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Immunohistochemical expression of vitamin D receptor and Wnt signaling pathway molecules in psoriasis

Amina Ismaeel[1] ✉, Fatima Alhashimi[2], Zainab Almossali[3], Safa Alshaikh[4], Samvel Selvam[1], Duha Janahi[4]

[1]Department of Pathology, College of Medicine and Medical Sciences, Arabian Gulf University, Manama, Bahrain. [2]Department of Pathology, Blood Bank and Laboratory Medicine, King Hamad University Hospital, Busaiteen, Bahrain. [3]Department of Dermatology, Salmaniya Medical Complex, Manama, Bahrain. [4]Department of Pathology, Salmaniya Medical Complex, Manama, Bahrain.

Abstract

Introduction: Psoriasis is a prevalent, complex, immune-mediated illness. There is some evidence in the literature supporting the involvement of the Wnt signaling pathway in psoriasis. No previous studies have focused on the association between the Wnt signaling pathway and vitamin D receptor (VDR) expression in psoriasis. This study investigates the expression of VDR and mediators of the canonical (β-catenin) and non-canonical (Wnt5a) Wnt signaling pathway in psoriatic lesional skin biopsy specimens compared to controls.

Methods: A cross-sectional study conducted on skin punch biopsy specimens from 42 psoriasis patients were stained with VDR, β-catenin, and Wnt5a and compared with 42 control biopsies. Patients' demographics, clinical data, and serum vitamin D levels were recorded.

Results: VDR showed nuclear localization with significant downregulation in the psoriasis specimens compared to controls. β-catenin (membranous) and Wnt5a (cytoplasmic) showed significant upregulation in the psoriasis specimens. When the expressions of VDR, β-catenin, and Wnt5a were compared based on disease severity, no differences were found between mild, moderate, and severe subgroups of the disease. Late-onset psoriasis patients had lower VDR and Wnt5a histoscores compared to the early-onset group. A trend toward a positive correlation was observed between the histoscores of VDR and Wnt5a.

Conclusions: Our findings confirm the significance of VDR signaling in the pathophysiology of psoriasis and strengthen the relationship between this disease and the Wnt signaling pathway. There was evidence that there is an association between VDR status and Wnt5a expression.

Keywords: psoriasis, Wnt signaling pathway, beta catenin, vitamin D receptor, immunohistochemistry

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Introduction

Immunological, genetic, and environment-related factors all contribute to the development and progression of psoriasis, making it a chronic, immune-mediated, multifactorial illness (1). The global prevalence of this skin condition is between 2% and 4% (2). Its psychological impact and multi-system involvement, such as rheumatological, cardiovascular, and metabolic consequences, have a substantial negative impact on the quality of life of psoriasis patients and on healthcare resources (1, 3–5). Pathogenic stimulation of dendritic cells and T-cells causes keratinocyte hyperproliferation and defective differentiation, which is the hallmark of psoriasis. Cytokines such as type I interferons, interleukin-23, interleukin-12, interferon-γ, interleukin-17, tumor necrosis factor-α, and interleukin-22 play a role in mediating this process (6, 7).

Wnt signaling is a complex cellular signaling pathway that provides cell-to-cell coordination and communication because it facilitates cell regeneration, growth, division, migration, and polarity (8–10). This pathway contains a family of 19 secreted glycol proteins known as Wnts, acting through frizzled receptors and low-density lipoprotein receptor–related proteins. It is subdivided into canonical and non-canonical pathways, which are dependent on or independent of β-catenin, respectively (8). Activation or inhibition of this pathway, mediated by genetic and epigenetic activities, is linked to the development of malignancies in the pancreas, lungs, and breast. In addition, this pathway plays a role in type 2 diabetes, neuronal disorders, rheumatoid arthritis, systemic sclerosis, inflammatory bowel disease, and cardiovascular diseases (8, 11–13).

The Wnt signaling pathway may play a role in the development of psoriasis, particularly the non-canonical signaling cascade, according to some published evidence (14–20). The *Wnt5a* gene is one of the important genes in psoriasis, according to a gene pathogenicity analysis utilizing samples from healthy and psoriatic skin (14). Several studies found that Wnt5a and its cognate receptors were upregulated in psoriatic skin compared to uninvolved or control epidermis with downregulation of the Wnt antagonist, the WIF-1 protein (15–18). Some studies have shown an upregulation of β-catenin staining in psoriasis, whereas others have shown reduced expression of β-catenin in biopsy specimens from psoriasis lesions, leading to conflicting conclusions about the Wnt canonical pathway involvement in psoriasis (15, 19, 20). The exact mechanism by which the Wnt pathway drives keratinocyte proliferation in psoriasis is not well established.

In psoriasis, studies have shown a reduction of vitamin D receptor (VDR) in psoriatic skin compared to normal skin with a significant inverse link between VDR expression and the severity and the duration of the disease (21, 22). There has been no previous research on the relationship between the Wnt signaling pathway and VDR expression in psoriasis, and this pathway should be investigated further. Studying this pathway in psoriasis is crucial for identifying new pieces in the puzzle of the complex pathogenesis

✉ Corresponding author: aminaaya@agu.edu.bh

of the disease, which might have prognostic and potentially therapeutic implications.

This study investigates the level of expression of VDR, mediators of the canonical Wnt signaling pathway (β-catenin), and mediators of the noncanonical Wnt signaling pathway (Wnt5a) in psoriatic lesional skin biopsy specimens compared to controls. The aims are to identify the relationship between the expression of VDR and Wnt pathway mediators with disease onset and severity, to identify the correlation between the expression of VDR and Wnt pathway mediators in psoriatic lesional-skin biopsy specimens, and to determine whether there is a connection between the expression of VDR in the epidermis and vitamin D levels in the serum in psoriasis patients.

Materials and methods

Study design

This is a cross-sectional study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (23). The study was conducted on 42 clinically and histologically confirmed psoriasis vulgaris patients and 42 specimens from control non-psoriatic subjects. Patients' demographics and clinical data were recorded, including age at diagnosis of psoriasis, severity of the disease, and current treatment. In addition, the patients' serum vitamin D levels at the time of the biopsy were recorded. The disease severity was categorized based on the body surface area affected into mild (< 3%), moderate (3–10%), and severe psoriasis (> 10%). Study subjects that were on systemic anti-psoriatic treatment in the 2 weeks preceding the biopsy were excluded. Formalin-fixed, paraffin-embedded skin punch biopsy specimens were obtained from the Pathology Department at Salmaniya Medical Complex, Bahrain, between January 2016 and December 2020. The study received approval from the Research and Ethics Committee, College of Medicine and Medical Sciences, Arabian Gulf University, Bahrain (E014-PI-11/20) and the Secondary Health Care Research Subcommittee, Ministry of Health, Bahrain (72090521).

Immunohistochemical staining

Paraffin blocks were cut into sections 4 µm thick, and the sections were stained with rabbit polyclonal anti-Wnt5a antibody (Abcam, Cambridge, UK, ab235966) diluted 1:200, rabbit polyclonal anti-vitamin D receptor antibody (Abcam, Cambridge, UK, ab134826) diluted 1:200, and mouse monoclonal anti-β-catenin antibody (Cell Marque-Sigma-Aldrich, California, USA, 224M, ready-to-use). Immunohistochemical staining was conducted using the VENTANA Benchmark System (Roche, Basel, Switzerland). Then, the histoscore was determined for each immunostain by two independent investigators, in all specimens based on the intensity and percentage of positive cells at 200× magnification. The histoscore was calculated using the following formula: histoscore = (1 × % weakly stained cells) + (2 × % moderately stained cells) + (3 × % strongly stained cells). The possible range of this score in each case is 0–300.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 28.0.1.0. The Mann–Whitney *U*-test was used to compare the psoriasis and control groups. Variables within the same group were compared using an independent-samples Kruskal–Wallis test. To assess significant correlation, the Kendall rank correlation coefficient was applied. A *p*-value lower than 0.05 was considered statistically significant.

Results

Characteristics of the participants

Among the 42 psoriasis specimens analyzed, 28 were from females and 14 were from males (M:F ratio 1:2), with a mean age of 36.7 ± 18.2 years. Most of the participants were Bahrainis (78.6%), and the remaining were non-Bahrainis (21.4%). In terms of age at diagnosis, 73.8% of participants were diagnosed before the age of 40 (early-onset psoriasis), whereas 26.2% were diagnosed at or after the age of 40 (late-onset psoriasis). Regarding disease severity, 28.6% had mild psoriasis, 45.2% had moderate psoriasis, and 26.2% had a severe form of the disease. The majority of the patients were receiving topical treatments (85.7%), and only 14.2% were receiving systemic treatments, divided equally between systemic non-biological treatments and systemic biological treatments. The skin biopsies were taken from psoriatic lesions present on various body regions, including the face, scalp, abdomen, back, upper limb, lower limb, axilla, and groin (Table 1). Forty-two specimens from control skin of non-psoriatic subjects were included in the control group.

Immunohistochemical analysis of VDR, β-catenin, and Wnt5a in psoriasis compared to controls

The immunohistochemical analysis of VDR, β-catenin, and Wnt5a in psoriasis lesional skin was compared to the non-psoriasis biopsy

Table 1 | **Characteristics of psoriasis patients (*N* = 42).**

Variable	Cases, *n* (%)
Age	
Mean ± *SD*	36.7 ± 18.2
Median	38.5
Sex	
Male	14 (33.3)
Female	28 (66.7)
Male:female ratio	1:2
Nationality	
Bahraini	33 (78.6)
Non-Bahraini	9 (21.4)
Psoriasis onset	
Early onset (< 40 years)	31 (73.8)
Late onset (≥ 40 years)	11 (26.2)
Psoriasis severity	
Mild	12 (28.6)
Moderate	19 (45.2)
Severe	11 (26.2)
Current treatment	
Topical treatment	36 (85.7)
Systemic non-biological treatment	3 (7.1)
Systemic biological treatment	3 (7.1)
Biopsy site	
Scalp/face	2 (4.8)
Abdomen	2 (4.8)
Back	6 (14.3)
Upper limb	4 (9.5)
Lower limb	15 (35.7)
Axilla	3 (7.1)
Groin	1 (2.4)
Not specified	9 (21.4)

SD = standard deviation.

specimens. VDR has a nuclear localization, and all epidermal layers stained positive in both groups (Fig. 1A and 1B). A significant reduction was observed in the proportion of positive cells ($p < 0.001$) and the histoscore ($p < 0.001$) in psoriasis compared to controls (Table 2).

All psoriatic and non-psoriatic skin biopsy specimens revealed β-catenin membranous localization, and all epidermal layers stained positive (Fig. 1C and 1D). All of the cells were positive for β-catenin in both groups; however, when the histoscore was compared, there was a significant increment in the β-catenin histoscore in psoriatic epidermis compared to controls ($p = 0.014$; Table 2).

Wnt5a expression was localized to the cytoplasm in both groups. In the psoriatic specimens, Wnt5a staining was positive in all epidermal layers with weak or negative staining in the basal layer; conversely, in the control skin, the staining was positive in the basal layer only (Fig. 1E and 1F). There was an increment in the percentage of positive cells ($p = 0.006$) and histoscore ($p = < 0.001$) in psoriatic skin compared to controls (Table 2).

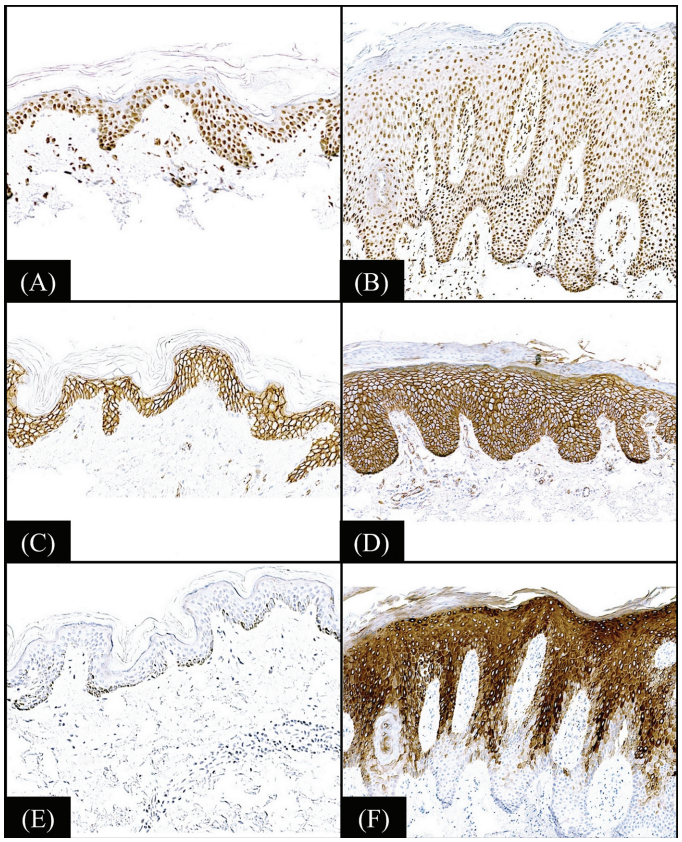

Figure 1 | Representative examples of immunohistochemical staining of control skin biopsies (left panel) and psoriatic lesional skin biopsies (right panel) stained with vitamin D receptor (VDR) (A, B), β-catenin (C, D), and Wnt5a (E, F), at 200× magnification.

Correlation between expression of VDR, β-catenin, and Wnt5a with severity of psoriasis and age of disease onset

When the expressions of VDR, β-catenin, and Wnt5a were compared based on disease severity, no statistically significant differences were found between mild, moderate, and severe subgroups of the disease ($p = 0.088$, 0.1, and 0.8, respectively). Regarding the age of disease onset, late-onset psoriasis patients had a lower VDR histoscore ($p = 0.026$) and Wnt5a histoscore ($p = 0.05$) compared to the early-onset group. Alternatively, no differences that are statistically significant were reached in β-catenin expression based on the age of disease onset ($p = 0.389$).

Correlation between expression levels of VDR and β-catenin or Wnt5a in psoriasis

When the relationship between VDR expression and Wnt5a expression in psoriasis specimens was tested, a trend toward a positive correlation was observed between the histoscores of the two immunostains. However, this correlation fell just short of being significant ($r = 0.197$, $p = 0.066$). No significant relationship was found between VDR and β-catenin expression. Wnt5a expression was also not significantly correlated with β-catenin levels.

Correlation between expression levels of VDR and serum vitamin D levels in psoriasis

The serum vitamin D levels of the psoriasis patients revealed that 13.6% of patients had sufficient serum vitamin D levels (> 50 nmol/l), 50% had vitamin D insufficiency (30–50 nmol/l), and 36.4% had vitamin D deficiency (< 30 nmol/l). No significant correlations were found between serum vitamin D levels and either disease severity or age at disease onset. Furthermore, vitamin D levels were not correlated with VDR expression.

Discussion

This study sought to ascertain the role of VDR and its relationship to Wnt signaling in psoriasis. Some evidence was found that there was an association between VDR status and Wnt5a expression in psoriasis. However, VDR expression does not appear to be associated with β-catenin expression.

β-catenin is a transcription factor of the Wnt pathway, and it contributes to keratinocyte development, differentiation, and proliferation (24). It also acts as an intracellular adhesion molecule that links E-cadherin to the actin cytoskeleton (24). This study found that β-catenin was overexpressed in psoriasis compared to controls, with membranous localization in both groups. In previously published reports, β-catenin was observed to be localized in

Table 2 | **Immunohistochemical expression of vitamin D receptor, β-catenin, and Wnt5a in control and psoriatic specimens.**

Variable	Mean ± *SD* (minimum–maximum) differences		*p*-value
	Controls	Psoriasis	
Vitamin D receptor			
% positive cells	97.0 ± 1.8 (93–100)	91.6 ± 5.2 (75–98)	‹ 0.001
Histoscore	261.3 ± 15.4 (223–286)	233.4 ± 31 (240–287)	‹ 0.001
β-catenin			
% positive cells	100.0 ± 0.0 (100–100)	100.0 ± 0 (100–100)	1
Histoscore	206.1 ± 24.2 (200–300)	223.8 ± 46.3 (120–300)	0.014
Wnt5a			
% positive cells	25.8 ± 19.6 (10–80)	65.0 ± 19.9 (30–90)	‹ 0.001
Histoscore	159.6 ± 65.4 (100–260)	208.9 ± 37.9 (150–280)	0.006

SD = standard deviation.

the cell membrane in the control biopsies, whereas it was nucleocytoplasmic in psoriasis lesional skin biopsies (20, 25). El-Wahed et al. reported that nuclear β-catenin was upregulated and membranous β-catenin was downregulated (25). Studies showed that there were epidermal layer-specific variations in the intensity of β-catenin expression between the psoriatic and non-psoriatic biopsy specimens. Downregulation of β-catenin was reported in the stratum basale, stratum spinosum, and stratum granulosum (24, 26). No correlation was found between the duration or severity of psoriasis and the level of β-catenin expression (24). Nevertheless, the development and spread of carcinomas in the colon, breast, liver, and other organs have all been associated with inappropriately active Wnt/β-catenin signaling (27).

Consistent with previously published studies, we showed that Wnt5a was upregulated in psoriasis compared to normal skin (17, 28, 29). When compared to control skin, keratinocytes from psoriasis patients had higher levels of Wnt5a mRNA in vitro (29). In contrast to our study, Wnt5a staining was shown to be correlated with psoriasis severity, but not with the duration of the disease (28). The molecular importance of Wnt5a in the immunopathogenesis of psoriasis, as well as the extent of this involvement, remain unknown (30, 31). It is proposed that Wnt5a-activated signaling pathways mediate the interactions of keratinocytes and cells of innate and adaptive immunity, including T-cells, dendritic cells, macrophages, and neutrophils and this might partially explain the role of this signaling cascade in psoriasis (31). Wnt5a promotes the production of pro-inflammatory cytokines, which have been implicated in the immunopathogenesis of psoriasis, including interferon-γ, interleukin-8, and interleukin-17A by keratinocytes (30). In addition, Wnt5a increases the sensitivity of keratinocytes to type I interferons (29). Wnt5a induces vascular alterations in psoriatic skin, promotes keratinocyte proliferation, and induces inflammatory immune responses via transglutaminase 2 (32). The involvement of Wnt signaling in cancer has been the subject of a significant amount of research in the published literature, where Wnt dysregulation was found to have a direct role in carcinogenesis and through crosstalk with immune cells to endorse immune tolerance and reduce the immune response to cancer (33, 34). Wnt signaling was hypothesized to play a role in cutaneous carcinogenesis by modulating the inflammatory tumor microenvironment and contributing to the development of malignant lesions from precancerous lesions, as well as promoting the epithelial-mesenchymal transition in squamous cell carcinoma (35).

VDR was downregulated in psoriatic specimens in comparison to the control skin in this study. This expression did not show any differences based on disease severity. However, when the age of onset of psoriasis was considered, late-onset psoriasis patients had a lower VDR histoscore compared to the early-onset group. According to a study by Chandra et al., the level of VDR expression in psoriasis is inversely correlated with the severity and duration of the disease; however, this pilot study had a small sample size (22). Serum vitamin D levels did not correlate significantly with VDR expression. Although vitamin D deficiency was common in our cohort, we observed no significant variations in serum vitamin D based on disease severity or age of disease onset. Vitamin D plays various roles in the skin through binding to VDR expressed by keratinocytes because it inhibits the proliferation of keratinocytes, promotes their differentiation, and induces their apoptosis. Furthermore, vitamin D aids in the formation of the skin barrier and modulates the humoral and cellular components of the immune systems (36). VDR's biological activities are maintained via various intracellular pathways and molecular targets (27). For instance, VDR expression in psoriasis has been associated with decreased tight junction integrity in the skin, raising the possibility that VDR contributes to the preservation of the skin barrier (21). By activating the transcription of target genes, vitamin D and β-catenin control the growth and differentiation of keratinocytes (37). Whereas β-catenin induces the proliferation of keratinocytes and suppresses their differentiation, vitamin D/VDR suppresses the activity of β-catenin, leading to the inhibition of keratinocyte proliferation (37).

Our findings further establish the importance of the Wnt signaling pathway in the development of psoriasis and reinforce the role of VDR signaling in the disease pathogenesis. We speculate that low vitamin D levels in psoriasis reduce the expression of VDR in the skin by enhancing β-catenin–independent Wnt signaling. The molecular mechanism of the crosstalk between the Wnt signaling molecules, VDR, and pro-inflammatory cytokines in psoriasis is elusive and requires more comprehensive studies. Therefore, in vivo studies focusing on interaction between vitamin D and VDR are necessary to fully comprehend the function and mechanism of Wnt5a-mediated immune response and inflammation in psoriasis. Targeting Wnt5a and VDR in the treatment of psoriasis requires a thorough understanding of this pathway. Our work is limited by its small sample size and the absence of information about the expression of the targeted molecules in non-lesional skin in psoriatic individuals.

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