

A Cross Sectional Study of Serum Uric Acid and Calcium Levels in Women with PCOS in Comparison to Healthy Controls**Bhumika Pareek¹, Manisha Verma², Chhavi Kabra³, S K Vardey⁴**¹Post Graduate M.Sc. (Medical Biochemistry), Department of Biochemistry, SMS Medical College, Jaipur, Rajasthan²Senior Demonstrator, Department of Biochemistry, SMS Medical College, Jaipur, Rajasthan³Assistant Professor, Department of Biochemistry, Indira Gandhi Medical College and Hospital, Shimla, Himachal Pradesh⁴Senior Professor & Former Head of Department, Department of Biochemistry, SMS Medical College, Jaipur, Rajasthan

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Corresponding Author: Dr. Bhumika Pareek

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Abstract:

Introduction: Polycystic ovarian syndrome (PCOS) is one of the most common endocrine diseases in women, affecting 5-10 % of women in the reproductive age is found to be a chronic condition that affects millions of females around the world. To emphasize uric acid is a metabolic end-product of purine metabolism, a strong reducing agent and potent antioxidant. High uric acid levels can lead to several diseases such as heart disease, diabetes, and kidney disease. Also, role of calcium is observed in oocyte maturation as well as in the resumption and progression of follicular development is well observed since times. Polycystic ovarian syndrome (PCOS) is characterized by hyperandrogenic chronic anovulation, theca cell hyperplasia, and arrested follicular development. This study is aimed to compare levels of serum uric acid and calcium levels of PCOS patients in comparison to healthy controls.

Aim and Objective: To evaluate and compare serum uric acid and calcium levels in PCOS patients with age matched healthy controls.

Material and Methodology: Cross-sectional study was conducted in Department of Biochemistry SMS Medical College in association with Department of Gynecology Mahila Chikitsalaya, Jaipur. 80 diagnosed cases of PCOS were included, Calcium and UA levels were compared with healthy controls.

Results: When compared to healthy controls women with PCOS had significantly higher levels of Uric acid and significantly lower levels of serum calcium levels ($p < 0.0001$).

Conclusion: Low serum calcium level seen in women with PCOS which shows disturbed calcium homeostasis in PCOS patients. While high UA levels shows presence of oxidative stress. Uric acid can be used as non-classic cardiovascular risk marker in PCOS patients for early prediction of disease.

Keywords: PCOS (polycystic ovarian syndrome), calcium homeostasis, Uric acid, Oxidative stress.

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Background:-

The multisystem endocrinopathy known as polycystic ovarian syndrome (PCOS) affects a variety of organ systems and manifests itself clinically in women of reproductive age as metabolic abnormalities expressed in the ovaries. [1] Increased ovarian and adrenal androgen secretion, hyperandrogenic metabolic syndrome symptoms such as hirsutism, acne and/or alopecia, irregular menstruation, and polycystic ovaries are its defining characteristics. It is both a metabolic condition and a reproductive endocrinopathy. [2] Around 7 percent of women worldwide and 4 to 11 percent of Indian women who are of reproductive age are affected. [3]

The aetiology is complicated and includes the hypothalamus-pituitary ovarian axis, ovarian theca cell hyperplasia, hyperinsulinemia, as well as a wide range of additional cytokine and adipocyte driven variables. Menstrual irregularities (Anovulation or oligo-ovulation), hyperandrogenic characteristics including hirsutism, acne, or male pattern baldness and infertility are the most common clinical manifestations of PCOS. Physical characteristics such as hirsutism, acne, obesity and other issues also contribute to PCOS's psychological suffering.

Calcium ions engage in regulation of various physiological processes including muscle contraction, cell adhesion, cell division during

growth, ion transport, protein folding, protein degradation, gene transcription, apoptosis and exocytosis. In addition, a number of proteins such as members of the S100 family of calcium binding proteins are also known to form higher order oligomers in a calcium-dependent manner. The importance of calcium in both oocyte activation and maturation, it was hypothesized that abnormalities in calcium homeostasis may, in part underlie the pathogenesis of PCOS. [4] Disordered calcium regulation could be responsible for the follicular arrest manifesting as the reproductive and menstrual disturbances characterizing, in part the PCOS. As PCOS is also characterised by hyperinsulinemia, dyslipidemia and other metabolic disturbances eventually leading to derangement of calcium levels so the present investigation was conducted as an exploratory and observational trial and provides evidence for this hypothesis. [4]

Uric acid being a metabolic by product of purine metabolism functions as a powerful reducer and antioxidant. Animal studies showing that androgens may raise blood uric acid levels by stimulating the hepatic metabolism of purines provide support for the potential link between androgens and serum uric acid concentrations. The few research that are currently available on serum uric acid levels in PCOS patients have shown mixed outcomes. [5] So we planned this study to estimate the levels of

serum calcium and uric acid levels in PCOS patients and to compare them with healthy controls.

Materials and Methods

A Hospital-based comparative study was conducted in department of Biochemistry SMS Medical College in association with department of Gynecology, Mahila Chikitsalaya, Jaipur. 80 Non-pregnant women with PCOS were included as a case and compared with age matched normal healthy women and evaluated for Serum calcium levels & Serum Uric acid levels. Non-pregnant women diagnosed with oligomenorrhoea / amenorrhoea, hyperandrogenism, Age between 18 to 40 years who gave informed consent and diagnosed as PCOS by ultrasound were included while female with Age < 18 yrs and > 40 yrs, Patients with diabetes mellitus, hypertension, thyroid disorder, renal diseases, cardiovascular diseases, Pregnant or lactating women, Female on Oral contraceptives or hormonal medication within the previous six weeks were excluded from this study.

Results

Total 80 patients of PCOS were included in this study and uric acid, calcium levels were estimated and compared with normal healthy females. Mean age in PCOS patients was 24.36 ± 4.85 years and in controls it was 25.68 ± 4.30 years. Difference was statistically non-significant ($p=0.70$).

Table 1: Comparison of Different variables between PCOS cases and Control group

Variables	No of Cases	Cases	Controls	p value
Age(years)	80	24.36 ± 4.85	25.68 ± 4.30	0.07
Calcium(mg/dl)	80	8.05 ± 1.53	9.27 ± 0.62	<0.0001
Uric acid(mg/dl)	80	4.09 ± 1.15	3.37 ± 0.57	<0.0001

Mean Calcium in patients with PCOS was 8.05 ± 1.53 mg/dl and in controls mean Calcium level was 9.27 ± 0.62 mg/dl. This difference was statistically significant ($p < 0.0001$).

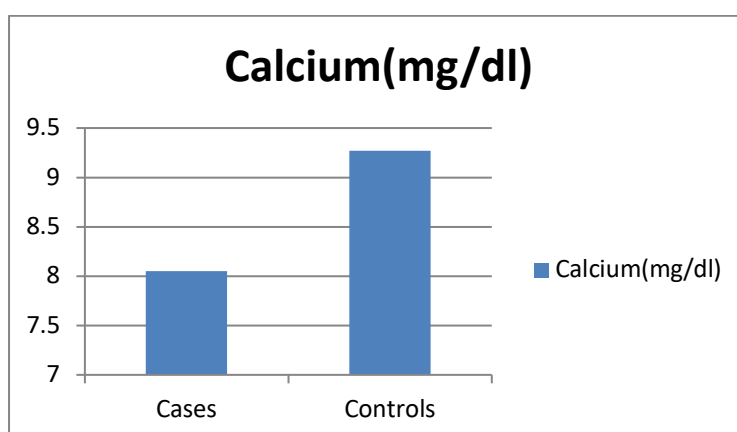


Figure 1: Comparison of Mean Calcium between PCOS and Control group

Mean Uric acid in patients with PCOS was 4.09 ± 1.15 mg/dl and in controls mean Uric acid level was 3.37 ± 0.57 mg/dl. This difference was statistically significant ($p < 0.0001$).

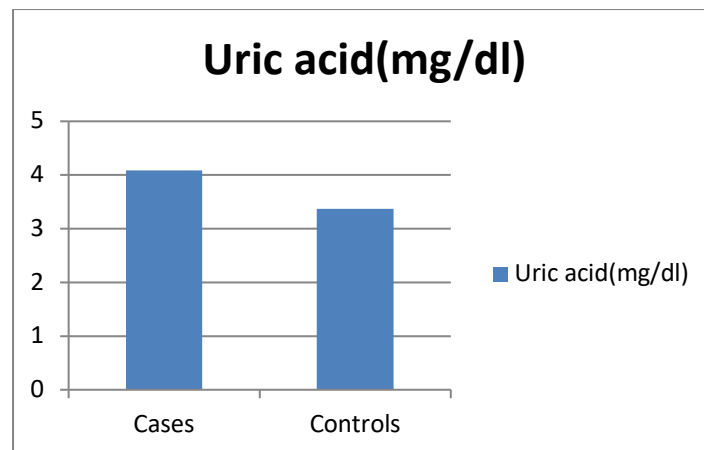


Figure 2: Comparison of Mean Uric acid between PCOS and Control group

Table 2: Correlation of Uric acid and Calcium in PCOS patients

Parameters	Correlation coefficient (r)	P-value
UA v/s Ca	-0.22	<0.05

We found significant negative correlation between Uric acid levels and Calcium levels in PCOS females.

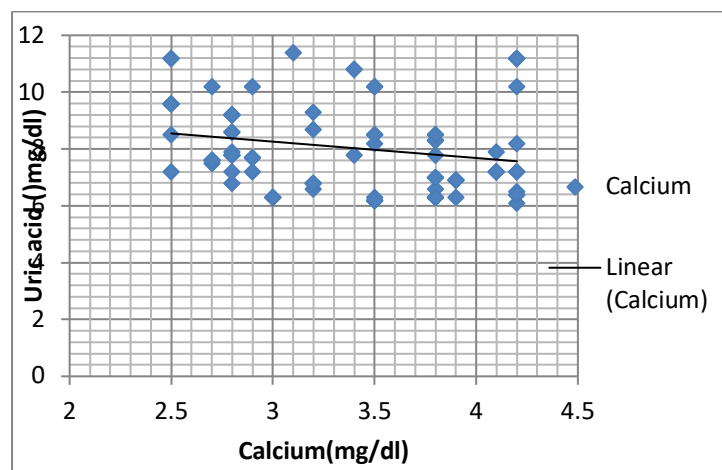


Figure 3: Correlation of Uric acid and Calcium in PCOS patients

Discussion

Polycystic ovarian syndrome (PCOS) is a heterogeneous, multisystem endocrinopathy in women of reproductive age manifested with various metabolic disturbances and a wide spectrum of clinical features such as obesity, menstrual abnormalities and hyperandrogenism. Current incidence of PCOS (5-6%) in women is related to change in lifestyle and stress [6]. Many scholars have conducted research on the relationship between uric acid or hyperuricemia and adiposity/ body fat distribution. [7] However, as far as we know, there are few epidemiological studies evaluating the relationship between uric acid or hyperuricemia and body fat distribution in patients with PCOS. There are suggestions that calcium has important role in activation and maturation of oocyte in animals [8]; therefore, abnormalities in calcium metabolism may play an important role in pathogenesis of PCOS.

Additionally, recent data have suggested that both calcium and vitamin D supplements may improve insulin sensitivity in PCOS women. [9] So our aim in this study was to investigate the levels of serum uric acid and serum calcium in PCOS patients and compare them with healthy controls. Mean age of patients with PCOS which was called as cases was 24.36±4.85 years and for normal healthy controls it was 25.68±4.30 years. There was no statistically significant(p=0.70) difference between both groups which shows our study is age matched in respect of cases and controls. In this study we found means serum uric acid levels in cases was 4.09±1.15 mg/dl while in controls mean levels of uric acid was 3.37±0.57 mg/dl. It shows significantly high (p<0.001) levels of Uric acid in patients with PCOS in comparison to controls. Similar results obtain by Sunita M. Aghade et al [10] in 2017 they found in their study that uric acid levels were significantly increased in PCOS women and showed positive correlation with BMI and W/H ratio. Another study

by N. Swetha et al [11] in 2013 found similar results, Ramzi J. et al [12] in 2017, Guddanti Rajeswari et al [13] in 2016 also found similar findings. They concluded that uric acid can be used as non-classic cardiovascular risk marker in PCOS patients for early prediction of disease. However contrast results found by Anttila et al [14] in 1996. and Manuel et al [15] in 2008 they reported that no differences in uric acid levels were detected between women with PCOS and control women. Increased uric acid levels in PCOS women can be explained by the inhibitory effect of hyperinsulinemia on renal excretion of uric acid [16]. Endothelial dysfunction and chronic inflammation in PCOS also contributes to elevated uric acid level. Studies have shown that, decrement in serum uric acid concentration of high-risk patients improved the endothelial function and resulted in reduced cardiovascular morbidity and mortality [17]. As PCOS women have 50% increased risk for cardiovascular complications, serum uric acid can be used for early detection of high risk patients. Another possible mechanism might be due to Androgen excess. Androgen excess is a common characteristic in PCOS and promotes metabolic disorders [18]. Androgens might also influence uric acid metabolism to some extent. Higher SUA concentrations in men compared with women supported a possible correlation between androgen and uric acid [19]. It was observed that free testosterone was positively associated with uric acid concentration in healthy female population [20].

In this study we found mean calcium level in cases 8.05 ± 1.53 mg/dl and in controls 9.27 ± 0.62 mg/dl. It shows significantly low ($p < 0.001$) levels of calcium in patients with PCOS. When we compared the uric acid and calcium levels in PCOS patients we found negative ($r = -0.22$) significant ($p < 0.05$) correlation between them. It shows in PCOS patients as uric acid levels increases calcium levels decreases. Similar study conducted by Sahar Mazloomi et al [21] in 2012 found women with PCOS had significantly lower calcium and 25-OHD concentrations than ovulatory normal women. This difference remained significant for both groups after adjustment for BMI. Similar finding describe by other studies conducted by T. Mahmoudi et al [22] 2010, S. Hahn R et al [23] in 2006. Yildizhan et al [24] in 2009. Contrast results found in the study conducted by Ashraf Moini al [25] in 2015 they found PCOS group had lower levels of calcium and 25(OH)D levels but this difference was not statistically significant. ($p=0.88$) A possible mechanism for this might be some researchers have demonstrated the role of calcium in oocyte activation and maturation [26] and hypothesized that disturbances in calcium homeostasis may mediate the pathogenesis of PCOS. Additionally, recent data have suggested

that both calcium and vitamin D supplements may improve insulin sensitivity in PCOS women [27]

Conclusion:-

Until now, management of PCOS is typically focused on the specific symptoms such as menstrual irregularity and infertility. However, looking into the intricate nature of the syndrome, a large number of complications will have to be addressed in the near future. PCOS has a long prodromal phase with noticeable abnormalities throughout the life cycle of affected women. Accordingly, adolescent girls with PCOS should be evaluated and treated in a manner analogous to adult PCOS. This will ensure quality health in adulthood, awareness and will reduce the healthcare burden. In our study, significantly increased uric acid levels and significantly decrease calcium levels found in PCOS patients. These parameters are associated with untoward healthcare outcome. Use of these simple biochemical variables might prove worthwhile in early perception of adverse health consequences in PCOS. This will help to redefine the paradigms of PCOS care in India. It seems that there is an emergent need for supplement therapy and screening programs among our women in reproductive age-PCOS and non-PCOS groups for these parameters.

References:-

1. Padubidri VG, Daftary SN. Disorders of the Ovary and Benign Tumours. In: Howkins and Bourne eds. Shaws textbook of gynaecology. 14th ed. India: Elsevier Publication. 2008: 331.
2. Anuradha Kalra, Sreekumaran Nair, Lavanya Rai. Association of obesity and insulin resistance with dyslipidemia in Indian women with polycystic ovarian syndrome. Indian J Med Sciences 2006; 60(11): 447-453.
3. Ramanand SJ, Ghongane BB, Ramanand JB, Patwardhan MH, Ghanghas RR, Jain SS. Clinical characteristics of polycystic ovary syndrome in Indian women. Indian J Endocr Metab 2013; 17:138-145.
4. Susan Thys-Jacobs a, Daniel Donovan b, Anatasio Papadopoulos b, Philip Sarrelc, John P Bilezikianb d Vitamin D and calcium dysregulation in the polycystic ovarian syndrome, June 1999;64(6); 430-435.
5. Manuel Luque-Ramirez, Francisco Alvarez-Blasco, Miguel Giovanni Uriol Rivera and Hector F. Escobar-Morreale. Serum uric acid concentration as non-classic cardiovascular risk factor in women with polycystic ovary syndrome: effect of treatment with ethinyl-estradiol plus cyproterone acetate versus metformin. Human Reproduction (2008); Vol.23: 1594-1601.

6. Disorders of the ovary and benign tumours. In: Padubidri VG, Daftary SN, editors. Howkins & Bourne Shaw's textbook of gynaecology. 15th ed. New Delhi: Elsevier; 2011; 369-71.
7. Rospleszcz S, Dermyski D, Muller-Peltzer K, Strauch K, Bamberg F, Peters A. Association of Serum Uric Acid With Visceral, Subcutaneous and Hepatic Fat Quantified by Magnetic Resonance Imaging. *Sci Rep*. 2020; 10(1):442.
8. DeFelici M, Dolci S, Siracusa G. An increase of intracellular free Ca²⁺ is essential for spontaneous meiotic resumption by mouse oocytes. *J Exp Zool*. 1991; 260(3): 401-405.
9. Kosta K, Yavropoulou MP, Anastasiou O, Yavos JG. Role of vitamin D treatment in glucose metabolism in polycystic ovary syndrome. *FertilSteril*. 2009; 92(3): 1053-1058.
10. Sunita M. Aghade, Jayashree S. Bavikar. Assessment of glycated hemoglobin and uric acid level in polycystic ovarian syndrome in a Tertiary Care Institute of Marathwada region *International Journal of Clinical Biochemistry and Research*, January-March, 2018;5(1):49-53
11. N. Swetha, R. Vyshnavi, P. Modagan, Balaji-Rajagopalan. A Correlative Study of Biochemical Parameters in Polycystic Ovarian Syndrome. *Int J Biol Med Res*. 2013;4(2):3148-54
12. Ramzi J, Dr. Fouzia. B, Mr. Prabhachandran. Evaluation of Biochemical Parameters in Polycystic Ovarian Syndrome. *JMSCR*. March 2017;5(3):19078-83.
13. Guddanti Rajeswari, Pasadugala Satya Gopal, Budidi Veerabhadru, Eadala Suresh. Study of Magnesium levels in Polycystic Ovarian Syndrome. *IJASR*. 2016;2(02):054-8.
14. Anttila L, Rouru J, Penttila T, Irjala K. Normal serum uric acid concentrations in women with polycystic ovary syndrome. *Hum Reprod*. 1996; 11:2405-7.
15. Luque-Ramirez M, Alvarez-Blasco F, Uriol Rivera MG, Escobar-Morreale HF. Serum uric acid concentration as non-classic cardiovascular risk factor in women with polycystic ovary syndrome: effect of treatment with ethinylestradiol plus cyproterone acetate versus metformin. *Hum Reprod*. 2008;23: 1594-601.
16. SeerlaLalitha Devi, Syed Abdul Jaweed. Homocysteine, C-Reactive Protein and Traditional Cardiovascular Risk Markers In Polycystic Ovary Syndrome. *Int J Cur Res Rev*. March 2013;5(6):59-68.
17. Letiția Elena Leustean, Cristina Dimitriu, Simona Fica, Maria-Christina Ungureanu, Cristina Preda, et al. Serum Uric Acid Concentration in Overweight and Obese Women with Polycystic Ovary Syndrome. *Revista Romana de Medicina de Laborator*. March 2015; 23(1): 107-114.
18. Condorelli RA, Calogero AE, Di Mauro M, Mongioi LM, Cannarella R, Rosta G, La Vignera S. Androgen excess and metabolic disorders in women with PCOS: beyond the body mass index. *J Endocrinol Investig*. 2018; 41:383-8.
19. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. *National Health and nutrition examination survey*. *Jama*. 2000; 283:2404-10.
20. Mantzoros CS, Georgiadis EI, Young R, Evagelopoulou C, Khoury S, Katsilambros N, Sowers JR. Relative androgenicity, blood pressure levels, and cardiovascular risk factors in young healthy women. *Am J Hypertens*. 1995; 8:606-14.
21. Sahar Mazloomi,¹ Faranak Sharifi,² Reza Hajhosseini,³ Sadroddin Kalantari,⁴ and Saideh Mazloomzadeh⁵ Association between Hypoadiponectinemia and Low Serum Concentrations of Calcium and Vitamin D in Women with Polycystic Ovary Syndrome *International Scholarly Research Network ISRN Endocrinology Volume 2012, Article ID 949427, 6.*
22. T. Mahmoudi, H. Gourabi, M. Ashrafi, R. S. Yazdi, and Z. Ezabadi, —Calcitropic hormones, insulin resistance, and the polycystic ovary syndrome, *Fertility and Sterility*, 2010; 93(4): 1208-1214.
23. S. Hahn, U. Haselhorst, S. Tan et al., —Low serum 25- hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome, *Experimental and Clinical Endocrinology and Diabetes*, 2006; 114(10): 577 -583.
24. R. Yildizhan, M. Kurdoglu, E. Adali et al., —Serum 25- hydroxyvitamin D concentrations in obese and non-obese women with polycystic ovary syndrome, *Archives of Gynecology and Obstetrics*, 2009; 280(4):559-563.
25. Ashraf Moini, M.D., Nooshin Shirzad, M.D., Marzieh Ahmadzadeh, M.D., Reihaneh Hosseini, M.D., Ladan Hosseini, M.Sc., Shahideh Jahanian Sadatmahalleh, Ph.D., 5 Comparison of 25-hydroxyvitamin D and Calcium Levels between Polycystic Ovarian Syndrome and Normal Women *Int J FertilSteril*, Apr-Jun 2015;9:1.
26. DeFelici M, Dolci S, Siracusa G. An increase of intracellular free Ca²⁺ is essential for spontaneous meiotic resumption by mouse oocytes. *J Exp Zool*. 1991; 260(3): 401-405
27. Kosta K, Yavropoulou MP, Anastasiou O, Yavos JG. Role of vitamin D treatment in glucose metabolism in polycystic ovary syndrome. *FertilSteril*. 2009; 92(3): 1053-1058.