The role of high serum uric acid levels in androgenic and non-androgenic polycystic ovarian syndrome patients

Ranakishor Pelluri^{a,b,*}, Kongara Srikanth^b, Harika Paritala^a, Vamsi Ravi^a,
Sri Pandu Mukharjee Kamma^a, Kishan Dravid Piduguralla^a, Unnam Venkateswarlu^a,
Jalasuthram Subrahmanyam^a, Kiranmayee Bannaravuri^a, Thanmayee Thunga^a,
Ragini Vemparala^a, Sruthi Doddapaneni^a, Naresh Avulamanda^a, Vathyam Sivani^a,
Srinivasababu Puttagunta^a

^a Department of Pharmacy Practice, Vignan Pharmacy College, Vadlamudi, 52213, Guntur, Andhra Pradesh, India

^b Department of Endocrinology and Metabolism, Endo-Life Speciality Hospital, Guntur, 522001, Andhra Pradesh, India

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ABSTRACT

Background: Serum uric acid (SUA) has been found to be an independent risk factor for metabolic syndrome (MS). However, the reports pertaining to link between uric acid levels among the androgenic, non-androgenic (clinical) PCOS subjects are conflicting. Hence, it was aimed to determine incidence of hyperuricemia and its association among the PCOS subjects.

Methodology: A single centre hospital based cross-sectional study conducted in south India PCOS subjects during the March 2021 to August 2021. A total 80 subjects were recruited and were stratified into androgenic and non-androgenic PCOS with each of forty subjects in both groups. The incidence of hyper uricemia was found to be 66.25% (n = 53).

Results: The mean and SD values of metabolic components such as HbA1C and FPG levels and triglycerides, low density lipoproteins and total cholesterol were showing statistically significant ($p < 0.05$) among the groups. The circulating sex hormone binding globulins (SHBG) are low in both groups. These levels are significantly low in androgenic PCOS subjects. The Total testosterone (TT), SHBG, HOMA-IR and LDL levels were positively correlated with both hyper and non-hyper uricemic groups and remaining parameters showed negative correlation.

Conclusion: The incidence of hyperuricemia is high in PCOS subjects. The TT and SHBG, HOMA-IR and LDL levels were positively correlated with both hyper and non-hyper uricemic groups. HbA1C and FPG and FSI are negatively correlated among the groups.

1. Introduction

The polycystic ovarian syndrome (PCOS) is the most common female endocrinopathy, affecting 8–12% of women of reproductive age¹ and 10–35% of obese women.^{2–5} PCOS is associated with infertility, hyperandrogenemia, impaired glucose tolerance and type 2 diabetes.⁶ During the development of PCOD, some subjects will appear an increase in serum uric acid levels than that of the normal population. Serum uric acid is one of the characteristic factors of metabolic syndrome, the occurrence and development of hyperuricemia is closely associated with insulin resistance, hyperandrogenemia and hyperinsulinemia in subjects with PCOS.⁷

Uric acid is a powerful scavenger of reactive oxygen species and is considered a key antioxidant in humans. However, high serum uric acid concentration is also associated with several diseases, including oxidative stress.⁸ In addition, serum uric acid (SUA) has been found to be an independent risk factor for metabolic syndrome.⁹ The influence of various endocrine hormone changes in women and their association with the SUA level has not been clearly elucidated. Many women with PCOS are characterized by disturbances in reproductive hormones, including androgen, the luteinizing/follicle-stimulating hormone (LH/FSH) ratio and estrogens.^{10–12} In south Indian PCOS individuals, there were inconsistent results and a paucity of data relative to SUA level.^{13–17} Hence, we were aimed to evaluate the incidence of

* Corresponding author. Department of Pharmacy Practice, Vignan Pharmacy College, Vadlamudi, 52213, Guntur, Andhra Pradesh, India.

E-mail address: ranampharm@gmail.com (R. Pelluri).

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hyperuricemia and association between SU and androgenic and non-androgenic PCOS patients.

2. Materials and methods

It was a hospital based cross-sectional study conducted at department of endocrinology and metabolism, Endo-Life Specialty Hospital, Guntur. Subjects with known history of polycystic ovarian syndrome with the age range of 16 years–35 years were included in the study. The study was carried out in serum and plasma samples collected from PCOS subjects attending obesity clinic.

a. Study Population

2.1. Inclusion criteria

All female subjects of PCOS from age range of 18–35 years with the diagnosis of PCOS require the presence of at least two out of the three following criteria (Rotterdam consensus):

- Oligo- or amenorrhoea
- Clinical (particularly hirsutism) and/or biochemical hyper-androgenism (increased testosterone)
- Polycystic ovaries on ultrasound (ovary containing 12 or more peripheral follicles measuring 2–9 mm)

2.2. Exclusion criteria

Subjects with diabetes mellitus, hypertension, thyroid diseases, renal diseases, cardiovascular disease, Cushing's syndrome, pregnant/lactating women, oral contraceptives users, hypoglycemic agents or lipid lowering agents users and hormonal medication users within previous 6 weeks and unwilling subjects were excluded from the study.

Sample size: 40 in each group.

b. Evaluation of Clinical parameters

Clinical variables such as body weight, height, waist circumference (WC) and blood pressure (BP) were measured in participants who had cysts in their ovary confirmed by 2D Transvaginal Ultrasound sonography, and PCOS history was interviewed or examined by a clinical expert. Reviewed the presence of hirsutism, acne, androgenic alopecia and skin pigmentation (at the nape of the neck, axillae, area beneath of the breasts, intertriginous areas and exposed areas (e.g., elbows, knuckles)) and the presence of virilizing signs at upper lip, chin, chest, upper abdomen, lower abdomen, thighs, back, arm and buttocks. The modified Ferriman-Gallwey (mFG) score is the gold standard for the clinical evaluation of hirsutism, if the score ≥ 7 were considered as significant hirsutism.¹⁸ Ovarian dysfunction history such as amenorrhoea of three months and oligomenorrhoea (inter menstrual intervals greater than 35 days) were evaluated. The response was recorded as Yes/No. BMI was calculated as weight (kg) divided by the square of height (m²). Subjects who had a BMI less than 25 kg/m² were enrolled according to the definition of obesity for Asians. 2 dimensional (2D) Trans vaginal ultrasound (TVS) 2D ultrasound was performed at second day menstrual cycle. TVS imaging study helps to examine the ovarian volume and follicular size of both right and left ovaries. Patients are advised to drink 32–35 ounces of water over a 30-min period 1 h before undergoing examination.

c. Evaluation of biochemical parameters

Blood samples were collected from enrolled subjects during the early hours with spontaneous menstrual cycles between the days 3 and 7 of a spontaneous menstrual cycle. The total testosterone levels, SHBG levels

and fasting serum insulin (FSI)S are measure with Electro-Chemiluminescence method (ECLIA). Free testosterone levels are measured by adopting the Enzyme Linked Immuno Sorbant Assay method (ELISA). Serum uric acid levels are measured by Enzymatic (Uricase) method. HbA_{1c} was measured by using VARIANT™ II Hemoglobin Testing System (HPLC of Bio-Rad A1C a fully automated) USA. Fasting plasma glucose (FPG) & Lipid Profile were measured using Roche Cobas c311 respectively. HOMA-IR is calculated using the FSI and FPG levels. The fasting blood samples were collated at second day menstrual cycle and the samples were quantified at central laboratory. The cut-off was fixed at 2.5.²⁹

d. Statistical methods

SPSS 22.0 software was used to analyze all the data. Data are reported as mean $\pm$ SD. The student t-test was applied to find the significance between the groups. The differences among the groups were evaluated by ANOVA test. Pearson's correlation was used to verify correlation between the variables. The p value < 0.05 was considered as statistically significant.

3. Results

In our study, the total eighty female subjects with PCOS were stratified to 40 androgenic and 40 non-androgenic PCOS. In the both groups, all subjects were having BMI > 25 kg/m². The mean blood pressure was significantly high in androgenic than non- androgenic PCOS subjects ($p < 0.05$) (Table 1). The history of PCOS was represented in Table 2. Skin pigmentation showed significant association among the groups. Reamings like hirsutism, androgenic alopecia and virilizing signs were not significant. Among the all PCOS subjects, they exhibit at least two signs and which was significant in both groups. The ovarian dysfunction history was statistically significant among the groups ($p < 0.05$).

Table 3 represents the biochemical parameters among the both groups. The mean and SD values of glycemic parameters such as HbA_{1c} and FPG levels were showing statistically significant in androgenic group ($p < 0.05$). The other glycemic parameters FSI and HOMA-IR values shows statistically non-significant among the groups ($p > 0.05$). The mean and SD levels of serum uric acid was high in androgenic PCOS group and hyperuricemia was significantly associated with androgenic PCOS ($p < 0.05$), hence it is an oxidative stress marker. The significant elevation of lipid levels (such as TG, LDL and Total cholesterol) was observed in androgenic PCOS group ($p < 0.05$). The androgens such as total testosterone and free testosterone levels are significantly high in androgenic PCOS group. The circulating sex hormone binding globulin (SHBG) is a carrier transport for androgens and

Table 1
Demographic characteristic of study subjects.

Parameters	Androgenic PCOS (N = 40)	Non-Androgenic (Clinical) PCOS (N = 40)	95%CI	SE	p. value
Age (Years)	27.28 $\pm$ 6.78	26.37 $\pm$ 5.56	−3.670-(-1.850)	1.386	0.513
BMI (Kg/m ²)	33.67 $\pm$ 1.22	27.05 $\pm$ 2.42	−7.473-(-5.766)	0.429	$< 0.0001^a$
WC (cm)	75.5 $\pm$ 6.6	73.9 $\pm$ 5.5	−4.304-1.104	1.358	0.242
SBP (mm of Hg)	107.65 $\pm$ 3.75	11.68 $\pm$ 4.74	2.127–5.932	0.956	0.0001 ^a
DBP (mm of Hg)	87 $\pm$ 2.44	82 $\pm$ 3.54	−6.353-(-3.646)	0.680	$< 0.0001^a$

BMI: Body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: Diastolic blood pressure.

^a p. value < 0.05 was considered to be statistically significant.

Table 2
PCOS and Ovarian dysfunction history.

PCOS History	Androgenic PCOS (N = 40, 100%)	Non-Androgenic (Clinical) PCOS (N = 40,100%)	p- value
Hirsutism (Yes)	65%	45%	0.074
Acne (Yes)	70%	60%	0.351
Androgenic alopecia (Yes)	55%	40%	0.371
Skin pigmentation (Yes)	70%	40%	0.007 ^a
Virilizing signs (Yes)	45%	35%	0.364
Any of Two above signs	65%	35%	0.007 ^a
Ovarian dysfunction History			
Amenorrhoea of three months (Yes)	75%	45%	0.005 ^a
Oligomenorrhea (Yes)	65%	55%	0.364

^a p. value < 0.05 was considered to be statistically significant.

SHBG will regulates the androgen excess. In our study, SHBG levels are typically low in androgenic PCOS subjects. The decreased SHBG levels are statistically associated with androgenic PCOS group and which was statistically significant ($p < 0.05$). Table 4 depicts the correlation of biochemical parameters among the hyper ($n = 53$) and non-hyper uricemic subjects ($n = 27$). The Total testosterone, SHBG, HOMA-IR and LDL levels were positively correlated with both groups and remaining parameters showed negative correlation.

4. Discussion

In the current study, we found that both the serum uric acid level and incidence of hyperuricemia was higher in androgenic PCOS patients. In addition, a high level of total testosterone was strongly correlated with hyper SUA level. Our results pirating to hypertension, characteristic hyper-androgenemia in young women with PCOS was associated with an elevated SBP and DBP independent of age, and BMI. The results were similar to study conducted at National Taiwan University Hospital, where the free androgen index, total testosterone, and sex hormone-binding globulin, but not the level of dehydroepiandrosterone sulfate, had significantly correlated with blood pressure.¹⁹ In our study, both androgenic and non-androgenic (clinical) PCOS subjects were obese. Hypertension and obesity are much common in androgenic PCOS patients, both of these factors provoke cardiovascular risk.²⁰ PCOS is likely to cause glucose intolerance or insulin resistance and elevation of fasting glucose levels are quite common in PCOS patients,^{21,22} in this present study, HbA1C levels are comparatively high in androgenic PCOS

subjects and FBG and HOMA-IR levels are high in non-androgenic PCOS patients, and the glycemic profile was statistically significant among the groups.

Subjects with Elevated LDL levels and low HDL levels in PCOS are having high risk of cardiovascular diseases. More than 70–80% of south Indian womens with PCOS were established abnormal anthropometric parameters, and lipid abnormalities such as low levels of high-density lipoprotein (HDL) cholesterol and high levels of triglycerides and low-density lipoprotein cholesterol were observed.²³ Similarly, In Iranian obese women with PCOS, were having higher triglycerides and fasting glucose levels are compared to non-PCOS womens. However, the total cholesterol level is higher in non-obese PCOS subjects than healthier.²⁴ In our study, androgenic PCOS subjects were having significantly higher TG and LDL levels than non-androgenic PCOS subjects. The elevated TG levels will aggravate the insulin resistance and pre-diabetes.

A total testosterone is likely to be more reliable than a free testosterone.²⁵ High level of total testosterone (≥ 200 ng/dL (≥ 6.9 nmol/L) is a warrant consideration of an ovarian cancer or adrenal tumor.²⁶ Fortunately, our androgenic and non-androgenic PCOS subjects were having < 3 nmol/L. These levels are significantly higher in androgenic PCOS subjects than non-androgenic PCOS subjects. It indicates that androgens are independent predictors in PCOS.¹⁹

The circulating sex hormone binding globulins (SHBG) are typically low in PCOS subjects and it was unable transport carrier that binds estrogen and androgens and regulates their biological activities, and hence it is a early biomarker as well as prognostic marker in PCOS.^{27,28} In our study, SHBG levels are below the normal value and which was

Table 4
Correlation of biochemical parameters among the hyper and non-hyperuricemic subjects.

Parameters	Hyper uricemia (N = 53)		Non-Hyper uricemia (N = 27)	
	r	p. value	r	p. value
Total Testosterone (nmol/L)	0.75	0.001	0.83	0.001 ^a
Free Testosterone (nmol/L)	−0.54	0.04	−0.66	0.024 ^a
SHBM (nmol/L)	0.61	0.025	0.94	0.031 ^a
HbA1C (%)	−0.12	0.169	−0.36	0.440
FPG (mg/dL)	−0.23	0.092	−0.34	0.379
FSI (mg/dL)	−0.17	0.239	−0.27	0.247
HOMA-IR	0.018	0.86	0.37	0.015
TG (mg/dL)	0.22	0.01	0.42	0.001 ^a
LDL (mg/dL)	−0.52	0.234	−0.63	0.173
HDL (mg/dL)	−0.44	0.823	−0.24	0.283
Total Cholesterol (mg/dL)	−0.56	0.971	0.96	0.151

^a p. value < 0.05 was considered to be statistically significant.

Table 3
Biochemical parameters of androgenic and non- androgenic PCOS subjects.

Parameters	Androgenic PCOS (N = 40) Mean, SD	Non-Androgenic (Clinical) PCOS (N = 40) Mean, SD	95%CI	SE	p. value
HbA1C [$< 6\%$]	5.5 $\pm$ 0.42	4.81 $\pm$ 0.64	−0.931-(−0.449)	0.121	< 0.0001
FPG [75–100 mg/dL]	89.61 $\pm$ 11.92	98 $\pm$ 9.22	3.646–13.133	2.383	0.0007
FSI [2.60–24.90 mg/dL]	23.85 $\pm$ 19.45	22.10 $\pm$ 15.76	−9.630-6.130	3.958	0.6596
HOMA-IR [< 2.5] ²⁹	2.34 $\pm$ 1.83	2.82 $\pm$ 0.95	−0.169-1.129	0.326	0.1450
SUA [2.4–5.7 mg/dL]	5.53 $\pm$ 0.96	4.03 $\pm$ 0.22	−1.810-(−1.190)	0.156	< 0.0001
TG [< 150 mg/dL]	168.32 $\pm$ 12.62	152 $\pm$ 10.04	−21.391-(−11.248)	2.547	< 0.0001
LDL [< 100 mg/dL]	116 $\pm$ 8.54	105 $\pm$ 2.65	−13.814-(−8.185)	1.414	< 0.0001
HDL [> 40 mg/dL]	33.62 $\pm$ 8.36	37.23 $\pm$ 4.62	0.603–6.616	1.510	0.0192
TC [< 200 mg/dL]	175 $\pm$ 22.7	174.9 $\pm$ 27.5	−11.324-11.1247	5.638	0.9859
TT [0.290–1.670 nmol/L]	2.13 $\pm$ 0.86	1.32 $\pm$ 0.35	−1.102-(−0.517)	0.147	< 0.0001
FT [0.00–2.85 pg/ml]	3.79 $\pm$ 0.62	1.98 $\pm$ 0.83	−2.136-(−1.483)	0.164	< 0.0001
SHBG [32.4–128.0 nmol/L]	28.7 $\pm$ 18.36	42.3 $\pm$ 15.22	6.093–21.107	3.771	0.0005

HbA1C- Glycated haemoglobin levels; FPG- Fasting plasma glucose; FSI- Fasting serum insulin; HOMA-IR- Homeostatic model for assessment of insulin resistance; SUA-Serum Uric Acid; LDL-Low density lipoproteins; HDL-High density lipoproteins; TC- Total Cholesterol; TT-Total Testosterone; FT- Free Testosterone; SHBG-sex hormone binding globulin.

p. value < 0.05 was considered to be statistically significant.

significantly high in non-androgenic subjects. In comparison of hyper and non-hyperuricemic subjects with PCOS, total testosterone, SHBG, HOMA-IR and TG levels were showing positive correlation in both groups. The remaining parameters were showing negative correlation among the group.

5. Conclusion

In summary, our findings confirmed that the incidence of hyperuricemia in PCOS subjects was 66.25%. Metabolic components such as HbA1C and FPG levels and TG, LDL and TC are significantly associated with androgenic PCOS. The significant reduction of SHBG was noticed in androgenic PCOS subjects. The Total testosterone, sex hormone binding globulin (SHBG), HOMA-IR and LDL levels were positively correlated with both hyper and non-hyper uricemic groups and remaining parameters showed negative correlation. Longitudinal studies are needed in the future to determine the role of androgens in the development of hyperuricemia.

Compliance with ethical standards

The study procedure was approved by the Institutional Ethics Committee of Endo-life Specialty Hospital, Guntur, India, and Dated: 25th February 2021 (IEC/21/Feb/08). The study was conducted in accordance with good clinical practice guidelines. Informed consent was obtained from all subjects.

Category 1

Conception and design of study: **Kongara Srikanth and Ranakishor Pelluri.**

Acquisition of data: **Sri Pandu Mukharjee Kamma, Kishan Dravid Piduguralla, Kiranmayee Bannaravuri, Thanmayee Thunga, Ragini Vemparala, Sivani Vathyam.**

Analysis and/or interpretation of data: **Ranakishor Pelluri, Harika Paritala, Vamsi Ravi, Naresh Avulamanda.**

Category 2

Drafting the manuscript: **Ranakishor Pelluri, Harika Paritala, Srinivasababu Puttagunta, Sruthi Doddapaneni.**

Revising the manuscript critically for important intellectual content: **Ranakishor Pelluri, Harika Paritala, Kishan Dravid Piduguralla, Unnam Venkateswarlu, Sivani Vathyam.**

Category 3

Approval of the version of the manuscript to be published (the names of all authors must be listed): **Kongara Srikanth and Ranakishor Pelluri.**

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