0.004	0.181	6.012	0.000	0.014	0.028
TyGI	0.816	0.029	0.868	28.514	0.000	0.760	0.873

Age, BMI, LDL-C and TyGI were the independent variables entered in the regression model.

The sum of squares = 5.721, R^2 = 0.877, R = 0.936, adjusted R^2 = 0.872, df^2 = 143, F change= 203.467, and significance=0.000.

Our research supported the findings of Iuhas et al.[27] about higher TC and LDL-C levels and lower HDL-C levels in PCOS women. Previous studies by Macut et al.[28] and Lath et al.[29] found that about 70% of women with PCOS had elevated lipid levels. PCOS women exhibited adverse lipid profiles, including a low level of HDL-C, high levels of TG, TC, and LDL-C, and significantly higher lipoprotein concentrations.[30-32] Different classes of dyslipidemia among women with PCOS may be because of androgenemia and IR, which are usually seen among PCOS women.

According to our findings, 58.7% of women with PCOS exhibited hyperandrogenemia (TT>109.5 ng/dL). Likewise, Livadas et al. reported that the prevalence of hyperandrogenemia was 58.8%,[33] but other studies indicated greater prevalence rates of 78.2% and 80%.[34,35] In women with PCOS, hyperandrogenism has been linked favorably to the degree of metabolic dysfunction.[36] Hyperandrogenemia is another risk factor for vascular diseases.[37] This study revealed significantly increased TT values in PCOS women, compared to non-PCOS women.

A direct relation between dyslipidemia and the risk of CVD is well known.[13,38] The AIP is regarded as a stand-alone measure for estimating cardiac risk.[39] Our study revealed a significant association between AIP and TC, LDL-C, TT, and TyGI. Several studies reported that PCOS raises the risk of clinical CVD events.[40,41] Additionally, PCOS women with hyperandrogenemia (TT>109.5 ng/dL) had a significant increase in the mean of AIP and decreased HDL-C level, compared with PCOS women with normal androgen. Moreover, we examined the dependence of AIP on age, BMI, TC, LDL-C, TT, and TyGI. Our study found that AIP was positively associated with TC, LDL-C, TT, and TyGI.

Our finding agreed with the study by Abashova et al.,[42] which demonstrated that PCOS women with hyperandrogenemia had a significant decrease in HDL-C level as an anti-atherogenic type of lipoproteins, compared with normo-androgenic PCOS. Thus, a decreased serum HDL-C level may be associated with cell system failures in implementing anti-inflammatory and antioxidant protection, which contributes to the development of atherogenic dyslipidemia in PCOS. Laura et al.[43] first suggested a positive association between the TyGI and CVD events, including coronary heart failure, cerebrovascular disease, and peripheral arterial disease, independent of confounding factors.

Increased serum cholesterol, LDL, triglycerides, and reduction in HDL indicate the presence of dyslipidemia. Some factors may contribute to the changes in lipid metabolism in patients with T2DM, including IR and/or relative insulin

deficiency and hyperglycemia. The marked significant reduction in vitamins A, E, C, and zinc has been reported by various studies, indicating metabolic abnormalities, which are related to increased cardiometabolic risks. Such reduction may be attributed to the increase in the need to control the excessive oxidative stress produced by abnormalities in glucose metabolism.[44]

The use of AIP may contribute to better and earlier identification of patients at high risk of CVD, especially among those with PCOS and hyperandrogenemia. Women with PCOS, in particular, frequently visit gynecologists for help with infertility and menstruation problems. PCOS patients exhibit a higher incidence of CVD risk factors than non-PCOS women. PCOS women should be screened, diagnosed, and treated early, which will almost certainly reduce the overall burden of CVD.

It is essential to consider the limitations of our study. In the future, a longitudinal study should be carried out to monitor these PCOS women for a certain amount of time and report the actual incidence of CVD. Our findings are regarded as the first study on Sudanese women with PCOS to provide information on the CVD risk. It focused on obesity, AIP, dyslipidemia, and hyperandrogenemia.

Conclusion

The risk of CVD in PCOS-afflicted Sudanese women was brought up in this study. Given that our data revealed a significant occurrence of hyperandrogenemia, dyslipidemia, AIP, and obesity, all of which are considered risk factors for CVD, more research is required on PCOS women under the age of 40. Additionally, relevant actions must be taken to ensure that the general population is educated about PCOS, CVD risk, and their prevention by a multidisciplinary team. The management of PCOS patients should include the early identification of CVD risk factors.

Ethical Considerations

The study was conducted in accordance with ethical principles of the Declaration of Helsinki and approved by the Sudanese Federal Ministry of Health (#: 10-2020). All participants provided written informed consent.

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Competing Interests

The authors declare that they have no competing interests.

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