

Role of Vitamin D in the Etiology of Polycystic Ovary Syndrome, A Review

Dr. Nahla Al-Bayyari

Department of Nutrition and Food Technology, Faculty of Al-Huson University College, Al-Balqa Applied University, Al-Salt, Jordan

***Correspondence to:** Dr. Nahla Al-Bayyari, Department of Nutrition and Food Technology, Faculty of Al-Huson University College, Al-Balqa Applied University, Al-Salt, Jordan.

Copyright

© 2018 Dr. Nahla Al-Bayyari. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received: 06 July 2018

Published: 23 July 2018

Keywords: *Vitamin D; Polycystic Ovary Syndrome; Hyperandrogenism; Insulin Resistance; Metabolic Disturbances*

Abstract

Polycystic ovary syndrome (PCOS) is a common cause of ovarian dysfunction in women suffering from anovulation. It is characterized by chronic anovulation, hyperandrogenism, and/or the presence of polycystic ovaries on ultrasonography. No single etiologic factor fully accounts for the spectrum of abnormalities in PCOS. Interactions between genetic and environmental factors such as genetic, gonadotropins and insulin contribute to the pathogenesis of PCOS. Vitamin D deficiency among PCOS women is prevalent and reaches 67 to 85 percent. The prevalence of vitamin D deficiency has been found to be associated with metabolic syndrome which may have great impact on public health. Low 25(OH)D levels may exacerbate the symptoms of PCOS, including insulin resistance, ovulatory, menstrual irregularities, infertility, hyperandrogenism, obesity and elevate the risk of cardiovascular diseases. Many observational studies suggest a possible role of vitamin D in an inverse association between vitamin D status and metabolic disturbances in PCOS, but it is still inconclusive to draw a definite conclusion in the causal relationship due to inconsistent findings from various studies and from meta-analysis report of a systematic review.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It is characterized by the presence of polycystic ovaries, menstrual dysfunction, infertility and elevated androgens as well as hirsutism and/or acne [1].

Vitamin D plays an important role in the health and fertility for women with polycystic ovary syndrome (PCOS). Despite the importance, research shows that 67–85% of women with PCOS are deficient in vitamin D [2]. A deficiency of Vitamin D not only causes poor bone mineralization but also has been implicated in numerous chronic diseases including diabetes, heart disease, poor immunity, various cancers, multiple sclerosis, rheumatoid arthritis, and high blood pressure.

Vitamin D deficiency may exacerbate symptoms of PCOS, with observational studies showing lower 25OHD levels were associated with insulin resistance, ovulatory and menstrual irregularities, lower pregnancy success, hirsutism, hyperandrogenism, obesity and elevated cardiovascular disease risk factors. There is some, but limited, evidence for beneficial effects of vitamin D supplementation on menstrual dysfunction and insulin resistance in women with PCOS. Vitamin D deficiency may play a role in exacerbating PCOS, and there may be a place for vitamin D supplementation in the management of this syndrome, but current evidence is limited and additional randomized controlled trials are required to confirm the potential benefits of vitamin D supplementation in this population. The objective of this review is to identify the role of vitamin D in the etiology of polycystic ovary syndrome.

Vitamin D synthesis and metabolism

Vitamin D is a steroid hormone. The 7-dehydrocholesterol is the vitamin D precursor present in the skin [3,4]. Ultraviolet B (UV-B) radiation induces conversion of 7-dehydrocholesterol to provitamin D₃, which spontaneously isomerizes to vitamin D₃ (cholecalciferol). (Vitamin D₃ is released into the circulation and transported by the vitamin D-binding protein (VDBP) [4]. Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (25[OH] D), which is metabolized in the kidneys by the enzyme 1 α -hydroxylase to its active form, 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) [3,4]. The active 1,25(OH)₂D can bind to vitamin D receptor- retinoic acid x-receptor complex (VDR-RXR) in the intestine, bone, and parathyroid glands to maintain mineral homeostasis for skeletal functions and other organs such as breast, colon and prostate for non-skeletal functions as illustrated in Figure (1) and (2) [5,6].

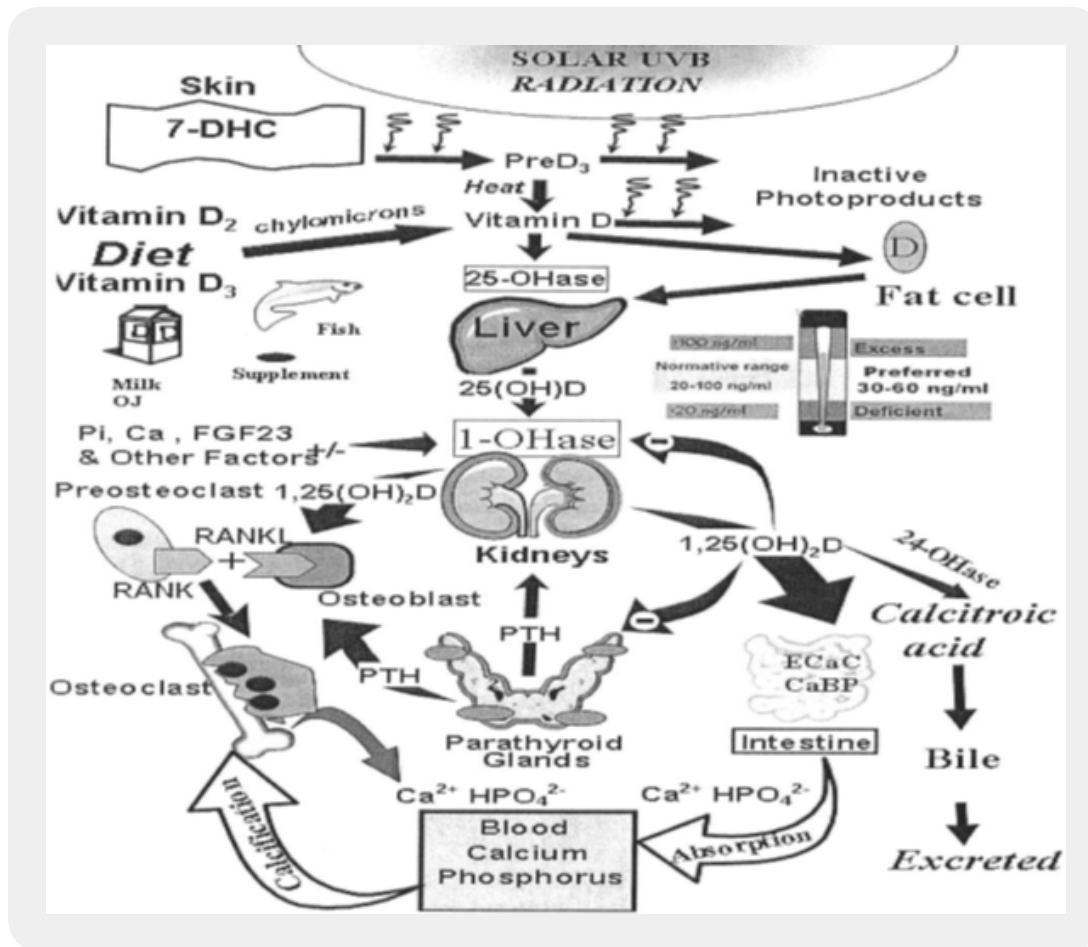


Figure 1: Synthesis and metabolism of vitamin D for regulating calcium, phosphorus, and bone metabolism

Source: Holick and Chen (2008)

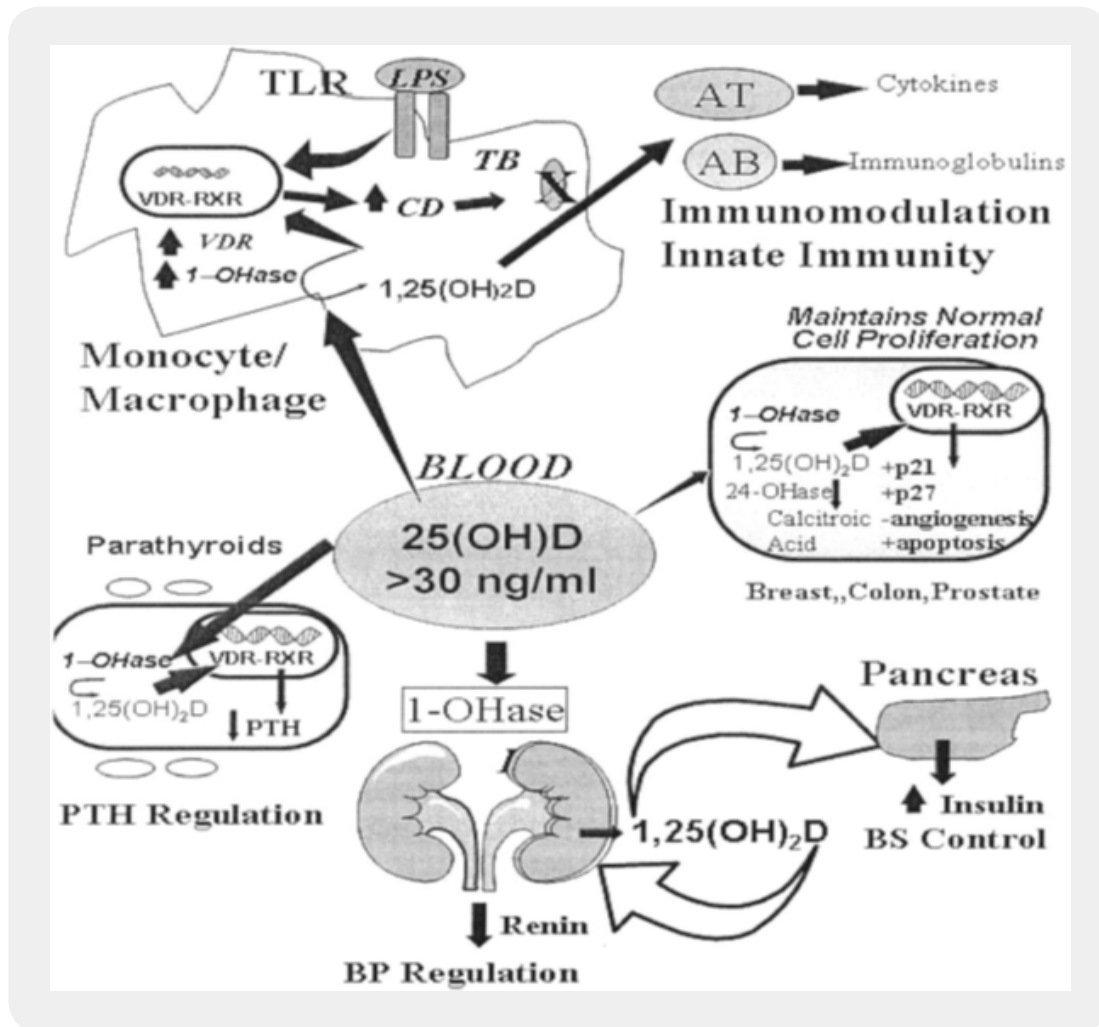


Figure 2: Metabolism of 25-hydroxyvitamin D [25(OH)D] to 1,25 dihydroxyvitamin D [1,25(OH)2D] for non-skeletal functions

Source: Holick and Chen (2008)

Vitamin D polymorphism in PCOS

Vitamin D receptor (VDR) polymorphisms are related to type 1 diabetes mellitus (T1DM) [7] as well as T2DM [8]. The VDR Apa-I is associated with defective insulin secretion [9] and glucose intolerance as well as metabolic syndrome [8]. While, (Oh and Barrett-Connor in (2002) [8] reported that the VDR Bsm-I polymorphism is associated with insulin resistance, others were not able to detect an association of VDR polymorphism with T2DM [10].

In the literature there is a little data published on the association of vitamin related polymorphism with PCOS. Zadeh-Vakili and his colleagues (2013) [11] conducted a case control study and found that the

distributions of genotypes and alleles did not differ between cases and controls, indicating that this single nucleotide polymorphism (SNP) is not associated with increased risk for PCOS but it is associated with the severity of the PCOS phenotype. Therefore, they concluded that the genetic variant of the VDR was found to have an association with severity of clinical features of PCOS, but not with the disease.

Vitamin D and PCOS

The relationship between vitamin D levels and different PCOS symptoms, including insulin resistance (IR), infertility and hirsutism has been demonstrated in several studies [12-14]. Science based evidence suggests that the levels of vitamin D are similar in women with and without PCOS [15]; however, lower levels [16,17] and higher levels [18] have been reported in women with PCOS. Many studies have reported low levels of 25(OH)D with a range between 11 and 31 ng/ml, [12,15,18,19] with the majority having values <20 ng/ml (67–85%) [2,12,13,15] in women with PCOS. Vitamin D deficiency is also common in the general population in different countries of the world, with 10–60% of adults having values <20 ng/ml [20].

Vitamin D and insulin resistance

Research evidence has proposed that low levels of vitamin D is a risk factor that plays an important role in the development of insulin resistance and the pathogenesis of T2DM through affecting either insulin sensitivity or β -cell function, or both [21,22]. The 1,25-dihydroxyvitamin D (1,25(OH)₂D) improves insulin sensitivity, β -cell function and protects β - cells from immune attacks directly and indirectly [23]. The potential role of vitamin D deficiency in insulin resistance is shown in Table (1) [6].

Role
<p>Inherited gene polymorphisms</p> <p>(1) Including DBP, VDR, and CYP1alpha gene polymorphisms.</p> <p>(2) Disturbance of vitamin D transport, action, and production.</p>
<p>Immunoregulatory function</p> <p>(1) Activating innate and adaptive immunity.</p> <p>(2) Enhancing dendritic cell maturation and macrophage differentiation, and cytokine release.</p> <p>(3) Enhancing T-cell proliferation.</p> <p>(4) Releases of IL-12, IL-2, INF-γ, and TNFα (destruction of the β-cell).</p>
<p>Inflammation</p> <p>(1) Upregulation of NF-κB and inducing TNFα proinflammatory actions.</p> <p>(2) Downregulates IκB-α by decreasing mRNA stability and increasing IκB-α phosphorylation.</p> <p>(3) Enhancing the expression of TLR2 and TLR4 protein and mRNA in human monocytes, reducing the release of cytokines.</p>

Other molecular actions of vitamin D to alter glucose homeostasis

- (1) Low calcium status: hypocalcemia can lower glucose-stimulated insulin secretion in β -cell.
- (2) PTH level: elevating PTH reduces glucose uptake by liver, muscle and adipose cell.
- (3) Obesity: vitamin D deficiency can increase adiposity, and increasing sequestration of vitamin D in adipose tissue.

VDBP: vitamin D binding protein; VDR: vitamin D receptor; CYP1 α : vitamin D 1 α -hydroxylase; IL-12: interleukin-12; INF- γ : interferon- γ ; TNF α : tumor necrosis factor α ; NF- κ B: nuclear factor κ B; I κ B- α : the inhibitor of NF- κ B; TLR: Toll-like receptors; PTH: parathyroid hormone.

Source: (Sung *et al.*, 2012)

Vitamin D levels and body mass index (BMI) in PCOS

Several research studies have reported an inverse association between body weight (BMI, body fat and waist measurements) and serum 25(OH)D levels in women with PCOS [12,19,24], and levels of 25(OH)D were reported to be 27-56% lower in obese women with PCOS compared with non-obese women with PCOS [12,19]. Muscogiuri and his colleagues (2012) [19] found that low levels of 25(OH)D were specified by the degree of adiposity (BMI and total fat mass) and were not directly affected by the development of IR in women with PCOS. Of the possible explanations of the high prevalence of vitamin D deficiency in women with PCOS is related to obesity [15], because vitamin D is trapped in adipose tissue [25], and obese women may spend less time outdoors exposed to sunlight. It is also possible that dietary preferences and vitamin D metabolism may differ between obese and non-obese individuals [2]. Meanwhile, there are inadequate data available regarding the difference in vitamin D status between lean and obese women with PCOS.

Vitamin D levels, pathogenesis of PCOS and insulin resistance

Vitamin D deficiency may contribute to the pathogenesis of IR and MS in PCOS as shown in Figure (3) [26,27]. The pathogenesis of PCOS has been linked to the effects of VDRs polymorphisms on luteinizing hormone (LH) and sex hormone binding globulin (SHBG) levels [28], testosterone levels, IR and serum insulin levels [16,29]. Vitamin D deficiency increases parathyroid hormone (PTH) production which is independently associated with PCOS, anovulatory infertility and increased testosterone [30]. It has been suggested that vitamin D deficiency and inadequate dietary calcium may be responsible for the menstrual abnormalities in case of PCOS [31]. Vitamin D regulates estrogen biosynthesis and aromatase gene expression by maintaining extracellular calcium homeostasis [32]. In human ovarian tissue, estrogen and progesterone production is stimulated by 1,25(OH)₂D₃, and testosterone production decreases may be by boosting of aromatase activity through vitamin D [33]. In the follicles of PCOS women compared to controls, aromatase gene expression decreased and LH levels had increased but follicular production of progesterone and estradiol decreased [34]. As a result of these effects, vitamin D deficiency may arise PCOS symptoms. Meanwhile, the exact mechanism underlying vitamin D and insulin resistance is not known but some cellular and molecular mechanisms have been attempted to explain this association [2]. For example,

1,25(OH)D may enhance insulin action by enhancing insulin synthesis and release, increasing insulin receptor expression or suppression of proinflammatory cytokines [35]. Furthermore, vitamin D may improve insulin sensitivity by improving calcium status, increasing local production of 25(OH)D, which leads to transcriptional regulation of specific genes or suppressing serum levels of PTH [35].

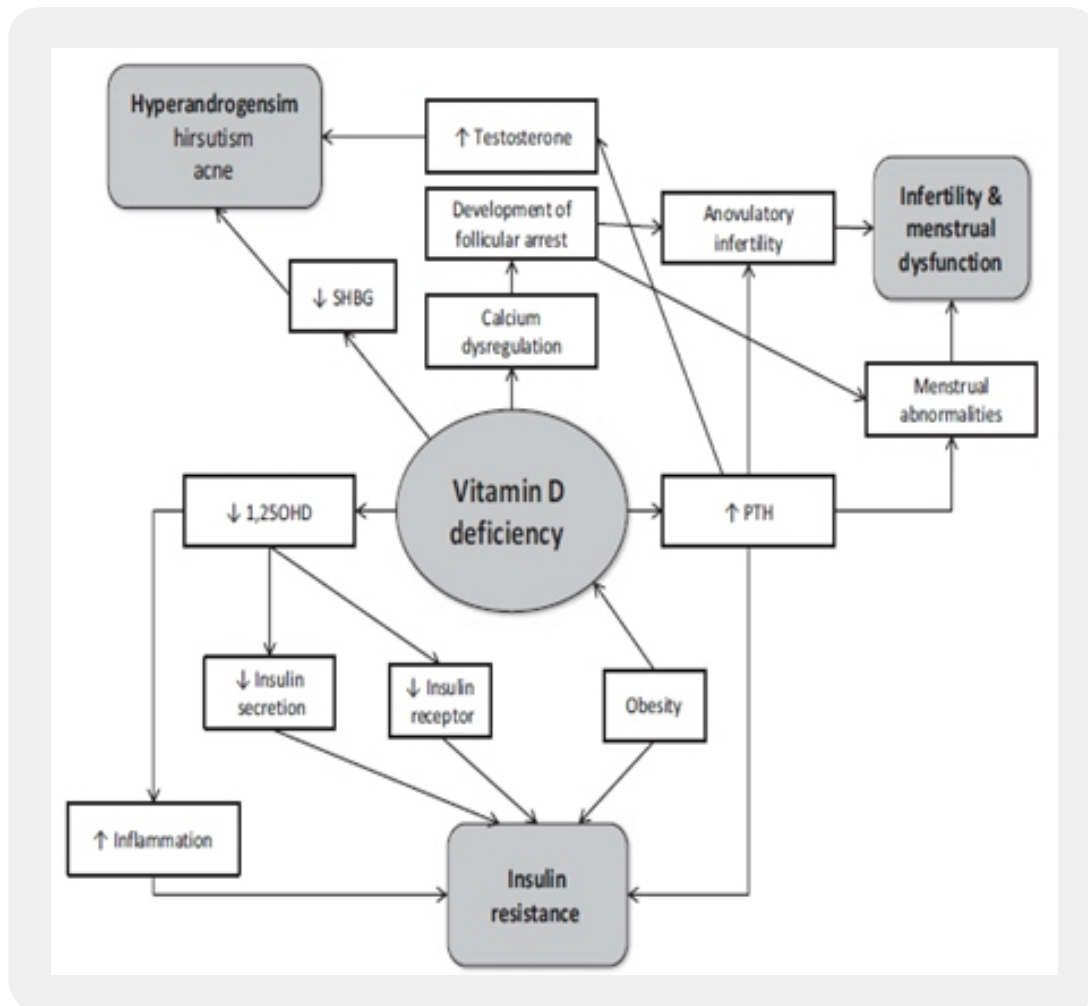


Figure 3: The role of vitamin D deficiency in the pathology of PCOS

Source: (Thomson *et al.*, 2012)

Vitamin D, PCOS and metabolic disturbances

Vitamin D deficiency was independently associated with lower insulin sensitivity, lower high-density lipoprotein cholesterol (HDL-C) levels [14,36] and obesity [37]. The association of low vitamin D levels with IR might be mediated by obesity [37]. Furthermore, 25(OH)D levels have been reported to be lower in obese PCOS women compared with normal weight PCOS women [18,37].

It has also been demonstrated by previous studies that vitamin D deficiency is associated with other features of metabolic syndrome (MS) including glucose intolerance, hypertension, dyslipidemia, and chronic inflammation [36,38]. These metabolic risk factors are commonly found in women with PCOS, but roles for vitamin D deficiency in PCOS and MS is not entirely clear yet [36,39].

The impact of vitamin D supplementation on metabolic disturbances was studied and results showed improvements in serum triglycerides (TG) and HDL, with no changes in BMI [40] and significant decreases in fasting and stimulated glucose, TG and hip circumference (HC), but total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol were increased, and BMI, HDL, blood pressure and waist circumference (WC) were unchanged [41]. Likewise, the improvement in 25(OH)D levels was significantly correlated with the reduction in high sensitivity c-reactive protein (CRP), but not with total cholesterol (TC), TG, HOMA-IR or free androgen index (FAI) [42].

Vitamin D and reproductive function in women with PCOS

There is accumulating evidence that vitamin D plays an important role in reproductive function because VDRs have been found in the ovary, endometrium and placenta [33,43]. Vitamin D deficiency is associated with calcium dysregulation, which participates in the development of follicular arrest in women with PCOS and results in menstrual and fertility dysfunction [31]. Ozkan, *et al.* (2010) [44] conducted a study on women with PCOS and undergoing in vitro fertilization (IVF), they found that the women who achieved pregnancy exhibited significantly higher follicular fluid levels of 25(OH)D and each ng/ml increase in follicular fluid 25(OH)D increased the likelihood for achieving pregnancy by 7% [44]. Moreover, 25(OH)D deficiency was associated with lower rates of follicle development and pregnancy after stimulation with clomiphene-citrate in women with PCOS, suggesting a possible role of vitamin D supplementation in infertile PCOS women who undergo ovarian stimulation [45].

Rashidi and his colleagues (2009) [46] studied the effects of calcium–vitamin D and metformin in regulating the menstrual cycle in women with PCOS and concluded that metformin and calcium–vitamin D could be effective for the treatment of anovulation and oligomenorrhoea in women with PCOS. Furthermore, in a recent uncontrolled pilot study on 46 women with PCOS, the authors also observed improvements in reproductive function and in menstrual frequency of oligo- or amenorrhoeic women after 24 weeks of weekly cholecalciferol (20,000 IU), which significantly increased 25(OH)D levels [41].

Vitamin D and hyperandrogenism in women with PCOS

The associations between markers of hyperandrogenism and vitamin D status have been found in observational studies [2]. Hirsute women with PCOS had lower 25(OH)D levels compared with women with PCOS but without hirsutism [13]. In women with PCOS, the 25(OH)D levels have been positively associated with SHBG [13,15] and negatively associated with the degree of hirsutism [13,37], free androgen index (FAI) [15], total testosterone and dehydroepiandrosterone sulphate [12]. Likewise, SHBG levels were lower in PCOS women with severe vitamin D deficiency, but after adjusting for BMI this was no longer significant [13,15,37], indicating that obesity is a common determinant for both SHBG and 25(OH)D [2]. Limited studies have examined the effect of vitamin D supplementation on hyperandrogenism measures, and have shown no changes in levels of testosterone, SHBG and FAI [41,47].

Conclusion

Many observational studies suggest a possible role of vitamin D in an inverse association between vitamin D status and metabolic disturbances in PCOS, but it is still inconclusive to draw a definite conclusion in the causal relationship due to inconsistent findings from various studies and from meta-analysis report of a systematic review.

Bibliography

1. Dunaif, A. (1997). Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocrinology Reviews*, 18(6), 774-800.
2. Thomson, R. L., Spedding, S. & Buckley, J. D. (2012). Vitamin D in the aetiology and management of polycystic ovary syndrome. *Clinical Endocrinology (Oxford)*, 77(3), 343-350.
3. Holick, M. F. & Garabedian, M. (2006). Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus, M. J. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. (6th Ed.). Washington, DC: American Society for Bone and Mineral Research, 129 -137.
4. Holick, M. F. (2007). Vitamin D deficiency. *New England Journal of Medicine*, 357, 266-281.
5. Holick, M. F. & Chen, T. C. (2008). Vitamin D deficiency: A worldwide problem with health. *American Journal of Clinical Nutrition*, 87(4), 1080-1086.
6. Sung, C. C., Liao, M. T., Kuo-Cheng Lu, K. C. & Chia-Chao Wu, C. C. (2012). Role of vitamin D in insulin resistance. *Journal of Biomedicine and Biotechnology*, 2012, 1-11.
7. Pani, M. A., Knapp, M., Donner, H., Braun, J., Baur, M. P. & Usadel, K. H., *et al.* (2000). Vitamin D receptor allele combinations influence genetic susceptibility to type 1 diabetes in Germans. *Diabetes*, 49(3), 504-507.
8. Oh, J. Y. & Barrett-Connor, E. (2002). Association between vitamin D receptor polymorphism and type 2 diabetes or metabolic syndrome in community-dwelling older adults: The Rancho Bernardo Study. *Metabolism*, 51(3), 356-359.
9. Hitman, G. A., Mannan, N., McDermott, M. F., Aganna, E., Ogunkolade, B. W., Hales, C. N., *et al.* (1998). Vitamin D receptor gene polymorphisms influence insulin secretion in Bangladeshi Asians. *Diabetes*, 47(4), 688.
10. Malecki, M. T., Frey, J., Moczulski, D., Klupa, T., Kozek, E. & Sieradzki, J. (2003). Vitamin D receptor gene polymorphisms and association with type 2 diabetes mellitus in a Polish population. *Experimental and Clinical Endocrinology and Diabetes*, 111(8), 505-509.

11. Zadeh-Vakili, A., Ramezani-Tehrani, F., Daneshpour, M. S., Zarkesh, M., Saadat, N. & Azizi, F. (2013). Genetic polymorphism of vitamin D receptor gene affects the phenotype of PCOS. *Gene*, 515(1), 193-196.
12. Yildizhan, R., Kurdoglu, M. & Adali, E. (2009). Serum 25-hydroxyvitamin D concentrations in obese and non-obese women with polycystic ovary syndrome. *Archives of Gynecology and Obstetrics*, 280(4), 559-563.
13. Wehr, E., Pilz, S., Schweighofer, N., Giuliani, A., Kopera, D. & Pieber, T. R. (2009). Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome. *European Journal of Endocrinology*, 161(4), 575-582.
14. Kim, J. J., Choi, Y. M., Chae, S. J., Hwang, K. R., Yoon, S. H., Kim, M. J., *et al.* (2014). Vitamin D deficiency in women with polycystic ovary syndrome. *Clinical and Experimental Reproductive Medicine*, 41(2), 80-85.
15. Li, H. W., Brereton, R. E., Anderson, R. A., Wallace, A. M. & Ho, C. K. (2011). Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. *Metabolism*, 60(10), 1475-1481.
16. Wehr, E., Trummer, O., Giuliani, A. *et al.* (2011). Vitamin D associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. *European Journal of Endocrinology*, 164(5), 741-749.
17. Lerchbaum, E., Giuliani, A., Gruber, H. J. *et al.* (2012). Adult-type hypolactasia and calcium intake in polycystic ovary syndrome. *Clinical Endocrinology*, 77(6), 834-843.
18. Mahmoudi, T., Gourabi, H., Ashrafi, M., Yazdi, R. S. & Ezabadi, Z. (2010). Calcitropic hormones, insulin resistance, and the polycystic ovary syndrome. *Fertility and Sterility*, 93(4), 1208-1214.
19. Muscogiuri, G., Policola, C., Prioletta, A., GianPioSorice, G., Mezza, T., Lassandro, A., *et al.* (2012). Low levels of 25(OH)D and insulin-resistance: 2 unrelated features or a cause-effect in PCOS? *Clinical Nutrition*, 31(4), 476-480.
20. Lips, P. (2010). Worldwide status of vitamin D nutrition. *The Journal of Steroid Biochemistry and Molecular Biology*, 121(1-2), 297-300.
21. Deleskog, A., Hilding, A. K., Brismar, K., Hamsten, A., Efendic, S. & Ostenson, C. G. (2012). Low serum 25-hydroxyvitamin D level predicts progression to type 2 diabetes in individuals with prediabetes but not with normal glucose tolerance. *Diabetologia*, 55(6), 1668-1678.
22. Forouhi, N. G., Ye, Z., Rickard, A. P., *et al.* (2012). Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: results from the European prospective investigation into cancer (EPIC)-Norfolk cohort and updated meta-analysis of prospective studies. *Diabetologia*, 55(8), 2173-2182.

23. Takiishi, T., Gysemans, C., Bouillon, R. & Mathieu, C. (2010). Vitamin D and diabetes. *Endocrinology and Metabolism Clinics of North America*, 39(2), 419-446.
24. Wehr, E., Möller, R., Horejsi, R., Giuliani, A., Kopera, D., Schweighofer, N., *et al.* (2009). Subcutaneous Adipose tissue topography and metabolic disturbances in polycystic ovary syndrome. *Wiener Klinische Wochenschrift*, 121(7-8), 262-269.
25. Lagunova, Z., Porojnicu, A. C., Lindberg, F. *et al.* (2009). The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Research*, 29(9), 3713-3720.
26. Ngo, D. T., Chan, W. P., Rajendran, S., Heresztyn, T., Amarasekera, A., Sverdlov, A. L., *et al.* (2011). Determinants of insulin responsiveness in young women: impact of polycystic ovarian syndrome, nitric oxide, and vitamin D. *Nitric Oxide*, 25(3), 326-330.
27. Khan, N. R., Shah, J., Stetter, C. M., Lott, M. E. J., Kunselman, A. R., Dodson, W. C., *et al.* (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), 1740-1746.
28. Ranjzad, F., Mahban, A., Irani Shemirani, A., Mahmoudi, T., Vahedi, M., Nikzamir, A., *et al.* (2011). Influence of gene variants related to calcium homeostasis on biochemical parameters of women with polycystic ovary syndrome. *Journal of Assisted Reproduction and Genetics*, 28(3), 225-232.
29. Mahmoudi, T. (2009). Genetic variation in the vitamin D receptor and polycystic ovary syndrome risk. *Fertility and Sterility*, 92(4), 1381-1383.
30. Panidis, D., Balaris, C., Farmakiotis, D., Rousso, D., Kourtis, A., Balaris, V., *et al.* (2005). Serum parathyroid hormone concentrations are increased in women with polycystic ovary syndrome. *Clinical Chemistry*, 51(9), 1691-1697.
31. Thys-Jacobs, S., Donovan, D., Papadopoulos, A., Sarrel, P. & Bilezikian, J.P. (1999). Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. *Steroids*, 64(6), 430-435.
32. Kinuta, K., Tanaka, H., Moriwake, T., Aya, K., Kato, S. & Seino, Y. (2000). Vitamin D is an important factor in Estrogen biosynthesis of both female and male gonads. *Endocrinology*, 141(4), 1317-1324.
33. Parikh, G., Varadinova, M., Suwandhi, P., Araki, T., Rosenwaks, Z., Poretsky, L., *et al.* (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), 754-757.
34. Sander, V. A., Hapon, M. B., Sı'caro, L., Lombardi, E. P., Jahn, G. A. & Motta, A. B. (2011). Alterations of folliculogenesis in women with polycystic ovary syndrome. *The Journal of Steroid Biochemistry and Molecular Biology*, 124(1-2), 58-64.
35. Teegarden, D. & Donkin, S. S. (2009). Vitamin D: emerging new roles in insulin sensitivity. *Nutrition Research Reviews*, 22(1), 82-92.

36. Hassan, N. E., El-Orabi, H. A., Eid, Y. M. & Mohammed, N. R. (2012). Effect of 25-hydroxyvitamin D on metabolic parameters and insulin resistance in patients with polycystic ovarian syndrome. *Middle East Fertility Society Journal*, 17(3),176-180.
37. Hahn, S., Haselhorst, U., Tan, S., Quadbeck, B., Schmidt, M., Roesler, S., *et al.* (2006). 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*, 114(10), 577-583.
38. Michos, E. D. & Melamed, M. L. (2008). Vitamin D and cardiovascular disease risk. *Current Opinion in Clinical Nutrition and Metabolic Care*, 11(1), 7-12.
39. Norman, R. J., Dewailly, D., Legro, R. S. & Hickey, T. E. (2007). Polycystic ovary syndrome. *Lancet*, 370(9588), 685-697.
40. Kotsa, K., Yavropoulou, M. P., Anastasiou, O. & Yovos, J. G. (2009). Role of vitamin D treatment in glucose metabolism in polycystic ovary syndrome. *Fertility and Sterility*, 92(3), 1053-1058.
41. Wehr, E., Pieber, T. R. & Obermayer-Pietsch, B. (2011). Effect of vitamin D3 treatment on glucose metabolism and menstrual frequency in PCOS women-A pilot study. *Journal of Endocrinological Investigation*, 34(10), 757-763.
42. Sathyapalan, T., Shepherd, J., Arnett, C., *et al.* (2010). Atorvastatin increases 25-hydroxy vitamin D Concentrations in patients with polycystic ovary syndrome. *Clinical Chemistry*, 56(11), 1696-1700.
43. Agic, A., Xu, H., Altgassen, C., Noack, F., Wolfler, M. M., Diedrich, K., *et al.* (2007). Relative expression of 1,25-rihydroxyvitamin D3 Receptor, vitamin D 1 α -hydroxylase, vitamin D 24-hydroxylase, and vitamin D 25-hydroxylase in endometriosis and gynecologic cancers. *Reproductive Sciences*, 14(5), 486-497.
44. Ozkan, S., Jindal, S., Greenseid, K., *et al.* (2010). Replete vitamin D stores predict reproductive success following in vitro fertilization. *Fertility and Sterility*, 94(4), 1314-1319.
45. Ott, J., Wattar, L., Kurz, C., *et al.* (2012). Parameters for calcium metabolism in women with polycystic ovary syndrome who undergo clomiphene citrate stimulation: A prospective cohort study. *European Journal of Endocrinology*, 166(5), 897-902.
46. Rashidi, B., Haghollahi, F., Shariat, M., *et al.* (2009). The effects of calcium-vitamin D and metformin on polycystic ovary syndrome: A pilot study. *Taiwanese Journal of Obstetrics and Gynecology*, 48(2), 142-147.
47. Selimoglu, H., Duran, C., Kiyici, S., Ersoy, C., Guclu, M., Ozkaya, G., *et al.* (2010). The effect of vitamin D replacement therapy on insulin resistance and androgen levels in women with polycystic ovary syndrome. *Journal of Endocrinological Investigation*, 33(4), 234-238.