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Serum Vitamin D Level and Insulin Resistance in Obese Adolescent with Polycystic Ovary Syndrome (PCOS)

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS is characterized by the presence of polycystic ovaries, menstrual dysfunction, infertility, and biochemical and clinical hyperandrogenism. The objective of this study was to evaluate the serum vitamin D Level and Insulin Resistance in Obese Adolescents with polycystic ovary syndrome (PCOS). The study was a cross-sectional study conducted among 94 PCOS women of reproductive age coming to the Department of Endocrinology & Metabolism of Bangabandhu Sheikh Mujib Medical University (BSMMU). The women with polycystic ovary syndrome were considered as the study population. Among the participants, around 91% had vitamin D deficiency and 4% had vitamin D insufficiency, no participants had a sufficiency. Among PCOS patients underweight was 42.10%, Healthy Weight 45.27%, pre-obese 9.63%, and obese 3.0%. Regarding fasting insulin levels (<20uIU/ml) among 14.9% of PCOS. In the comparison of clinical characteristics of the participants, less than half (37.2%) had painful menstruation and 67% had hirsutism. Adolescent girls with PCOS are mostly vitamin D deficient and the rate of obesity is also high. The results of this study brought the true picture of insulin resistance and metabolic syndrome among different phenotypes of women with PCOS in Bangladesh, very likely contributing to a better understanding of the management of PCOS, and patients will benefit individually in their

management. Estimation of vitamin D levels & and examination the obesity may help the clinician to manage obesity cases with PCOS adolescents more efficiently.

Keywords: PCOS, Serum Vitamin D Level, Insulin Resistance, Metabolic Syndrome, Adolescent girls

1. Background

Polycystic ovary syndrome (PCOS) is a complex disorder affecting the hypothalamic-pituitary- ovarian axis with an estimated prevalence of 5-10% in reproductive age women (Ehrmann, 2005). PCOS is characterized by chronic anovulation leading to menstrual irregularities and hyperandrogenism associated with hirsutism and acne. PCOS is often associated with obesity and insulin resistance leading to metabolic disturbances including impaired glucose tolerance, type 2 diabetes mellitus, and dyslipidemia (Wild et al., 2011). Other associated health concerns include infertility, endometrial hyperplasia, and cancer. Vitamin D is thought to regulate gene transcription through vitamin D receptors (VDR) that are widely distributed in tissues including ovaries (Ehrmann, 2005). Lower, similar, and higher concentrations have been reported in women with PCOS (Thys-Jacobset al., 1999; Rashidi et al., 2009; Parikh et al., 2010). Given the high rate of obesity among women with PCOS and the fact that, in the general population, a low concentration of vitamin D has been associated with obesity (Pal et al., 2012; Raja-Khan et al., 2014). Elevated androgen levels in PCOS cause unfavorable derangements in adipose tissue and in glucose metabolism (Tsakova et al., 2012). It has been proposed that the connection between vitamin D and PCOS arises from the endocrine pathways affected in PCOS, such as sex hormone synthesis and insulin secretion (Yildizhan et al., 2009; Mahmoudi et al., 2010). However, clinical trials involving vitamin D supplementation in women with PCOS have shown conflicting or weak results in terms of improving insulin sensitivity and other metabolic factors, such as low-grade inflammation and androgen levels (Gordon, et al., 2004; Dong et al., 2010; Holick et al., 2011). Vitamin D has important roles in various parts of the body, especially in the bones. The active form of vitamin D plays an important role in bone metabolism, regulation of calcium-phosphorus equilibrium, and cell differentiation and proliferation (Walter 1992, Studzinski et al., 1993). Vitamin D deficiency is quite common in the general population. In fact, in several studies, vitamin D levels were found to be below 20ng/ml in 10-60% of adults (Prentice 2008, Lips 2010). Serum 25-hydroxy vitamin D (25-OHD) concentrations of below 20ng/ml are considered as vitamin D deficiency and serum 25-OHD concentrations of 20-30ng/ml are considered as vitamin D insufficiency (Holick 2007). 1,25-OHD increases insulin synthesis and secretion (Teegarden et al., 2009) and regulates steroidogenesis in the human ovarian tissue (Parikh et al., 2010). In addition, genetic PCOS related to vitamin D receptor variants has been described (Ranjzad et al., 2011).

In the light of this information, there is a debate about whether vitamin D deficiency plays a role in PCOS pathogenesis. Studies comparing vitamin D levels between patients with PCOS and healthy adolescents with normal ovulation have yielded conflicting results. Some studies have shown that vitamin D levels do not change in patients with PCOS (Li et al., 2011, Panidis et al., 2005), while others have reported higher levels (Mahmoudi et al., 2012) or low levels (Wehr et al., 2010, Mazloomi et al., 2012) of vitamin D. A study by Begum F, 2009 showed insulin resistance was 42% in PCOS patients and another study by Islam S, 2015 showed metabolic syndrome in PCOS patients was 15.3% in Bangladesh. To our knowledge, no study has yet been done to see the vitamin D status of PCOS adolescent patients in Bangladesh. So, the present study is designed to determine the status of vitamin D in PCOS adolescents and to find out its relationship with BMI in polycystic ovary syndrome in Bangladesh.

This study focuses on the serum vitamin D level and insulin resistance in obese adolescents with polycystic ovary syndrome (PCOS).

2. Methodology

This cross-sectional study was conducted in the Department of Endocrinology & Metabolism of Bangabandhu Sheikh Mujib Medical University (BSMMU) for a year period. The adolescent with polycystic ovary syndrome (PCOS) was considered as the study population. In this study total of 94 adolescent girls with PCOS were enrolled

who visited the Endocrinology and Metabolism Department for treatment purposes. Written informed consent was taken from their guardians and verbal consent was taken from the participants. PCOS was diagnosed by Rotterdam criteria. The participants were unmarried adolescents aged between 17-19 years. A semi-structured questionnaire was used to collect the data by face-to-face interview. To estimate the Vitamin D level blood sample were collected between 8 am to 10 a.m. Then vitamin D levels were estimated. The [25(OH) D] cutoffs to define deficiency and insufficiency vary and have most recently been framed by the 2011 desirable levels of the Institute of Medicine Report and the Endocrine Society Guidelines. According to these guidelines, vitamin D deficiency was defined in the present study as a concentration of 25(OH) D < 20 ng/mL and between 20 and 29.9 ng/mL as insufficiency and a concentration ≥ 30 ng/mL as sufficient. The BMI of the participants was calculated using a standard formula, $BMI = \text{Weight (kg)} / [\text{height (m)}]^2$ and classified according to the WHO guideline (WHO, 2021)

3. Results

Table 1 shows the socio-demographic parameters of the participating adolescent girls. Most of the participant's (48.2%) age was ≥ 16 years. 87% of the respondents were unmarried and around 48.9% of the participants had family member's ≥ 5 . Around 29.8% of the parents of the participants were private service holders. Around half of the participants (48.9%) had less than 40,000 takas monthly family income. Next to them, 39.4% of the participants had a family income of 40000 to 1 lac taka.

Table 1: Sociodemographic characteristics of the respondents (N=94)

Characteristics		n (%)
Age (years)	< 16 years	46 (46.5)
	≥ 16 years	48 (48.5)
Marital status	Married	8 (8.1)
	Unmarried	86 (86.9)
Family Member	<5 persons	48 (51.1)
	≥ 5 persons	46 (48.9)
Parents Occupation	Government Service	7 (7.4)
	Private Service	23 (24.5)
	Businessman	13 (13.9)
	Farmer	28 (29.8)
	Labor	23 (24.5)
Monthly Family Income	<40000	46 (48.9)
	40000-1 Lac	37 (39.4)
	>1 Lac	11 (11.7)
Monthly Family Income (In thousand) [Mean \pm SD]		51968 \pm 33725

Figure 1 shows the vitamin D level of the respondents. The mean Vitamin D of the patients was 13.13 ± 3.27 ng/ml. The majority of the participants, 90.9% had deficient vitamin D levels as < 20 ng/ml. Only 4% of participants were in the insufficient level of vitamin D as 20-29.9 ng/ml. In this study, no respondents had a sufficient level of vitamin D as ≥ 30 ng/ml.

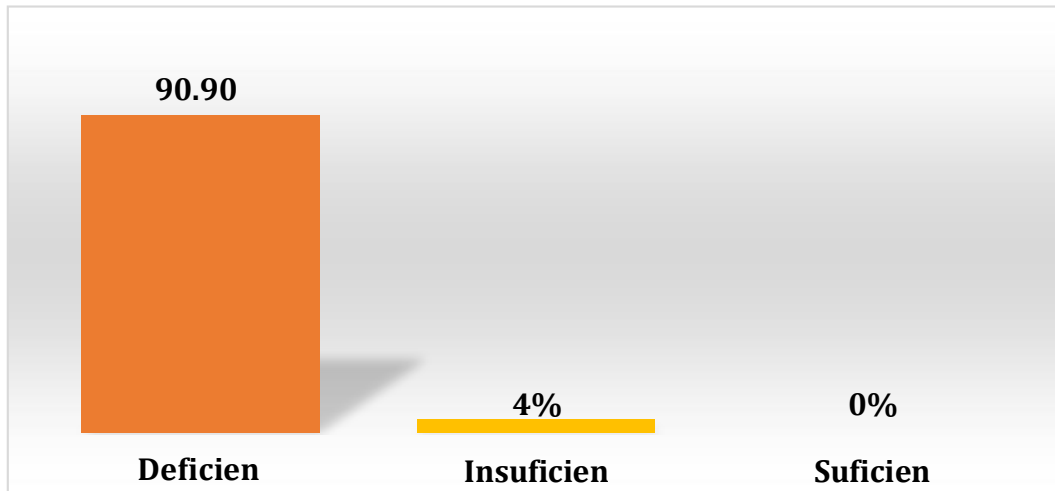


Figure 1: Vitamin D level of the respondents

Table 2 shows the clinical characteristics of the participants. Here participants with irregular menstruation were 100%, lower abdominal pain 37.2%, hirsutism 67.0%.

Table 2: Clinical characteristics of respondents

Characteristics		n (94)	%
Menstruation cycle	Irregular	94 (100)	
Lower Abdominal Pain	Yes	35 (37.2)	
	No	59 (62.8)	
Hirsutism	Yes	63 (67.0)	
	No	31 (33.0)	

Figure 2 shows that 47.5% of respondents were underweight, 34.3% within the normal range. Around 10.1% of respondents were pre-obesity and only 3% of respondents were in Obesity.

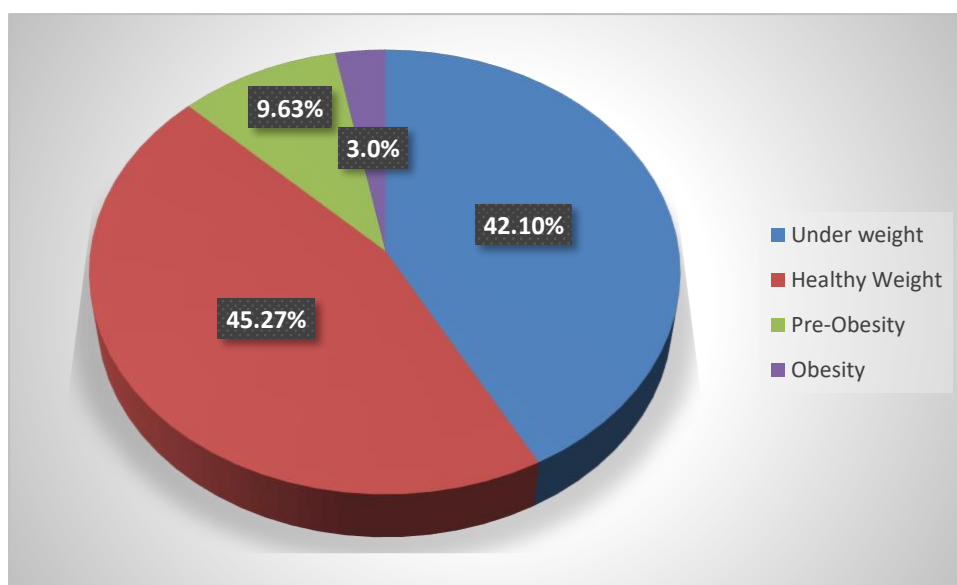


Figure 2: BMI status among participants (N=94)

In most of cases, Polycystic ovary syndrome (PICOS) women's vitamin D level with Fetal bovine serum (FBS) was very low (51.58%). Chi square test shows that the association between vitamin D with FBS was not significant ($p=.841$). The association between vitamin D with BMI was also very low (43.16%) and was not significant ($p=.381$).

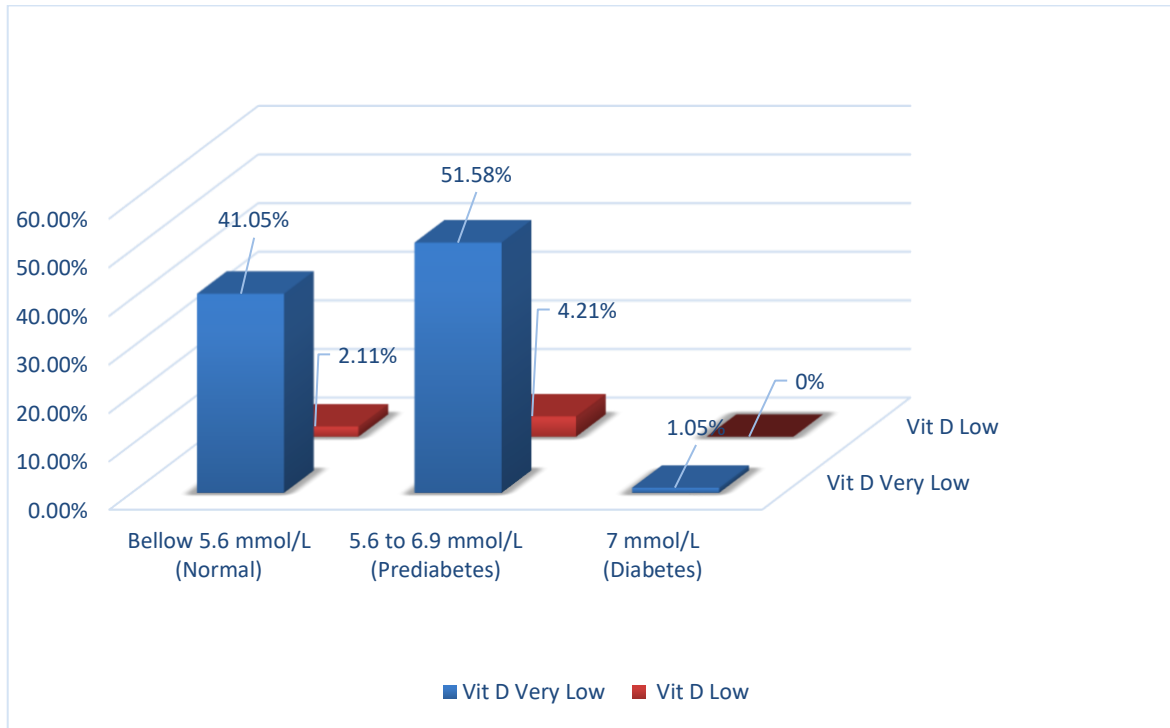


Figure 3: Association between Vitamin D and FBS (N=94)

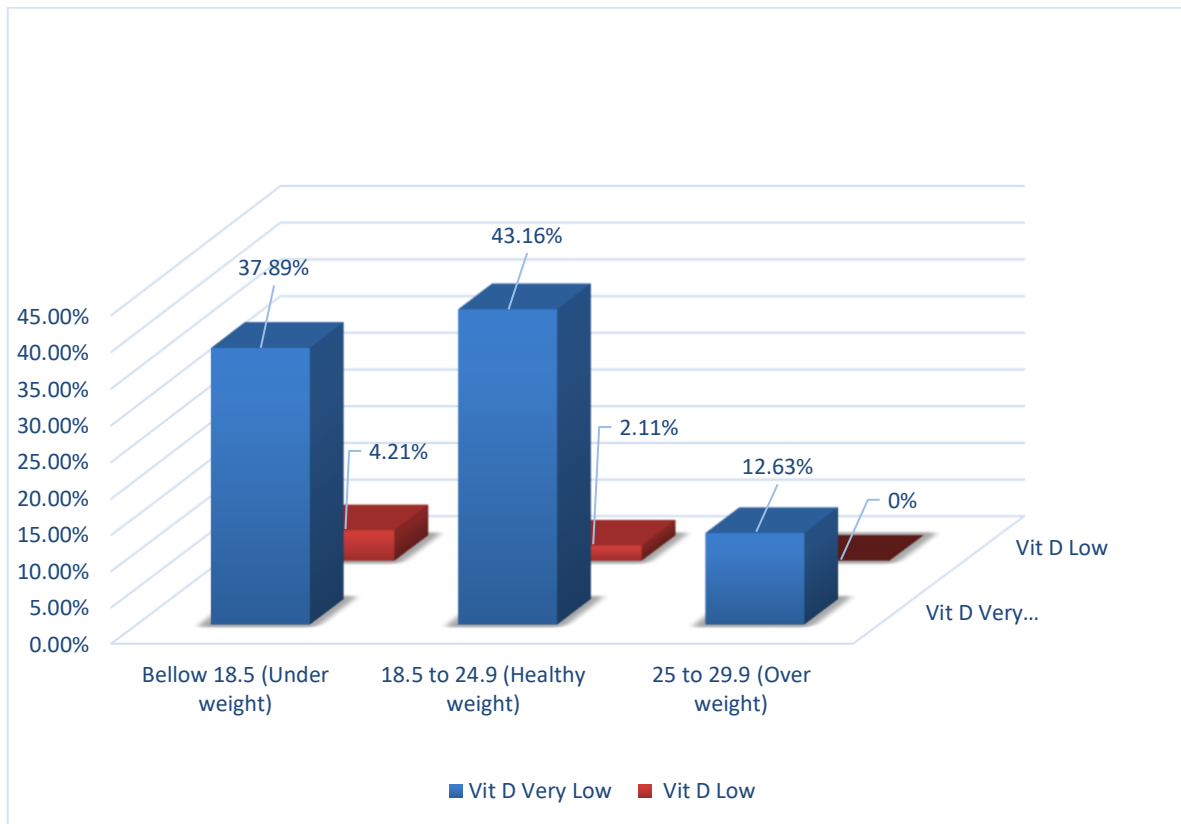


Figure 4: Association between Vitamin D and BMI (N=94)

4. Discussion

The cross-sectional study found the frequency of vitamin D deficiency among adolescents with PCOS to be 92.6%. They also have high insulin resistance and obesity.

Although vitamin D primarily plays a role in bone metabolism, it has important functions in the reproductive system. Vitamin D receptors are found in ovarian and endometrial tissues and play an important role in steroidogenesis. A high prevalence of vitamin D deficiency has been reported all over India for all age groups including neonates, infants, school-going children, adolescents, adults, pregnant and lactating women, and senior citizens. This is probably a result of poor sun exposure, dark skin complexion, atmospheric pollution, vegetarian food habits, absence of food fortification with vitamin D, and poor intake of vitamin D supplements. Garg et al. did a study in 2015 (India) where Vitamin D deficiency was observed in 92.8% of all PCOS patients while the rest had vitamin D insufficiency (≥ 30 ng/mL) (Kokila et al., 2017).

Mazloomi S et al in their study have reported low levels of vitamin D in women with PCOS, with average vitamin D (25-OHD) levels between 11-31 ng/mL, and the majority having values < 20 ng/mL (67–85%) which is comparable to our study. Apart from other risk factors, PCOS itself was found to be associated with decreased vitamin D levels, which is similar to our study. In the present study, among 94 total cases of PCOS, the mean age was 15.34 ± 1.91 years. Age ranged from 12 years to 18 years. Many studies have reported inverse associations between body weight (BMI, body fat, and waist measurements) and serum 25-OHD levels in women with PCOS, with reports of levels 27–56% lower in obese women with PCOS, compared to non-obese women with PCOS. A recent study in women with PCOS also found low 25-OHD levels were significantly determined by the degree of adiposity (BMI and total fat mass) and were not directly affected by the development of insulin resistance (Ardabili et al., 2012). Consequences of vitamin D deficiency include a broad range of health problems. A lack of vitamin D has been linked to an increased likelihood of developing life-threatening malignancies, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus (Michael, 2004). It has been proposed because of the association between low sun exposure and the development of many internal malignancies, the incidence, and mortality from these cancers could be prevented if adequate vitamin D blood level is maintained. Hence, the importance of screening of those at risk especially obese with BMI of ≥ 35 provided that cost-effective analysis is considered. The adolescent girls with PCOS had fasting insulin levels (< 20 uIU/ml) among 14.9% of PCOS. On other hand, high fasting Insulin level (> 20 uIU/ml) among 85.1% of PCOS. Insulin sensitivity may not be influenced by circulating 25(OH) vitamin D in some populations. The associations of 25(OH) D with insulin sensitivity (determined with a euglycemic-hyperinsulinemic clamp) in morbidly obese Caucasian women. Serum 25(OH) D was not associated with insulin sensitivity in these subjects either before bariatric surgery or 5- and 10- years post-surgery suggesting that they found low serum 25(OH) D concentrations before and after bariatric surgery do not negatively affect insulin sensitivity (Manco, 2010).

In the present study BMI 28.31 ± 4.46 kg/m², Insulin 22.07 ± 4.23 μ IU/ml, FBS 6.88 ± 1.56 mmol/L, and HOMA-IR 6.98 ± 1.79 . Some biochemical and hormonal data are presented in Table. Only 2 (2.1%) women were in the normal limits of vitamin D levels as ≥ 30 ng/ml. The mean value of vitamin D was 12.9 (4.2-31.4). In the study conducted by Setenay Arzu Yılmaz, the mean Vitamin D level of the lean PCOS cases was 16.52 ng/ml. In patients with PCOS, vitamin D levels were found too below.

In our study total 94 PCOS patients with vitamin D deficiency 80 (85.1%) participants had markers of insulin resistance like acne, hirsutism, acanthosis nigricans. Among patient's with irregular menstruation was 94 (100%), Lower abdominal Pain 35 (37.2%), Hirsutism 63 (67.0%).

Under Normal BMI 23 (24.5%), Overweight 45 (47.9%) and Obese 26 (27.7%). In addition, advice on diet and lifestyle modification was also instructed. Other insulin sensitizers like Myo-inositol, D-chiro inositol, berberine were not used in any of these patients. In patients with vitamin D deficiency, we had supplemented them with Injection Vitamin D, 6 Lakh IU has given intramuscularly, 2 doses 6 weeks apart, and in those with insufficiency oral vitamin D supplementation was given in the form of 60,000 IU, once a week for 8 weeks and thereafter once a month as maintenance. In all these patients, oral calcium 500 mg tablets were also added once daily. In the

patients with insulin resistance and obesity, metformin 500 mg tablet was given in the oral form. In addition, advice on diet and lifestyle modification was also instructed.

This is a significant observation. Our study can be compared to the study done by Thys-Jacobs S et al where the aim of their study was to determine whether vitamin D and calcium dysregulation contribute to the development of follicular arrest in women with PCOS, resulting in reproductive and menstrual dysfunction. Vitamin D repletion with calcium therapy resulted in normalized menstrual cycles within 2 months for seven women, with two experiencing resolutions of their dysfunctional bleeding. Two became pregnant, and the other four patients maintained normal menstrual cycles (Kokila et al., 2017). Many studies have reported inverse associations between body weight (BMI, body fat, and waist measurements) and serum 25-OHD levels in women with PCOS, with the report of levels 27–56% lower in obese women with PCOS, compared to non-obese women with PCOS (Rebecca, 2012).

A recent study in women with PCOS also found low 25-OHD levels were significantly determined by the degree of adiposity (BMI and total fat mass) and were not directly affected by the development of insulin resistance (Kokila et al., 2017). Thus, Vitamin D deficiency is common in patients of PCOS, both lean and obese. Supplementation with Vitamin D and Calcium can improve the menstrual disorders associated with PCOS and with a favorable reproductive outcome. However, our study has its limitations in the small sample size. More randomized controlled studies with a large number of patients will confirm the potential benefits of Vitamin D supplementation in PCOS patients.

5. Conclusion

The majority of adolescent females who have PCOS have an insufficient level of vitamin D, and the prevalence of obesity is also rather high. It is extremely likely that the findings of this study will contribute to a better understanding of how PCOS is managed, and patients will benefit individually from having a better grasp of how to manage their condition. The results of this study brought the true image of insulin resistance and metabolic syndrome among diverse phenotypes of women with PCOS in Bangladesh. The clinician may be able to manage cases of obesity in teenagers with PCOS more effectively if they estimate vitamin D levels and examine the level of obesity in the patient.

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References

- Ardabili, H.R., Gargari, B.P. and Farzadi, L., 2012. Vitamin D supplementation has no effect on insulin resistance assessment in women with polycystic ovary syndrome and vitamin D deficiency. *Nutrition Research*, 32(3), pp.195-201.
- Dong, Y., Pollock, N., Stallmann-Jorgensen, I.S., Gutin, B., Lan, L., Chen, T.C., Keeton, D., Petty, K., Holick, M.F. and Zhu, H., 2010. Low 25-hydroxyvitamin D levels in adolescents: race, season, adiposity, physical activity, and fitness. *Pediatrics*, 125(6), pp.1104-1111.
- Dunaif, A., Segal, K.R., Futterweit, W. and Dobrjansky, A., 1989. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes*, 38(9), pp.1165-1174.
- Ehrmann, D.A., 2005. Polycystic ovary syndrome. *New England Journal of Medicine*, 352(12), pp.1223-1236.
- Gordon, C.M., DePeter, K.C., Feldman, H.A., Grace, E. and Emans, S.J., 2004. Prevalence of vitamin D deficiency among healthy adolescents. *Archives of pediatrics & adolescent medicine*, 158(6), pp.531-537.

- Holick, M.F., Vitamin D deficiency N Engl J Med. 2007; 357: 266–81 doi:10.1056.NEJMra070553.
- Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H. and Weaver, C.M., 2011. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology & metabolism*, 96(7), pp.1911-1930.
- Holick, M. F. (2004). Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *The American journal of clinical nutrition*, 80(6), 1678S-1688S.
- Kokila, B.T. and Agrawal, P., 2017. Relationship between vitamin d and insulin resistance in polycystic ovary syndrome women. *Journal of South Asian Federation of Obstetrics and Gynaecology*, 9(3), pp.211-215.
- Li HW, Brereton RE, Anderson RA, Wallace AM, Ho CK. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. *Metabolism* 2011; 60:1475-81.
- Mahmoudi, T., Gourabi, H., Ashrafi, M., Yazdi, R.S. and Ezabadi, Z., 2010. Calcitropic hormones, insulin resistance, and the polycystic ovary syndrome. *Fertility and Sterility*, 93(4), pp.1208-1214.
- Manco, M., Putignani, L., & Bottazzo, G. F. (2010). Gut microbiota, lipopolysaccharides, and innate immunity in the pathogenesis of obesity and cardiovascular risk. *Endocrine reviews*, 31(6), 817-844.
- Mazloomi S, Sharifi F, Haji hosseini R, Kalantari S, Mazloomzadeh S. Association between Hypoadiponectinemia and Low Serum Concentrations of Calcium and Vitamin D in Women with Polycystic Ovary Syndrome. *ISRN Endocrinol* 2012; 2012:949427.
- Mazloomi, S., Sharifi, F., Hajihosseini, R., Kalantari, S. and Mazloomzadeh, S., 2012. Association between hypoadiponectinemia and low serum concentrations of calcium and vitamin D in women with polycystic ovary syndrome. *International Scholarly Research Notices*, 2012.
- Pal, L., Berry, A., Coraluzzi, L., Kustan, E., Danton, C., Shaw, J. and Taylor, H., 2012. Therapeutic implications of vitamin D and calcium in overweight women with polycystic ovary syndrome. *Gynecological Endocrinology*, 28(12), pp.965-968.
- Panidis D, Tziomalos K, Misichronis G, Papadakis E, Betsas G, Katsikis I, et al. 2011. Insulin resistance and endocrine characteristics of the different phenotypes of polycystic ovary syndrome: a prospective study. *Hum Reprod*, 27(2), 541-9.
- Parikh G, Varadinova M, Suwandhi P, Araki T, Rosenwaks Z, Poretsky L, et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. *Horm Metab Res* 2010;42:754-7.
- Parikh, G., Varadinova, M., Suwandhi, P., Araki, T., Rosenwaks, Z., Poretsky, L. and Seto-Young, D., 2010. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. *Hormone and metabolic research*, 42(10), pp.754-757.
- Prentice A. Vitamin D deficiency: a global perspective. *Nutr Rev* 2008;66 (10 Suppl 2):153-64.
- Raja-Khan, N., Shah, J., Stetter, C.M., Lott, M.E., Kunselman, A.R., Dodson, W.C. and Legro, R.S., 2014. High-dose vitamin D supplementation and measures of insulin sensitivity in polycystic ovary syndrome: a randomized, controlled pilot trial. *Fertility and sterility*, 101(6), pp.1740-1746.
- Ranjad F, Mahban A, Shemirani AI, Mahmoudi T, Vahedi M, Nikzamir A, et al. Influence of gene variants related to calcium homeostasis on biochemical parameters of women with polycystic ovary syndrome. *J Assist Reprod Genet* 2011;28:225-32.
- Rashidi, B., Haghollahi, F., Shariat, M. and Zayerii, F., 2009. The effects of calcium-vitamin D and metformin on polycystic ovary syndrome: a pilot study. *Taiwanese Journal of Obstetrics and Gynecology*, 48(2), pp.142-147.
- Studzinski GP, McLane JA, Uskokovic MR. Signaling pathways for vitamin D-induced differentiation: implications for therapy of proliferative and neoplastic diseases. *Crit Rev Eukaryot Gene Expr* 1993;3:279-312.
- Teegarden D, Donkin SS. Vitamin D: emerging new roles in insulin sensitivity. *Nutr Res Rev* 2009;22:82-92.
- Thomson, R. L., Spedding, S., & Buckley, J. D. (2012). Vitamin D in the aetiology and management of polycystic ovary syndrome. *Clinical endocrinology*, 77(3), 343-350.
- Thys-Jacobs, S., Donovan, D., Papadopoulos, A., Sarrel, P. and Bilezikian, J.P., 1999. Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. *Steroids*, 64(6), pp.430-435.
- Tsakova, A.D., Gateva, A.T. and Kamenov, Z.A., 2012. 25 (OH) vitamin D levels in premenopausal women with polycystic ovary syndrome and/or obesity. *Int J Vitam Nutr Res*, 82(6), pp.399-404.
- Walters MR. Newly identified actions of the vitamin D endocrine system. *Endocr Rev* 1992;13:719-64.
- Wehr E, Trummer O, Giuliani A, Gruber HJ, Pieber TR, Obermayer-Pietsch B. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. *Eur J Endocrinol* 2011;164:741-9.
- WHO. Obesity and overweight [Internet]. 9 June 2021. 2022 [cited 2022 Feb 4]. Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
- Wild, R.A., Rizzo, M., Clifton, S. and Carmina, E., 2011. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. *Fertility and sterility*, 95(3), pp.1073-1079.

Yildizhan, R., Kurdoglu, M., Adali, E., Kulusari, A., Yildizhan, B., Sahin, H.G. and Kamaci, M.,2009. Serum 25-hydroxyvitamin D concentrations in obese and non-obese women with polycystic ovary syndrome. *Archives of gynecology and obstetrics*, 280(4), pp.559-563.