Polymorphisms of Vitamin D Receptor and the Effect on Metabolic and Endocrine Abnormalities in Polycystic Ovary Syndrome: A Review

Authors

Talida Vulcan¹, Gabriela Adriana Filip² , Lavinia Manuela Lenghel³, Tudor Suciu⁴, Paula Ilut¹, Lucia Maria Procopciuc⁵

Affiliations

- 1 Iuliu Hatieganu University of Medicine and Pharmacy
Faculty of Medicine, Dermatology Cluj Napoca, Romania
- 2 Iuliu Hatieganu University of Medicine and Pharmacy
Faculty of Medicine, Physiology Cluj Napoca, Romania
- 3 Iuliu Hatieganu University of Medicine and Pharmacy
Faculty of Medicine, Radiology, Cluj Napoca, Romania
- 4 Iuliu Hatieganu University of Medicine and Pharmacy
Faculty of Medicine, Maxillofacial Surgery and Radiology,
Cluj Napoca, Romania
- 5 Iuliu Hatieganu University of Medicine and Pharmacy
Faculty of Medicine, Medical Biochemistry, Cluj Napoca,
Romania

Key words

vitamin D receptor polymorphism, PCOS, hyperandrogenism, insulin resistance

received 22.02.2021

accepted after revision 07.06.2021

published online 20.09.2021

Bibliography

Horm Metab Res 2021; 53: 645–653

DOI 10.1055/a-1587-9336

ISSN 0018-5043

© 2021. Thieme. All rights reserved.

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Gabriela Adriana Filip
Iuliu Hatieganu University of Medicine and Pharmacy Faculty
of Medicine, Physiology
Barsei no 1/17 Cluj Napoca
400349 Cluj Napoca
Romania
Tel.: +40 745268704
adrianafilip33@yahoo.com

ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorder in women of reproductive age. Vitamin D and its receptor are thought to play an important role in PCOS susceptibility, although the impact of vitamin D receptor (VDR) polymorphisms on the hormonal and metabolic profile is still controversial. A literature search in PubMed and Embase was performed up to September 2020 for case-control studies in women suffering from PCOS, with outcome related to VDR polymorphisms effect on metabolic/endocrine disturbances. We have found 16 eligible studies including 2566 women with PCOS and 2430 controls. Apal polymorphism seemed to be associated with hyperandrogenism in both Asian and Caucasian population. FokI variant was correlated with metabolic/endocrine parameters especially in Asian population, while a relation between Cdx2 genotypes and insulin sensitivity was observed in both ethnicities. VDR polymorphisms have an important role in PCOS development and related hormonal and metabolic abnormalities. Few case-control studies analysed the interaction between VDR variants and metabolic/endocrine parameters with the majority of the articles focused on the Asian region. Further research on various ethnic populations with larger sample size are still needed for a definitive conclusion, in order to allow early diagnosis and prevention of PCOS comorbidities.

Introduction

Polycystic ovary syndrome (PCOS) is a highly prevalent disorder among women of reproductive age, with a wide range of signs and symptoms, accompanied by a high risk of metabolic and cardiovascular diseases. It is a heterogeneous condition characterized by hyperandrogenism (HA), ovulatory dysfunction and polycystic ovar-

ian morphology [1] affecting 4–21 % of women worldwide depending on the diagnostic criteria used [2]. The Rotterdam criteria are internationally accepted and require the presence of two of the three findings: clinical/biochemical HA, chronic ovulatory dysfunction and polycystic ovarian morphology at ultrasound examination, after exclusion of secondary causes [3]. National Institutes of

Health (NIH) criteria confirm the diagnosis in the presence of clinical/biochemical HA and ovulatory dysfunction [3, 4] this set of criteria still being in use in literature reports.

The etiology of PCOS is multifactorial and not fully understood. Some of the main known mechanisms to date are represented by alteration in the secretion of gonadotropin-releasing hormone, defects in androgen synthesis, development of insulin resistance (IR) and ovarian follicular arrest [5].

Disturbances of the hypothalamic-pituitary axis determine elevated levels of luteinizing hormone (LH) and normal/low levels of follicle stimulating hormone (FSH), due to a higher frequency of gonadotropin-releasing hormone pulses [6]. LH stimulates androgen production and interferes with normal follicular development [5].

IR is one of the key components in this complex disorder. IR with compensatory hyperinsulinemia (HI) determine HA by acting synergically with LH on ovarian steroidogenesis. Moreover, by inhibiting the liver synthesis of sex hormone binding globulin it increases testosterone availability [7]. HI increases risk for type 2 diabetes, hypertension, endothelial dysfunction, atherosclerosis, and cardiovascular diseases [6]. HI and HA can disrupt follicle growth, accompanied by menstrual irregularity and accumulation of immature follicles (► **Fig. 1**). In addition, higher levels of anti-Müllerian hormone (AMH) are a result of increased number of small antral follicles [1], impairing the follicle growth and the selection of a dominant follicle [8].

The clinical manifestations are consecutive to androgen excess, which lead to dermatological and gynecological disturbances. Specific cutaneous features include hirsutism, acne, seborrhea, androgenic alopecia, and acanthosis nigricans. Hirsutism is used as an indicator of HA, being in some studies reported as the most common skin manifestation in PCOS and closely related to metabolic abnormalities [9]. Acanthosis nigricans is a known marker of HI, while obesity is independently associated with it [10, 11].

The phenotypic classification allows a better characterization the syndrome: phenotype A: androgen excess, ovulatory dysfunction and polycystic ovarian morphology; phenotype B: androgen excess and ovulatory dysfunction; phenotype C: androgen excess and polycystic ovarian morphology; and phenotype D: ovulatory dysfunction and polycystic ovarian morphology [12]. Different phenotypes were observed to be predominant in various populations. PCOS also determines anovulatory infertility in 70 % of women, being the most common cause of ovulatory dysfunction [12].

Vitamin D and PCOS

Vitamin D (vit D) is a steroid hormone, synthesized mainly by the skin under ultraviolet type B radiation, while food sources contribute in small part to its circulating levels [13]. Beside its well-known role in maintaining calcium homeostasis and bone mineralization [14], vit D has anti-inflammatory, antioxidant, immunomodulatory, antiangiogenic, and antiproliferative proprieties [15] (► **Fig. 2**). Accumulating evidence suggest that vit D status has a close association with the pathogenesis of IR and metabolic syndrome in PCOS [16]. Despite the thoroughly studied relation between vit D level and PCOS per se, the results are still controversial. It seems

that most of the connections are between vit D receptor polymorphism and PCOS.

Vitamin D receptor polymorphisms

Vit D biological actions in different tissues are mediated by the vit D receptor (VDR), a ligand-dependent transcription factor of steroid/thyroid hormone receptor super family, which regulates ~3 % of the human genome [17]. By binding to VDR, vit D generates the transcription of vit D related genes [18].

VDR gene is located on chromosome 12q13, it contains 14 exons [19] and covers over 75 kb of genomic DNA. It is formed by two promoter regions, eight protein coding exons (2–9) and six untranslated exons (1a–1 f) [20]. The gene is highly polymorphic and many allelic variants due to single nucleotide polymorphisms have been reported, which are variable among different ethnic groups [20, 21].

The most studied VDR polymorphisms related to PCOS are represented by: FokI (CC:CT:TT genotypes, C:T alleles), BsmI (AA:AG:GG genotypes, A:G alleles), Apal (AA:AC:CC genotypes, A:C alleles), TaqI (TT:TC:CC genotypes, T:C alleles), Tru9I (GG:GA:AA genotypes, G:A alleles), and Cdx2 (GG:GA:AA genotypes, G:A allele).

Over the past decade, researchers focused on several candidate genes involved in steroidogenesis, insulin signaling pathway, gonadotropin secretion [22] or vitamin D metabolism, in the attempt to increase knowledge about PCOS pathogenesis.

The results obtained so far are inconsistent; therefore, the aim of this review is to examine the association between VDR polymorphisms and metabolic or endocrine disturbances in women with PCOS, in different ethnic groups.

Materials and Methods

Two databases (PubMed and Embase) were searched up to September 2020 for original case-control studies that investigated the association between VDR polymorphisms and endocrine or metabolic parameters in PCOS. The search strategy included the following keywords in all possible combinations: PCOS OR polycystic ovary syndrome and VDR OR vitamin D receptor polymorphism; PCOS OR polycystic ovary syndrome and BsmI, Apal, FokI, TaqI, Cdx2, Tru9I. The references of the included studies were also searched manually to find additional publications potentially missed.

Studies were chosen if they met the following criteria: 1) published studies in English; 2) studies reporting evidence in humans only; 3) inclusion of women with PCOS and a control group; 4) inclusion of at least one of the following VDR polymorphisms–FokI, BsmI, Apal, TaqI, Cdx2, Tru9I and their correlation with at least one metabolic or endocrine parameter as the main outcome; and 5) PCOS defined by Rotterdam or NIH criteria. We excluded case reports, editorials, reviews, conference abstracts, duplicates, or studies in other language than English (see flow chart, ► **Fig. 3**). The following information was extracted from each included study: name of the first author, ethnicity, selection criteria, number of participants, studied polymorphism and the main outcome (► **Table 1**).

► **Fig. 1** Schematic representation of the mechanisms interplay in PCOS. Androgen excess facilitates IR and metabolic dysfunction by favoring abdominal and visceral adiposity. Increased estrogen production by ovaries and fat tissue determines menstrual irregularities and risk for endometrial hyperplasia. IR and compensatory HI favor anovulation; HA causes metabolic and cardiovascular complications. PCOS: Polycystic ovary syndrome; IR: Insulin resistance; HI: Hyperinsulinemia; HA: Hyperandrogenism; GnRH: Gonadotrophin releasing hormone; H: Hypothalamus; PG: Pituitary gland; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; P: Pancreas; L: Liver; SHBG: Sex hormone binding globulin; A: Adrenal gland; O: Ovary; AT: Adipose tissue; T2DM: Type 2 diabetes mellitus; NAFLD: Non-alcoholic fatty liver disease; AN: Acanthosis nigricans; PCOM: Polycystic ovarian morphology.

Results

PCOS and FokI polymorphism

FokI polymorphism (rs2228570, previously named rs10735810) located on exon 2 of the coding region of VDR gene is a T→C transition in the exon. It alters the first translation site, creating a new start codon, modifying the transcriptional activity of the gene, producing an altered protein, containing 427 amino acids instead of 424 amino acids [23, 24]. Thus, two protein variants can exist, each

one corresponding to the site where the translation starts from: a long version (the “F” allele) and the shortened version by 3 amino acids (the “f” allele) [25].

VDR FokI “AG” genotype was reported to be significantly associated with increased levels of testosterone [18]. On the other hand, Wehr et al. showed no association of VDR FokI polymorphisms with anthropometric, endocrine and metabolic parameters, in a study involving Caucasian women with PCOS [16].

► **Fig. 2** Vitamin D action in classic and non-classic target tissues. Vitamin D circulates bound to plasma vitamin D binding protein (VDBP) to the liver and kidney for metabolic activation. The active form binds to vitamin D receptor-retinoid X receptor heterodimer (VDR-RXR), which is widely distributed throughout tissues in order to exert its functions.

Previously, in 2009 Mahmoudi et al. found that subjects with the “FF” genotype had increased risk for abnormal serum insulin levels and IR than those with the “Ff/ff” genotypes [26], while another study reported that Indian women with “TT” genotype presented increased risk for infertility, acne, alopecia and elevated cholesterol levels [27]. In a small study carried on 33 Saudi women, weight, vit D, LH were higher in PCOS group. Interestingly, a positive correlation was found between the level of vit D and FSH, but only in the control group [21]. In a study carried on obese PCOS women in Western Asia, both FokI “FF” and Apal “AA” genotypes showed lower levels of androstenedione and vit D status [28].

When analyzing the classic PCOS phenotype, higher waist circumference and android to gynoid fat deposit ratio were observed, but also higher levels of serum fasting glucose, insulin, triglycerides and testosterone. Sex hormone binding globulin levels were lower compared to healthy controls. Regarding the genotype frequencies, there was no variation between groups. Moreover, no difference was observed between FokI genotypes and metabolic or anthropometric parameters [29].

AMH is a good marker for determining the ovarian reserve. Szafrowska and co-workers examined the influence of vit D and VDR polymorphisms on AMH levels, which were higher in PCOS group, while vit D levels were lower. Only FokI and Apal heterozygous or mutant genes had a significant correlation with AMH values, while Apal “AA” type presented higher vit D levels [30].

PCOS and Apal polymorphism

Apal polymorphism (rs7975232) is located in intron 8 at the 3rd end of the VDR gene. The 3'-UTR (untranslated) region is involved in mRNA stability and post-transcriptional processes [17]. The results about Apal polymorphism and the association with PCOS are contradictory, mainly because it does not alter the amino acid sequence, but it is involved in regulation of the gene's expression [23]. A recent meta-analysis confirmed the association between Apal and PCOS risk, highlighting the individual differences in susceptibility to PCOS: variant “aa” offers susceptibility to PCOS in Asian population, while Apal “a” and “aa + Aa” haplotype offer increased risk in Caucasian women [15].

Thirteen of the reviewed studies determined VDR gene Apal polymorphism, but only in 6 of them have we found significant correlations with metabolic/endocrine parameters. Wehr et al. showed that Apal “AA” genotype had lower testosterone levels. No association with metabolic parameters was observed, neither with PCOS susceptibility [16]. On the contrary, Mahmoudi et al. was the first one to show association between VDR Apal and PCOS in Asian subjects: the “aa” genotype was associated with increased risk for PCOS, whereas the “Aa” genotype appeared as a marker of decreased susceptibility [26].

Dasgupta et al. found that “CC” genotype had increased risk for infertility, while heterozygote genotypes showed alopecia and acanthosis traits. Overall, genotype “AA” was associated with elevated testosterone levels, although not significant [27]. Another study carried on Indian women showed that androstenedione levels were significantly higher in Apal “AA” compared to “CC” genotype, while “CC” genotype was associated with lower estradiol levels. Moreover, overweight/obesity was higher in PCOS group alongside with insulin, dehydroepiandrosterone sulfate, 17-hydroxyprogesterone values, whereas vit D mean serum levels were lower [31].

Santos and co-workers investigated metabolic and endocrine abnormalities in a group selected by Rotterdam criteria. The subjects had significantly higher total testosterone and free androgen index values, with lower sex hormone binding globulin levels, but vit D was similar between groups. To notice, in PCOS women lower vit D levels were related to metabolic syndrome and its isolated components: higher glucose, waist circumference and triglycerides. Apal “CC” genotype had a higher risk for metabolic syndrome in PCOS group compared to “CA + AA” genotype and it was also associated with higher systolic blood pressure, total cholesterol and low-density lipoprotein-cholesterol in both groups, suggesting that Apal variant might be correlated with metabolic syndrome in PCOS women [32].

Regarding prolactin levels, Kadhim et al. revealed that Apal “CC” and “CA” genotypes, alongside FokI “CC” and TaqI “CC” genotypes had higher levels of prolactin hormone in PCOS women [33].

PCOS and BsmI polymorphism

BsmI polymorphism (rs 1544410) is located in intron 8 at the 3rd end of the gene near to Apal. It is known as a silent polymorphism, which does not change the amino acids sequence. Due to its location in the gene, it might be involved in regulation of gene expression through influencing mRNA stability [24, 34].

The association between BsmI and PCOS remains to be determined; while some authors consider it is not associated with PCOS

► **Fig. 3** Flow chart of the methodology of selection of papers for this review.

susceptibility [35] or endocrine/metabolic parameters [16], others report the other way around [17, 34, 36]. Mahmoudi et al. highlight that BsmI “Bb” genotype appeared to be a marker of decreased PCOS risk [34]. Previously, the same author found that BsmI “bb” and TaqI “TT” genotypes had higher vit D serum levels compared to those with “BB/Bb” or “Tt/tt” [26]. The rest of the reports failed to find correlations with endocrine or metabolic parameters [16, 34, 37].

PCOS and TaqI polymorphism

TaqI polymorphism (rs 731236) is a restriction fragment length polymorphism located in exon 9, very close to the 3'-UTR region [24] that acts especially by modulating mRNA stability without altering the encoded amino acid, generating a synonymous mutation [23]. The majority of the studies confirmed the relationship between TaqI polymorphism and PCOS risk [17, 20, 23, 36, 38]. Xavier et al. reported that TaqI “CC” type was more frequent in the PCOS group [23], result that is consistent with another study [38]. Dasgupta et al. found that the mean values of FSH, LH and cholesterol were higher for “TC” genotype, while TaqI “CC” exhibited the highest mean value of testosterone. Moreover, women with PCOS with “CC” or “CT” genotype were found to be relatively more hirsute [27]. A small study found that the PCOS group had higher vit D and LH levels, while a significant positive correlation was seen be-

tween vit D and FSH in control group only. Interestingly, TaqI “CC” genotype was associated with vit D level in PCOS group, but not with LH level [21]. Another study carried on Caucasian women found significantly higher values of hirsutism score, cholesterol, triglycerides, fasting blood glucose and insulin, higher LH and androgens levels, alongside with lower sex hormone binding globulin, FSH and vit D values in PCOS group. Prevalence of TaqI “CC” genotype and “C” allele were significantly higher, while “C” allele was more frequent in obese women, showing the interaction between TaqI genotype and obesity. Moreover, women carrying “CC” and “TC” genotype had higher body mass index, fasting insulin, HOMA-IR (homeostasis model assessment-estimated insulin resistance index), androgen hormones, with lower levels of vit D and Quantitative insulin sensitivity check index (QUICKI) than the homozygous variants for T alleles. The haplotype TaqI C/Apal C was frequent in PCOS group and it was associated with lower levels of vit D and increased levels of androgens. El-Shal et al. also found that vit D levels were negatively correlated with body mass index, cholesterol and triglycerides in both groups, but in PCOS women the levels were decreased when compared with healthy controls. As a particularity of the study, vit D levels were correlated negatively with hirsutism score and TaqI polymorphism was an independent risk factor for PCOS [20].

► **Table 1** Summary data on association between VDR gene polymorphisms and PCOS metabolic/endocrine abnormalities.

Publication	Ethnicity	Case selection	Number of participants	Studied SNP	Conclusion
Mahmoudi et al. (2009) [26]	Western Asian	NIH criteria	PCOS:162 Control: 162	FokI Apal BsmI TaqI	<ul style="list-style-type: none"> FokI “FF”: higher insulin levels; increased risk for IR BsmI “bb” and TaqI “TT”: higher 25(OH)D levels
Wehr et al. (2011) [16]	Caucasian	Rotterdam criteria	PCOS: 545 Control: 145	FokI Apal BsmI Cdx2 TaqI	<ul style="list-style-type: none"> Apal “AA”: lower testosterone levels Cdx2 “AA”: lower fasting insulin and HOMA-IR; higher QUICKI
El-Shal et al. (2013) [20]	Caucasian	Rotterdam criteria	PCOS:150 Control: 150	Apal TaqI	<ul style="list-style-type: none"> TaqI “C” allele: more frequent in obese PCOS women TaqI “CC” and “TC”: higher BMI, AFC, fasting insulin, HOMA-IR, testosterone, DHEA-S, androstenedione; lower 25(OH)D levels, QUICKI “TaqI C/ Apal C”: lower 25(OH)D levels; higher testosterone, DHEA-S, androstenedione
Zadeh-Vakili et al. (2013) [22]	Western Asian	NIH criteria	PCOS: 260 Control: 221	Tru9I	<ul style="list-style-type: none"> “GA + AA”: severe hirsutism and oligo-amenorrhea
Dipanshu et al. (2015) [31]	Southern Asian	Rotterdam criteria	PCOS: 125 Control: 82	FokI Apal	<ul style="list-style-type: none"> Apal “CC”: lower estradiol and androstenedione levels
Jedrzejuk et al. (2015) [29]	Caucasian	Rotterdam criteria	PCOS: 92 Control: 85	FokI Apal BsmI TaqI	<ul style="list-style-type: none"> No difference between gene variants and metabolic parameters in PCOS group
Dasgupta et al. (2015) [27]	Southern Asian	Rotterdam criteria	PCOS: 250 Control: 250	FokI Apal Cdx2 TaqI	<ul style="list-style-type: none"> FokI “TT”: increased risk for infertility, acne, alopecia, elevated cholesterol levels Apal “AA”: higher testosterone levels TaqI “TC”: higher levels of FSH, LH, cholesterol TaqI “CC”: higher testosterone Cdx2 “GG”: traits like acne, hirsutism, AN, increased cholesterol levels Cdx2 “AA”: higher testosterone levels; risk for infertility
Mahmoudi et al. (2015) [34]	Western Asian	NIH criteria	PCOS: 35 Control: 35	FokI Apal BsmI TaqI Tru9I	<ul style="list-style-type: none"> No relationship between gene variants and insulin metabolism in PCOS group
Kadhim et al. (2017) [33]	Western Asian	Rotterdam criteria	PCOS: 50 Control: 50	FokI Apal TaqI	<ul style="list-style-type: none"> FokI “CC”, Apal “CC”, “CA”, TaqI “CC”: higher prolactin levels
Al Thomali et al. (2018) [21]	Western Asian	Rotterdam criteria	PCOS: 16 Control: 17	FokI Apal TaqI + others	<ul style="list-style-type: none"> TaqI “CC”: associated with vitamin D levels
Humadi et al. (2018) [28]	Western Asian	Rotterdam criteria	PCOS:100 Control: 100	FokI Apal	<ul style="list-style-type: none"> FokI “FF”, Apal “AA”: lower levels of vitamin D and androstenedione
Santos et al. (2018) [32]	Caucasian	Rotterdam criteria	PCOS: 191 Control: 100	Apal BsmI TaqI	<ul style="list-style-type: none"> Apal “CC”: higher risk for Mets; higher systolic blood pressure, total cholesterol, LDL-c
Hamdi et al. (2018) [39]	Western Asian	Rotterdam criteria	PCOS: 45 Control: 43	Cdx2	<ul style="list-style-type: none"> Cdx2 “AA”: lower fasting serum glucose, insulin and HOMA-IR Cdx2 “GG”: higher LH, LH/FSH ratio; lower 25(OH)D levels
Song et al. (2019) [18]	Asian	NIH criteria	PCOS: 432 Control: 927	FokI Apal BsmI Cdx2	<ul style="list-style-type: none"> FokI “AG”: increased levels of total testosterone Cdx2 “CC”: increased level of fasting insulin and HOMA- IR
Szafarowska et al. (2019)[30]	Caucasian	Rotterdam criteria	PCOS: 75 Control: 23	FokI Apal BsmI Cdx2	<ul style="list-style-type: none"> FokI “CT”, “TT” and Apal “CA”, “CC”: higher AMH levels Apal “AA”: higher 25(OH)D values
Ramezani et al. (2020) [37]	Western Asian	NIH criteria	PCOS: 38 Control: 40	BsmI	<ul style="list-style-type: none"> No association between BsmI genotypes and metabolic/ endocrine parameters

IR: Insulin resistance; HOMA-IR: Homeostasis model assessment-estimated insulin resistance; QUICKI,: Quantitative insulin sensitivity check index; BMI: Body mass index; AFC: Antral follicle count; DHEA-S: Dehydroepiandrosterone sulfate; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; AN: Acanthosis nigricans; Mets: Metabolic syndrome; LDL-c: Low density lipoprotein-cholesterol; AMH: Anti-Müllerian hormone.

All in all, studies suggest that higher values of androgen hormones are correlated with TaqI “CC” variant in both Caucasian and Asian population [20, 27], the same genotype being also associated with vit D levels [20, 21, 26].

PCOS and Cdx2 polymorphism

Cdx2 polymorphism (rs 11568820) is a guanine to adenine sequence, located in the 1 a promoter area of VDR gene, acting as a transcription factor [16, 24, 27]. Even though Cdx2 polymorphism was investigated only in 5 selected articles, it seemed that its variants are associated with IR and insulin sensitivity, yet the results are inconsistent. The findings of a Korean study suggest that Cdx2 “CC” genotype was associated with increased level of fasting insulin and HOMA-IR in PCOS women, but the association was not statistically significant after multiple linear regressions. However, “AA” genotype was correlated with higher fasting insulin in controls [18] this result being inconsistent with the observations of Wehr et al. who showed that Cdx2 “AA” presented lower fasting insulin and HOMA-IR, with significantly higher QUICKI in PCOS group. The Austrian group found no association of Cdx2 polymorphism with vit D levels or endocrine parameters [16]. Hamdi et al. showed that Cdx2 “AA” genotype presented lower fasting serum glucose and insulin, but also “GG” genotype was predisposed to higher LH levels, with lower vit D values [39].

On the other hand, Dasgupta et al. concluded that Cdx2 “GA” genotype and “A” allele had a significantly higher frequency in cases compared to controls and seemed to confer protection against developing PCOS [27]. In contrast, Szafarowska et al. showed that “GG” genotype had higher frequency in PCOS population [30]. In addition, in Indian population “GG” genotype showed greater frequency for traits like acne, hirsutism, acanthosis and elevated cholesterol, while “GA” variant had relatively higher mean values for testosterone, being at risk for alopecia. Moreover, “AA” genotype was associated with elevated testosterone and “GA” and “AA” genotypes were at higher risk for infertility [27].

PCOS and Tru9I polymorphism

Tru9I polymorphism (rs 757343) located in intron 8, is an adenine to guanine polymorphism of VDR gene, less investigated than the aforementioned variants. A study from Iran showed that the combined genotype “GA + AA” was significantly associated with increased risk of severity of PCOS phenotype, including severe hirsutism and oligo-amenorrhea. Additionally, “A” allele was associated with disease severity and HOMA-IR had higher values in severe phenotype compared to the mild one, suggesting a possible impact of Tru9I on PCOS pathology [22].

Discussion

PCOS is a complex multigenic disease, where various genes interact with each other and with environmental factors, influencing the development and the manifestations of the syndrome. Vitamin D is involved in a wide variety of biological processes and it mediates its actions through VDR. VDR is distributed across many tissues, including pancreatic beta cells, skin, parathyroid, pituitary gland or reproductive tissue, taking part in regulation of several endocrine, metabolic or reproductive functions [40].

Vitamin D deficiency is considered to take part in the pathogenesis of insulin resistance related diseases, including obesity and diabetes [41] but the interdependency between PCOS and vitamin D status is still questionable. When analyzing vitamin D impact in lean versus obese PCOS women, the results mainly show that lower serum concentrations are associated with obesity and IR but not with PCOS per se [42]. Moreover, when studying the effects of vitamin D supplements on androgen levels and hirsutism in overweight women with PCOS, recent data suggest that testosterone levels and hirsutism score decreased, while sex hormone binding globulin increased. Furthermore, improvement in the regularity of menstrual cycles was observed, highlighting the beneficial effects of vitamin D when PCOS is correlated with increased body mass index [43].

An aspect to keep in mind is the phenotypic classification of PCOS. The classic phenotypes A and B are associated with more severe features such as increased insulin levels and higher rates of insulin resistance, more pronounced menstrual dysfunction, higher risk for metabolic syndrome and obesity. Phenotype C (the “ovulatory PCOS”) usually has intermediate levels of androgen hormones, insulin or prevalence of metabolic syndrome, whereas phenotype D (the “non-hyperandrogenic PCOS”) is considered to have the mildest endocrine and metabolic dysfunction [2]. Between the articles selected for this paper, only one novel study investigated VDR polymorphisms in phenotype A, concluding that the homogeneous classic phenotype is not associated with vitamin D deficiency and VDR gene polymorphism in Caucasian population [29].

Conclusion

This review summarizes the main findings concerning VDR polymorphisms of vit D receptor and metabolic and endocrine abnormalities in PCOS. The review concluded that VDR gene can be a good candidate for PCOS and the polymorphisms might have an impact on the metabolic and endocrine disturbances in various ethnic populations. Our findings indicated that Apal polymorphism was associated with hyperandrogenism in both Asian and Caucasian population. Moreover, FokI variant was correlated with metabolic and endocrine parameters especially in Asian population, while a relation between Cdx2 genotypes and insulin sensitivity was observed in both ethnicities.

The limits of the studies are related to several aspects. First, only a few studies are available in the literature regarding VDR gene polymorphisms and metabolic or endocrine manifestations in PCOS and all the mentioned studies for this review were conducted using restriction fragment length polymorphism method (RFLP). Second, there are many differences in terms of diagnostic criteria, ethnicity, and the lack of dividing patients in specific phenotypes. The variation in the environmental factors or the small sample size of the studied groups determined also inconsistent results. Therefore, further functional studies on various homogeneous populations with larger sample size are needed to confirm the current findings, in order to allow prevention or treatment of PCOS comorbidities.

Acknowledgements

The authors wish to acknowledge support from Iuliu Hațieganu University of Medicine and Pharmacy (Doctoral research project no. 2461/85/17.01.2020 Cluj-Napoca, Romania).

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- [1] Azziz R, Carmina E, Chen Z et al. Polycystic ovary syndrome. *Nat Rev Dis Primers* 2016; 2: 1–18
- [2] Lizneva D, Suturina L, Walker W et al. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil Steril* 2016; 106: 6–15
- [3] Reis GVOP, Gontijo NA, Rodrigues KF et al. Vitamin D receptor polymorphisms and the polycystic ovary syndrome: A systematic review. *J Obstet Gynaecol Res* 2017; 43: 436–446
- [4] Bozdogan G, Mumusoglu S, Zengin D et al. The prevalence and phenotypic features of polycystic ovary syndrome: A systematic review and meta-analysis. *Hum Reprod* 2016; 31: 2841–2855
- [5] Andrade VH, Mata AM, Borges RS et al. Current aspects of polycystic ovary syndrome: a literature review. *Rev Assoc Med Bras* 2016; 62: 867–871
- [6] Bednarska S, Siejka A. The pathogenesis and treatment of polycystic ovary syndrome: what's new? *Adv Clin Exp Med* 2017; 26: 359–367
- [7] De Leo V, Musacchio MC, Cappelli V et al. Genetic, hormonal and metabolic aspects of PCOS: an update. *Reprod Biol Endocrinol* 2016; 14: 38
- [8] Carvalho LML, Dos Reis FM, Candido AL et al. Polycystic ovary syndrome as a systemic disease with multiple molecular pathways: A narrative review. *Endocr Regul* 2018; 52: 208–221
- [9] Ozdemir S, Ozdemir M, Gökemli H et al. Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism. *Acta Obstet Gynecol Scand* 2010; 89: 199–204
- [10] Hong JS, Kwon HH, Park SY et al. Cutaneous manifestations of the subtypes of polycystic ovary syndrome in Korean patients. *J Eur Acad Dermatol Venereol* 2015; 29: 42–47
- [11] Feng JG, Guo Y, Ma LA et al. Prevalence of dermatologic manifestations and metabolic biomarkers in women with polycystic ovary syndrome in north China. *J Cosmet Dermatol* 2018; 17: 511–517
- [12] Neven ACH, Laven J, Teede HJ et al. Summary on polycystic ovary syndrome: diagnostic criteria, prevalence, clinical manifestations, and management according to the latest international guidelines. *Semin Reprod Med* 2018; 36: 5–12
- [13] Nyagolova PV, Mitkov MD, Orbetsova MM. Role of vitamin D and adipose tissue hormones in women with reproductive disorders. *Folia Med (Plovdiv)* 2015; 57: 5–10
- [14] Niu YM, Wang YD, Jiang GB et al. Association between vitamin D receptor gene polymorphisms and polycystic ovary syndrome risk: A meta-analysis. *Front Physiol* 2019; 9: 1902
- [15] Liang F, Ren N, Zhang H et al. A meta-analysis of the relationship between vitamin D receptor gene Apal polymorphisms and polycystic ovary syndrome. *Adv Clin Exp Med* 2019; 28: 255–262
- [16] Wehr E, Trummer O, Giuliani A et al. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. *Eur J Endocrinol* 2011; 164: 741–749
- [17] Siddamallla S, Reddy TV, Govatati S et al. Vitamin D receptor gene polymorphisms and risk of polycystic ovary syndrome in South Indian women. *Gynecol Endocrinol* 2018; 34: 161–165
- [18] Song DK, Lee H, Hong YS et al. Vitamin D receptor and binding protein polymorphisms in women with polycystic ovary syndrome: A case control study. *BMC Endocr Disord* 2019; 19: 145
- [19] Shi XY, Huang AP, Xie DW et al. Association of vitamin D receptor gene variants with polycystic ovary syndrome: A meta-analysis. *BMC Med Genet* 2019; 20: 32
- [20] El-Shal AS, Shalaby SM, Aly NM et al. Genetic variation in the vitamin D receptor gene and vitamin D serum levels in Egyptian women with polycystic ovary syndrome. *Mol Biol Rep* 2013; 40: 6063–6073
- [21] Al Thomali A, Daghestani MH, Daghestani MH et al. Polymorphic variations in VDR gene in Saudi women with and without polycystic ovary syndrome (PCOS) and significant influence of seven polymorphic sites on anthropometric and hormonal parameters. *J Med Biochem* 2018; 37: 415–425
- [22] Zadeh-Vakili A, Ramezani TF, Daneshpour MS et al. Genetic polymorphism of vitamin D receptor gene affects the phenotype of PCOS. *Gene* 2013; 515: 193–196
- [23] Xavier LB, Gontijo NA, Rodrigues KF et al. Polymorphisms in vitamin D receptor gene, but not vitamin D levels, are associated with polycystic ovary syndrome in Brazilian women. *Gynecol Endocrinol* 2019; 35: 146–149
- [24] Vasilovici AF, Grigore LE, Ungureanu L et al. Vitamin D receptor polymorphisms and melanoma. *Oncol Lett* 2019; 17: 4162–4169
- [25] Uitterlinden AG, Fang Y, Van Meurs JB et al. Genetics and biology of vitamin D receptor polymorphisms. *Gene* 2004; 338: 143–156
- [26] Mahmoudi T. Genetic variation in the vitamin D receptor and polycystic ovary syndrome risk. *Fertil Steril* 2009; 92: 1381–1383
- [27] Dasgupta S, Dutta J, Annamaneni S et al. Association of vitamin D receptor gene polymorphisms with polycystic ovary syndrome among Indian women. *Indian J Med Res* 2015; 142: 276–285
- [28] Humadi EH, Showman HA, Al-azzawie RMHF. Association of vitamin-D receptor gene polymorphisms (FokI and Apal) and vitamin D serum levels in a sample of Iraqi women with polycystic ovary syndrome. *Indian J Public Health Res Dev* 2018; 9: 867–874
- [29] Jedrzejuk D, Łączmański Ł, Milewicz A et al. Classic PCOS phenotype is not associated with deficiency of endogenous vitamin D and VDR gene polymorphisms rs731236 (TaqI), rs7975232 (ApaI), rs1544410 (BsmI), rs10735810 (FokI): a case-control study of lower Silesian women. *Gynecol Endocrinol* 2015; 31: 976–979
- [30] Szafarowska M, Dziech E, Kaleta B et al. Anti-Müllerian hormone level is associated with vitamin D receptor polymorphisms in women with polycystic ovary syndrome. *J Assist Reprod Genet* 2019; 36: 1281–1289
- [31] Dipanshu S, Chakravorty R. Genetic polymorphism in the vitamin D receptor gene and 25-hydroxyvitamin D serum levels in East Indian women with polycystic ovary syndrome. *J Mol Biomark Diagn* 2015; 6: 247
- [32] Santos BR, Lecke SB, Spritzer PM. Apa-I polymorphism in VDR gene is related to metabolic syndrome in polycystic ovary syndrome: A cross-sectional study. *Reprod Biol Endocrinol* 2018; 16: 38
- [33] Kadhim SJ, Abdul-hassan IA. Correlation between vitamin D receptor gene polymorphisms and levels of some hormones in Iraqi infertile women with polycystic ovary syndrome. *Iraqi J Biotechnol* 2017; 16: 104–113
- [34] Mahmoudi T, Majidzadeh-AK, Farahani H et al. Association of vitamin D receptor gene variants with polycystic ovary syndrome: A case control study. *Int J Reprod Biomed* 2015; 13: 793–800

- [35] Bagheri M, Rad IA, Jazani NH et al. Lack of association of vitamin D receptor FokI (rs10735810) (C/T) and BsmI (rs1544410) (A/G) genetic variations with polycystic ovary syndrome risk: a case-control study from Iranian Azeri Turkish women. *Maedica (Bucur)* 2012; 7: 303–308
- [36] Ranjzad F, Mahban A, Shemirani AI 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: 225–232
- [37] Ramezani N, Ostadsharif M, Nayeri H. Association of BsmI variant of vitamin D receptor gene with polycystic ovary syndrome: A case-control study. *Int J Reprod BioMed* 2020; 18: 877–884
- [38] Bagheri M, Abdi RI, Hosseini JN et al. Vitamin D receptor TaqI gene variant in exon 9 and polycystic ovary syndrome risk. *Int J Fertil Steril* 2013; 7: 116–121
- [39] Hamdi RA, Abdul-Qahar ZH, Ahmed SJ et al. Assessment of vitamin D receptor gene polymorphism in Iraqi women with polycystic ovary syndrome. *J Clin Diagnostic Res* 2018; 12: 27–30
- [40] Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor? *Arch Biochem Biophys* 2012; 523: 123–133
- [41] Szymczak-Pajor I, Śliwińska A. Analysis of association between vitamin D deficiency and insulin resistance. *Nutrients* 2019; 11: 794
- [42] Hahn S, Haselhorst U, Tan S et al. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. *Exp Clin Endocrinol Diabetes* 2006; 114: 577–583
- [43] Al-Bayyari N, Al-Domi H, Zayed F et al. Androgens and hirsutism score of overweight women with polycystic ovary syndrome improved after vitamin D treatment: A randomized placebo controlled clinical trial. *Clin Nutr* 2021; 40: 870–878