Al-Kindy College Medical Journal (KCMJ)

Research Article

Free Testosterone, Dihydrotestosterone, and Adiponectin in the Evaluation of Vitamin D Supplementation for Polycystic Ovarian Syndrome: A Metformin Comparative Study

Zainab Nur-Eldeen Aziz[1*], Basil O. Saleh[1], Ansam Zeki Thaker[2]

[1] Department of Clinical biochemistry, College of Medicine, University of Baghdad, Baghdad, Iraq
[2] Kamal Al- Samarraei hospital for infertility management and IVF, Baghdad, Iraq

* Corresponding author's email: zainabnureldeen79@gmail.com

Article history:
Received 1 October 2024
Accepted 7 November 2024
Available online 1 December 2024

https://doi.org/10.47723/nb5he078

Keywords: PCOS; Vitamin D; Androgen hormone; HOMA-IR; Metformin

ABSTRACT

Background: Among women of the reproductive age, the most prevalent endocrine disease with (15-44) percentile is the polycystic ovarian syndrome (PCOS). Last decades, many studies indicated that vitamin D deficiency in women with PCOS may aggravate hyperandrogenism and insulin resistance.

Objectives This study was designed to investigate the role of some biochemical markers and hormonal status in evaluation the efficacy of vitamin D supplementation in treatment of polycystic ovary syndrome.

Subjects and Methods: This cross-sectional study was carried out at Department of Biochemistry, College of Medicine, University of Baghdad. It included: group I: Twenty-five women with PCOS who were treated with metformin and followed for 8 weeks, and group II: Twenty-five women with PCOS who were treated with vitamin D3 and followed for 8 weeks. Serum investigations included measurements of HOMA-IR, 25 hydroxyvitamin D3, adiponectin, androgen indices by ELISA technique

Results: The mean (±SD) values of HOMA-IR, free testosterone, dihydrotestosterone, and adiponectin levels were significantly improved after treatment in both groups of metformin and vitamin D supplement compared with before their treatment ($p < 0.05$). In addition, there was no significant differences after treatment between women treated with metformin and those treated with vitamin D supplement for all the measured parameters ($p > 0.05$). PCOS women treated with vitamin D showed significant negative correlation between SHBG and BMI ($r= -0.976$, $p <0.001$)

Conclusions: Measurements of serum free testosterone, dihydrotestosterone and adiponectin are good indicators for efficacy of vitamin D supplement in improvement of insulin resistance and androgen disturbances of PCOS.

Introduction

Among women of the reproductive age, the most prevalent endocrine disease with (15-44) percentile is the polycystic ovarian syndrome (PCOS), it affects between 20% and 50% of women all over the world (1, 2). The Rotterdam criteria, are the most widely accepted and appropriate, that are internationally used for significant diagnosis of PCOS, are required women to meet two out of the following three criteria: Ultrasonography evidence of polycystic ovaries and/or biochemical or clinical indicators of hyperandrogenism, such as oligo- or anovulation (2, 3).

Noticeably, PCOS is heterogeneous disorder, so women may associate with several of; reproductive (infertility or menstrual dysfunction, or may be pregnancy complications), or endocrine as (acne, hirsutism or hyperandrogenism), or metabolic (glucose intolerance, insulin resistance, compensatory hyperinsulinemia, dyslipidemia, increases the risk of diabetes mellitus type II) and psycho-social (anxiety, depression and poor quality of life) symptoms (1, 3).

Hyperandrogenism and Insulin resistance are considered as the most typical features of the PCOS syndrome, with their adjacent relationship and influences on reproductive function, and the metabolic profile of PCOS patients, irrespective of BMI (4, 5). Insulin receptors that have been found in ovaries promote the ability of insulin for steroidogenesis and ovarian growth, thus result in increased intra ovarian androgen synthesis along with disruption in normal folliculogenesis, resulting in the development of innumerable ovarian cysts and enlarged ovary (6).

Metformin as one of the insulin sensitizers, at a dose of (1700-2000) mg/day with or without lifestyle is widely used as a very effective and adaptive drug for PCOS treatment, due to its efficacy and safety (7, 8).

Metformin beneficial effects are increasing, especially in combined with lifestyle modifications, leading to the improvement of the pathogenetic mechanisms that underlying PCOS, by restoring the ovarian function and also improving the metabolic profile, particularly insulin sensitivity (4, 9). Also, Metformin with and without lifestyle may associated with a significant improvement on BMI and menstrual cycles (10).

Last decades, many studies have revealed women with PCOS frequently associated with vitamin D deficiency, serum 25-hydroxyvitamin D concentrations of <20 ng/ml (11, 12). Adequate vitamin D levels (≥30 ng/ml) should be required in women with PCOS, otherwise deficiency of vitamin D may aggravate hyperandrogenism and insulin resistance (11, 13).

Few investigations have reported that vitamin D deficiency may have a role in the development of metabolic syndrome because vitamin D is essential for the formation of the adrenal cortex hormones. Therefore; the management of PCOS needs treatment of vitamin D deficiency (12, 14). Vitamin D as an oral, relatively safe and almost inexpensive vitamin, may enhance in the improvement of the common ovulation dysfunction in PCOS, by promoting the follicular development and enhance menstruation, and it may be used in all infertile women of childbearing age (15, 16).

Subjects and Methods

This cross-sectional study was carried out at Department of Biochemistry, College of Medicine, University of Baghdad, and at Kamal Al-Samarraei hospital for infertility management and IVF, during the period from September 2022 to June 2023. It included 50 infertile women who priorly diagnosed with polycystic ovary syndrome with age range (18-40 year) and without any related treatment for two months at least. They were diagnosed by Gynecologist after proper physical, biochemical and gynecological examinations and confirmed by ultrasound. According to Rotterdam consensus; the presence of two over three of the following criteria (oligo/anovulation, hyperandrogenism and polycystic ovaries [≥ 12 follicles measuring with diameter of (2-9) mm and/or an ovarian volume more than 10 mL in at least one ovary], would confirm the polycystic ovarian syndrome morphology (17).

All women enrolled in this study were without any infertility related treatment for two months at least. They were classified into two sub-grouped: **Group I:** Twenty-five women who were treated with metformin 850 mg/twice a day and followed for 8 weeks and **Group II:** Twenty-five women who were treated with vitamin D3 50.000 IU/wk. and followed for 8 weeks.

This study excluded women with any type of cancer, acute and chronic illness, DM, chronic liver disease, pregnant women, smokers, endocrine disorders and chronic renal failure.

Blood samples was collected from each included women of the two studied groups after (10-12) hours of overnight fasting state, in the follicular phase between the 2nd and 7th day of the menstrual cycle, before starting of their designed treatment, left to clot for 15 minute, then centrifuged at 2500 rpm for 10 minute to obtain serum that stored in aliquots at -20 °C till the day of measurement of fasting serum glucose, insulin, 25 hydroxyvitamin D3, adiponectin, free Testosterone, dihydrotestosterone, dehydroepiandrosterone-sulfate (DHEA-S) and sex-hormone binding globulin (SHBG) by the quantitative sandwich and competitive enzyme immunoassay technique for the in vitro determination of human serum and plasma. HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) was calculated by equation: HOMA-IR = [insulin (mU/L) * glucose (mg/dl)]/ 405 (18). Weight and height of the included women was measured and the body mass index (BMI) was calculated by equation: BMI (Kg/m^2) = Weight (Kg)/height (m^2) (19). Both ovaries were scanned using transvaginal ultrasound at Kamal Al- Samarraei hospital for infertility management and IVF, in order to determine the total number of early antral follicles using a 6.5 MHz transducer.

Results

The results of the PCOS studied groups revealed that, there were no significant differences between the two groups before metformin or vitamin D treatment regarding to the comparison of demographic, biochemical and hormonal parameters as represent in table (1).

The results of follow up study of PCOS women showed that 18 of women who were treated with metformin and 13 of women who were treated with vitamin D supplement were completed the 8 wk. follow up of their treatment.

Table (2) shows the comparison of demographic, biochemical and hormonal parameters before and after metformin treatment. Women after metformin treatment compared with before showed significantly lower mean values of BMI (27.56 ± 5.30 kg/m^2 vs. 30.76 ± 6.40; $p<0.001$), HOMA-IR (2.84 ± 1.25 vs. 4.37 ± 1.19; $p < 0.001$), free testosterone (3.22 ± 0.42 pg/ml vs. 4.24 ± 0.28; $p < 0.001$) and dihydrotestosterone (450 ± 33.25 pg/ml vs. 496 ± 15.88; $p < 0.001$). On the other hand, there was significantly improved by increasing the mean values of adiponectin (4.25 ± 0.39 ng/ml vs. 2.49 ± 0.29; $p < 0.001$), 25 hydroxyvitamin D (13.63 ± 1.64 ng/ml vs. 12.35 ± 1.65; $p=0.01$), and SHBG levels (17.64± 4.66 ng/ml vs. 14.68 ± 4.67; $p < 0.001$) after treatment compared with before. However, there was no

significant changes in the levels of DHEA-S after metformin treatment ($p > 0.05$).

Table 1: Mean (±SD) values of BMI, 25 hydroxyvitamin, adiponectin and Androgen profile between the studied groups before the treatment

Parameter	Before metformin treatment (n=25)	Before vitamin D treatment (n=25)
BMI (kg/m²) NS	30.76 ± 6.40	28.62 ± 6.15
HOMA-IR NS	4.37 ± 1.19	4.17 ± 1.69
Adiponectin NS (ng/ml)	2.49 ± 0.29	2.54 ± 0.30
25 hydroxyvitamin NS D (ng/ml)	12.35 ± 1.65	12.26 ± 1.61
Free testosterone NS (pg/ml)	4.24 ± 0.28	4.28 ± 0.41
Dihydrotestosterone NS (pg/ml)	496 ± 15.88	498 ± 16.03
DHEA-S NS (ng/ml)	315 ± 7.99	315 ± 7.58
SHBG NS (ng/ml)	14.68 ± 4.67	16.43 ± 5.06

t- test revealed NS: Not significant (p>0.05); BMI: Body mass index, DHEAS: Dehydroepiandrosterone; SHBG: Sex hormone binding globulin

Table 2: Mean (±SD) values of Demographic, Biochemical and Hormonal parameters, before and after metformin treatment (Group 1) patients

Parameter	Before metformin treatment (n=25)	After metformin treatment (n=18)	p value
BMI (kg/m²)	30.76±6.40	27.56±5.30	< 0.001 Ŧ S
HOMA-IR	4.37 ± 1.19	2.84 ± 1.25	< 0.001 Ŧ S
Adiponectin (ng/ml)	2.49 ± 0.29	4.25 ± 0.39	< 0.001 Ŧ S
25 hydroxyvitamin D (ng/ml)	12.35±1.65	13.63±1.64	0.01 Ŧ S
Freetestosterone (pg/ml)	4.24 ± 0.28	3.22 ± 0.42	< 0.001 Ŧ S
Dihydrotestosterone (pg/ml)	496± 15.88	450± 33.25	< 0.001 Ŧ S
DHEA-S (ng/ml)	315 ± 7.99	316 ± 7.35	0.122 Ŧ NS
SHBG (ng/ml)	14.68±4.67	17.64±4.66	< 0.001 Ŧ S

BMI: Body mass index, DHEA-S: Dehydroepiandrosterone-sulfate; SHBG: Sex hormone binding globulin; Ŧ: paired sample t test, NS: Not significant (p>0.05); S: Significant ($p \leq 0.05$).

Table (3-3) depicts the comparison of demographic, biochemical and hormonal parameters before and after vitamin D treatment. PCOS women after vitamin D treatment in comparison with before showed significantly lower mean values of BMI (24.75 ± 3.28 kg/m² vs. 28.62 ± 6.15; p<0.007), waist circumference (89.46 ± 8.59 cm vs. 97.04 ± 12.07; p<0.012), HOMA-IR (2.88 ± 1.72 vs. 4.17 ± 1.69; p < 0.001), free testosterone (3.19 ± 0.55 pg/ml vs. 4.28 ± 0.41; p < 0.001) and dihydrotestosterone (450 ± 33.25 pg/ml vs. 496 ± 15.88; p < 0.001).

In addition, there was significantly improvement by elevating the mean values of adiponectin (4.23 ± 0.32 ng/ml vs. 2.54 ± 0.30; p < 0.001) and 25 hydroxyvitamin D levels (18.20 ± 1.93 ng/ml vs. 12.26 ± 1.61; p < 0.001) after vitamin D treatment compared with before treatment. However, there was also no significant changes in the levels of DHEA-S (p=0.472) and SHBG (p=0.196).

Table 3: Mean (±SD) values of Demographic, Biochemical and Hormonal parameters, before and after vitamin D treatment (Group 2) patients

Parameter	Before vitamin D treatment (n=25)	After vitamin D treatment (n=13)	p value
BMI (kg/m²)	28.62 ± 6.15	24.75 ± 3.28	0.007 Ŧ S
HOMA-IR	4.17 ± 1.69	2.88 ± 1.72	< 0.001 Ŧ S
Adiponectin (ng/ml)	2.54 ± 0.30	4.23 ± 0.32	< 0.001 Ŧ S
25 hydroxyvitamin D (ng/ml)	12.26 ± 1.61	18.20 ± 1.93	< 0.001 Ŧ S
Free testosterone (pg/ml)	4.28 ± 0.41	3.19 ± 0.55	< 0.001 Ŧ S
Dihydrotestosterone (pg/ml)	498 ± 16.03	444 ± 15.26	< 0.001 Ŧ S
DHEA-S (ng/ml)	315 ± 7.58	316 ± 4.47	0.388 Ŧ NS
SHBG (ng/ml)	16.43 ± 5.06	20.23 ± 4.56	0.196 Ŧ NS

BMI: Body mass index; DHEA-S: Dehydroepiandrosterone-sulfate; SHBG: Sex hormone binding globulin; Ŧ: paired sample t test, NS: Not significant (p>0.05); S: Significant ($p \leq 0.05$).

Table (3-4) shows that there were non-significant differences in the mean values of the measured and calculated parameters after treatment between the metformin and vitamin D groups including BMI, HOMA-IR and hormonal status (for all, $p > 0.05$).

PCOS women treated with metformin revealed significant negative correlation between HOMA-IR with SHBG (r= -0.593, *p*=0.009), SHBG with BMI (r= -0.880, *p*<0.001) as well as significant positive correlation between HOMA-IR and BMI (r= 0.631, *p*=0.003). while PCOS women treated with vitamin D showed significant negative correlation between SHBG and BMI (r= -0.976, *p* <0.001).

Table 4: Mean (±SD) values of Demographic, Biochemical and Hormonal parameters among the two studied groups after the treatment

Parameters	After metformin treatment (n=18)	After vitamin D treatment (n=13)
BMI (kg/m²) NS	27.56 ± 5.30	24.75 ± 3.28
HOMA-IR NS	2.84 ± 1.25	2.88 ± 1.72
Adiponectin (ng/ml) NS	4.25 ± 0.39	4.23 ± 0.32
Free testosterone NS (pg/ml)	3.22 ± 0.42	3.19 ± 0.55
Dihydrotestosterone NS (pg/ml)	450 ± 33.25	444 ± 15.26
DHEAS (ng/ml) NS	316 ± 7.35	316 ± 4.47
SHBG (ng/ml) NS	17.64 ± 4.66	20.23 ± 4.56

t- test revealed NS: Not significant ($p>0.05$); BMI: Body mass index, DHEAS: Dehydroepiandrosterone; SHBG: Sex hormone binding globulin

Discussion

This study revealed that, the PCOS patients had higher levels of BMI, HOMA-IR, free testosterone, dihydrotestosterone and DHEA-S, On the other hand, there were low levels of; adiponectin, 25 hydroxyvitamin and SHBG, with no significant differences between the studied groups before metformin and vitamin D treatment.

Saleh BO (2015) demonstrated that, there were high levels of BMI and free testosterone among the PCOS groups (20). The higher mean of testosterone level in the PCOS women can prevent regular periods and fertilization even with a small increase (21). Alawad (2018) revealed that, there were mostly deficient or insufficient levels of 25 hydroxyvitamin in PCOS women, which was consistent with this study (22).

A study done by Qasim MN et al., (2022) mentioned that, the mean values of BMI were significantly more significant in the PCOS group, while serum level of vitamin D3 have decreased significantly in PCOS group. They also revealed that, women who suffer from PCOS were more prone to lack vitamin D levels than those without PCOS; resulting that obesity contributes to vitamin D deficiency risk (23).

Teede et al., (2019) demonstrated that there were statistically significant improvements with metformin for fasting insulin, management of weight and metabolic outcomes (reduction of BMI and HOMA-IR) for PCOS women across all BMI categories (24), which was consistent with this study. Witchel et al., (2019) confirmed that metformin uses with and without lifestyle changes in PCOS women resulted in significant and beneficial effects on BMI (10). It has been also reported that therapeutic intervention with metformin in women with PCOS were improved several effects on reducing weight; reduction of BMI and in turn HOMA-IR (25), which was also consistent with this study.

In addition, it has been demonstrated that metformin treatment was associated with significantly increased serum adiponectin concentrations and consequently improvement of metabolic complication (26), which was concordant with this study.

After metformin treatment PCOS women of the present study also improved significantly lower levels of free testosterone and dihydrotestosterone compared with before treatment. On the other hand, there was significantly higher levels of SHBG (table 3-2). Williams et al., (2020) confirmed that metformin can reduce the hyperandrogenic signs and symptoms of PCOS patients by reducing the levels of androgen (2). Other revealed that there was statistically significant difference post-treatment with metformin for testosterone for all participants (24). As well Lashen et al. (2010) mentioned that several effects related to metformin therapeutic intervention in PCOS women as reducing circulating androgen levels with confirmed increased serum levels of SHBG (25). Upon these findings, their results were consistent with this study.

Williams et al., (2020) revealed that vitamin D supplementation for PCOS patients improved insulin resistance and other metabolic profiles (reduction of BMI and HOMA-IR) (2), and a significantly increased in serum 25 hydroxyvitamin D, which was consistent with this study.

However, other revealed that vitamin D supplementation did not change the HOMA-IR in women with PCOS (26). There was improved evidence of the therapeutic uses of Vitamin D in PCOS patients depend on the prognosis of PCOS (27). Vitamin D had an important role in the development of metabolic, endocrine and reproductive abnormalities or dysfunctions in PCOS, it might be mediated through an overall effect on insulin resistance (6, 28).

Vitamin D revealed a significant impact on insulin synthesis via enhancing the expression of insulin receptors and suppressing pro-inflammatory cytokines, thus improving glucose metabolism (6, 27). Though, after vitamin D treatment there were a significant reduction in fasting plasma glucose, insulin resistance with a significant improvement (28).

The present study revealed that PCOS women after vitamin D treatment also improved free testosterone and dihydrotestosterone compared with before treatment. A study by Alomda et al., 2019 confirmed that vitamin D supplementation can help significantly in decreasing the androgenic profile in a woman PCOS (29). The existence of Vitamin D receptors (VDRs) in the granulosa cells and the cumulus oophorus cells in humans and animals supports the assertion that, Vitamin D plays a crucial role in the appropriate regulation of the female reproductive cycle (30). PCOS women with vitamin D supplementation can restore their normal concentration of vitamin D, with disappearance of acne include (31). A study by Xue et al., (2017) mentioned that there was no significant change in DHEA-S levels after vitamin D supplementation in women with PCOS (32).

Conclusion

Serum measurements of free testosterone, dihydrotestosterone and adiponectin along with HOMA-IR and BMI are good indicators for efficacy of vitamin D supplement in treatment of PCOS women. Vitamin D supplements (50.000 IU/wk.) alone can significantly improve metabolic, hormonal, and androgens disturbances that seen in vitamin D-deficient/insufficient PCOS women.

ORCID

Zainab Aziz 0009-0009-8637-5746
Basil Saleh 0009-0001-0053-5422

References

[1] Zhao JF, Li BX, Zhang Q. Vitamin D improves levels of hormonal, oxidative stress and inflammatory parameters in polycystic ovary syndrome: a meta-analysis study. Annals of Palliative Medicine. 2021 Jan;10(1):16983-183. https://doi.org/10.21037/apm-20-2201

[2] Williams A, Babu JR, Wadsworth DD, Burnett D, Geetha T. The effects of vitamin D on metabolic profiles in women with polycystic ovary syndrome: a systematic review. Hormone and Metabolic Research. 2020 Jul;52(07):485-91. https://doi.org/10.1055/a-1160-9902

[3] Deswal R, Narwal V, Dang A, Pundir CS. The prevalence of polycystic ovary syndrome: a brief systematic review. Journal of human reproductive sciences. 2020 Oct 1;13(4):261-71. https://doi.org/10.4103/jhrs.jhrs_95_18

[4] Armanini D, Boscaro M, Bordin L, Sabbadin C. Controversies in the pathogenesis, diagnosis and treatment of PCOS: focus on insulin resistance, inflammation, and hyperandrogenism. International journal of molecular sciences. 2022 Apr 8;23(8):4110. https://doi.org/10.3390/ijms23084110

[5] Pasquali R. Contemporary approaches to the management of polycystic ovary syndrome. Therapeutic advances in endocrinology and metabolism. 2018 Apr;9(4):123-34. https://doi.org/10.1177/2042018818756790

[6] Hamdi RA, Abdul-Qahar ZH, Kadhum EJ, Alsaeed FA. Assessment of Serum Vitamin D Levels in Women with Polycystic Ovary Syndrome. Journal of the Faculty of Medicine Baghdad. 2018 Sep 2;60(2):93-7. https://doi.org/10.32007/jfacmedbagdad.60212

[7] Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F, Kumar M. Polycystic ovary syndrome: etiology, current management, and future therapeutics. Journal of Clinical Medicine. 2023 Feb 11;12(4):1454. https://doi.org/10.3390/jcm12041454

[8] Luque-Ramirez M, Nattero-Chavez L, Ortiz Flores AE, Escobar-Morreale HF. Combined oral contraceptives and/or antiandrogens versus insulin sensitizers for polycystic ovary syndrome: a systematic review and meta-analysis. Human reproduction update. 2018 Mar 1;24(2):225-41. https://doi.org/10.1093/humupd/dmx039

[9] Guan Y, Wang D, Bu H, Zhao T, Wang H. The effect of metformin on polycystic ovary syndrome in overweight women: a systematic review and meta-analysis of randomized controlled trials. International journal of endocrinology. 2020;2020(1):5150684. https://doi.org/10.1155/2020/5150684

[10] Witchel SF, Oberfield SE, Peña AS. Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. Journal of the Endocrine Society. 2019 Aug;3(8):1545-73. https://doi.org/10.1210/js.2019-00078

[11] Morgante G, Darino I, Spanò A, Luisi S, Luddi A, Piomboni P, Governini L, De Leo V. PCOS physiopathology and vitamin D deficiency: biological insights and perspectives for treatment. Journal of clinical medicine. 2022 Aug 2;11(15):4509. https://doi.org/10.3390/jcm11154509

[12] Israel NB, Shamdeen MY. The relation between polycystic ovary syndrome and Vitamin D deficiency. Medical Journal of Babylon. 2019 Jul 1;16(3):234-7.

[13] Gokosmanoglu F, Onmez A, Ergenç H. The relationship between Vitamin D deficiency and polycystic ovary syndrome. African health sciences. 2020 Dec 16;20(4):1880-6. https://doi.org/10.4314/ahs.v20i4.45

[14] Menichini D, Forte G, Orrù B, Gullo G, Unfer V, Facchinetti F. The role of vitamin D in metabolic and reproductive disturbances of polycystic ovary syndrome: A narrative mini-review. International Journal for Vitamin and Nutrition Research. 2020 Dec 7. https://doi.org/10.1024/0300-9831/a000691

[15] Mohan A, Haider R, Fakhor H, Hina F, Kumar V, Jawed A, Majumder K, Ayaz A, Lal PM, Tejwaney U, Ram N. Vitamin D and polycystic ovary syndrome (PCOS): A review. Annals of Medicine and Surgery. 2023 Jul 1;85(7):3506-11. https://doi.org/10.1097/ms9.0000000000000879

[16] Zhuang L, Wei CU, Jianxiang CO, Zhang Y. Efficacy of vitamin D combined with metformin and clomiphene in the treatment of patients with polycystic ovary syndrome combined with infertility. Iranian Journal of Public Health. 2019 Oct;48(10):1802.

[17] Rotterdam ES. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19-25. https://doi.org/10.1016/j.fertnstert.2003.10.004

[18] Lewandowski KC, Skowrońska-Jóźwiak E, Łukasiak K, Gałuszko K, Dukowicz A, Cedro M, Lewiński A. How much insulin resistance in polycystic ovary syndrome? Comparison of HOMA-IR and insulin resistance (Belfiore) index models. Archives of Medical Science. 2019 May 1;15(3):613-8. https://doi.org/10.5114/aoms.2019.82672

[19] World Health Organization, editor. International Statistical Classification of Diseases and related health problems: Alphabetical index. World Health Organization; 2004.

[20] Saleh BO, Ibraheem WF, Ameen NS. The role of anti-Mullerian hormone and inhibin B in the assessment of metformin therapy in women with polycystic ovarian syndrome. Saudi medical journal. 2015 May;36(5):562. https://doi.org/10.15537/smj.2015.5.11112

[21] Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocrine reviews. 2016 Oct 1;37(5):467-520. https://doi.org/10.1210/er.2015-1104

[22] Alawad ZM. Level of follicular fluid vitamin D and embryo quality in a sample of Iraqi women undergoing IVF. Journal of the Faculty of Medicine Baghdad. 2018;60(4):215-21 https://doi.org/10.32007/jfacmedbagdad.604758

[23] Qasim MN, Kadhem HK, El-Yassin HD. CORRELATION BETWEEN VITAMIN D3 DEFICIENCY AND SERUM LEPTIN LEVELS IN A PATIENT WITH POLYCYSTIC OVARY SYNDROME. Biochemical & Cellular Archives. 2022 Oct 1;22(2). http://dx.doi.org/10.51470/bca.2022.22.2.3773

[24] Teede H, Tassone EC, Piltonen T, et al. Effect of the combined oral contraceptive pill and/or metformin in the management of polycystic ovary syndrome: A systematic review with meta-analyses. Clinical Endocrinology. 2019; Volume91, Issue4: 479-489

https://doi.org/10.1111/cen.14013
[25] Lashen H. Role of metformin in the management of polycystic ovary syndrome. Therapeutic advances in endocrinology and metabolism. 2010 Aug;1(3):117-28. https://doi.org/10.1177/2042018810380215
[26] Duan X, Zhou M, Zhou G, Zhu Q, Li W. Effect of metformin on adiponectin in PCOS: A meta-analysis and a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2021 Dec 1;267:61-7. https://doi.org/10.1016/j.ejogrb.2021.10.022
[27] Angellotti E, D'Alessio D, Dawson-Hughes B, Nelson J, Cohen RM, Gastaldelli A, Pittas AG. Vitamin D supplementation in patients with type 2 diabetes: the vitamin D for established type 2 diabetes (DDM2) study. Journal of the Endocrine Society. 2018 Apr;2(4):310-21. https://doi.org/10.1210/js.2018-00015
[28] Menichini D, Facchinetti F. Effects of vitamin D supplementation in women with polycystic ovary syndrome: a review. Gynecological Endocrinology. 2020 Jan 2. https://doi.org/10.1080/09513590.2019.1625881
[29] Alomda FA, Hashish MA, El-Naggar WE, Mosallam AM. The effect of vitamin D supplementation on the androgenic profile in patient with polycystic ovary syndrome. The Egyptian Journal of Hospital Medicine. 2019 Apr 1;75(3):2461-6. https://dx.doi.org/10.21608/ejhm.2019.30963
[30] Mohan A, Haider R, Fakhor H, Hina F, Kumar V, Jawed A, Majumder K, Ayaz A, Lal PM, Tejwaney U, Ram N. Vitamin D and polycystic ovary syndrome (PCOS): A review. Annals of Medicine and Surgery. 2023 Jul 1;85(7):3506-11. https://doi.org/10.1097/ms9.0000000000000879
[31] Sulaiman EA, Dhiaa S, Merkhan MM. Overview of vitamin D role in polycystic ovarian syndrome. MMSL. 2022 Mar 4;91(1):37-43.
[32] Xue Y, Xu P, Xue K, Duan X, Cao J, Luan T, Li Q, Gu L. Effect of vitamin D on biochemical parameters in polycystic ovary syndrome women: a meta-analysis. Archives of Gynecology and Obstetrics. 2017 Feb;295:487-96. https://doi.org/10.1007/s00404-016-4247-y

To cite this article: Aziz ZN, Saleh BO, Thaker AZ. Free Testosterone, Dihydrotestosterone, and Adiponectin in the Evaluation of Vitamin D Supplementation for Polycystic Ovarian Syndrome: A Metformin Comparative Study. Al-Kindy Col. Med. J. 2024;20(3):239-244. https://doi.org/10.47723/nb5he078