Brief Report

Assessing the Association between Psoriasis and Cardiovascular Ischemia: An Investigation of Vascular Endothelial Growth Factor, Cutaneous Angiogenesis, and Arterial Stiffness

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Abstract

Background: Vascular endothelial growth factor (VEGF)-mediated angiogenesis's role in developing psoriasis and cardiovascular events has been established. However, the interplay between the two diseases regarding this cytokine remains an understudied area. **Aim and Objectives:** This case–control study aimed to investigate the relationship between VEGF-mediated angiogenesis and cardiovascular ischemia in patients with psoriasis. **Materials and Methods:** The study included 200 clinically diagnosed treatment-naïve cases of psoriasis and 200 controls. The VEGF level, cutaneous vascularity, and cardiovascular ischemia were measured between cases and controls. Cutaneous vascularity was assessed using non-invasive imaging technique such as laser doppler imaging (LDI) and measuring skin blood flow measurement (SBFM). Cardiovascular ischemia was evaluated using noninvasive techniques by measuring carotid intima–media thickness (CIMT) and pulse-wave velocity (PWV). The arterial vasa vasorum was evaluated using ultrasound imaging. **Results:** The study found a significant correlation between psoriasis severity and levels of VEGF ($P < 0.001$). Cases had significantly higher CIMT and PWV levels ($P = 0.001$ and <0.001, respectively). There was a significant positive correlation between the severity of psoriasis and the levels of cutaneous angiogenesis ($r = 0.7$, $P < 0.001$). **Conclusion:** According to this study, patients with psoriasis are at a higher risk of developing cardiovascular ischemia due to excessive angiogenesis associated with the condition. VEGF plays a key role in atheroma formation in psoriasis patients.

Keywords: *Atherosclerosis, psoriasis, VEGF*

Introduction

The prevalence of psoriasis in adults varies widely, with estimates ranging from 0.27% to 11.4%.[1-3] The factors that contribute to these differences include age, gender, location, ethnicity, genetics, and environment.[4] The disease is also associated with cardiovascular comorbidity and metabolic syndrome.

Angiogenesis, a relatively understudied component of psoriasis, is identified as a key player in developing both psoriasis and atherosclerosis. Vascular endothelial growth factor (VEGF), a well-established mediator of pathological angiogenesis, is upregulated in psoriasis. VEGF-mediated angiogenesis also plays a cardinal role in the pathogenesis of acquired cardiovascular diseases.[5,6] However, the interplay between the two diseases regarding this cytokine remains an understudied area. This study aimed to investigate the relationship between VEGF-mediated angiogenesis and cardiovascular ischemia in patients with psoriasis.

Aim and Objectives

The aim of this study was to determine whether cutaneous vascularity could be used as a predictor of disease prognosis and health outcomes in patients with psoriasis. The specific objectives of the study were as follows: comparison of VEGF levels, cutaneous vascularity, and cardiovascular ischemia measures between patients with psoriasis and healthy controls. We also studied the correlation between VEGF levels, cutaneous vascularity, and cardiovascular ischemia measures in patients with psoriasis.

Materials and Methods

Study design and participants

This was a case–control study conducted in the department of dermatology at our

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tertiary care hospital from March 2022 to December 2022. The study was approved by the ethical review committee, and written informed consent was obtained from all participants before enrollment.

The study included 200 treatment-naïve patients with psoriasis (including chronic plaque psoriasis, erythrodermic psoriasis, and pustular psoriasis) and 200 age- and sex-matched healthy controls. The patients were recruited from our dermatology outpatient and inpatient department, and the controls were recruited from the general population. The inclusion criteria for psoriasis patients were as follows: (1) age over 18 years; (2) diagnosis of psoriasis on clinical grounds by a senior dermatologist; (3) confirmed diagnosis of psoriasis by histopathological examination in clinically ambiguous cases; and (4) no prior treatment for psoriasis. Exclusion criteria were as follows: (1) age <18 years; (2) concurrent presence of any other inflammatory skin disease; (3) presence of any systemic illness or chronic disease; (4) pregnancy or lactation; and (5) presence of congenital or acquired immunodeficiency.

Data collection

After obtaining informed consent, patients' demographic data, medical history, and medication history were collected using a structured questionnaire. The severity of psoriasis was graded as mild and moderate-to-severe based on the Psoriasis Area and Severity Index (PASI) and joint involvement as follows: mild psoriasis: PASI <7 and/or oligoarticular joint involvement (≤4 peripheral joints); moderate-to-severe psoriasis: PASI ≥7 or >4 peripheral joints or ≥1 axial joint involvement.[7]

Cutaneous vascularity was assessed using noninvasive imaging with laser doppler imaging (LDI) and measuring skin blood flow measurement (SBFM). Cardiovascular ischemia was evaluated using noninvasive techniques by measuring carotid intima–media thickness (CIMT) and pulse-wave velocity (PWV). The arterial vasa vasorum was evaluated using ultrasound imaging.

Blood sample collection and analysis

Peripheral venous blood samples of 5 ml were collected from all participants and allowed to clot at room temperature for 30 minutes. The samples were then centrifuged at 2000 g for 10 min to separate the sera. Serum VEGF levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. All assays were performed in duplicate, and the mean value was used for statistical analysis.

Sample size calculation and statistical analysis

The sample size was determined based on the following assumptions: (1) alpha = 0.05, (2) power = 80%, (3) effect size = 0.5, and (4) two-sided test. The minimum required sample size was calculated to be 200 per group. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), while categorical variables were expressed as frequencies and percentages. Differences between groups were compared using the *t*-test for continuous variables and the Chi-square for categorical variables. A *P* value <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 2. To avoid patient selection bias, patients with psoriasis and controls were recruited from the same geographic area and matched for age and sex. The controls were selected from the general population belonging to the same geographical region as cases, to ensure that they were representative of the general population and not biased toward any particular group.

Results

The mean age of patients was 40.2 ± 10.2 years, and 60% were male. The mean PASI score was 12.3 ± 5.4. Of 200 patients, 84 (42%) had moderate-to-severe psoriasis (PASI >10). The mean VEGF level was significantly higher in psoriasis cases than in healthy controls (375.3 ± 31.2 pg/mL vs. 198.2 ± 20.5 pg/mL, $P < 0.001$). The mean VEGF level was found to be significantly higher in patients with moderate-to-severe psoriasis than in those with mild psoriasis (450.3 ± 45.2 pg/mL vs. 320.6 ± 30.5 pg/mL, $P < 0.05$).

The results found a significant positive correlation between the severity of psoriasis and the levels of VEGF (r = 0.6, $P < 0.001$) and cutaneous angiogenesis (r = 0.7, $P < 0.001$).

The mean CIMT of cases was 0.9 ± 0.2 mm, while that of controls was 0.6 ± 0.1 mm (*P* value <0.001) [Table 1]. The mean PWV of cases was 10.3 ± 1.3 m/s, while that of controls was 7.8 ± 1.0 m/s (*P* value <0.001) [Table 2].

Similarly, the study showed that cutaneous angiogenesis was significantly higher in patients with moderate-to-severe

Table 1: Results of carotid intima–media thickness (CIMT) measurements in patients with psoriasis and control subjects

Group	Mean CIMT (mm) ±SD	*P**
Psoriasis	0.9±0.2	<0.001
Control	0.6±0.1	

*Chi-square test

Table 2: Results of pulse-wave velocity (PWV) measurements in patients with psoriasis and control subjects

Groups	Mean PWV (m/s) ±SD	*P**
Psoriasis	10.3±1.3	<0.001
Control	7.8±1.0	

*Chi-square test

psoriasis than in those with mild psoriasis ($P < 0.001$). The arterial vasa vasorum evaluation results also showed that the vasa vasorum density was significantly higher in patients with severe psoriasis than in those with mild psoriasis ($P < 0.001$). There was also a significantly positive correlation between PASI and CIMT ($P = 0.02$) and PWV ($P = 0.04$) [Figures 1 and 2]. The results also suggested that patients with psoriasis have significantly higher CIMT and PWV values than control subjects [Tables 1 and 2]. This implies that patients with psoriasis are at a higher risk of developing cardiovascular ischemia. The *P* values less than 0.001 indicate a statistically significant difference between the two groups, supporting the hypothesis that excessive angiogenesis associated with psoriasis is a cause of cardiovascular ischemia.

Confounding factors such as diabetes, hypertension, hyperlipidemia, and obesity are known psoriasis associations and could potentially impact the results. In fact, psoriasis itself is now considered part of the metabolic syndrome. Given the intrinsic link between psoriasis and these other factors, it was unlikely to find psoriasis patients who did not have any of these comorbidities. That is precisely why we recruited healthy controls for comparison. Furthermore, an internal subgroup analysis was conducted to account for the influence of these confounding factors on the results.

Within the group of cases, psoriasis patients with diabetes ($P = 0.04$), hypertension ($P = 0.0001$), and obesity ($P = 0.01$) had significantly high CIMT than those psoriasis patients who did not have these comorbidities. Similarly, psoriasis patients with diabetes ($P = 0.03$), hypertension ($P = 0.001$), and obesity ($P = 0.02$) also had significantly higher PWV than those psoriasis patients who did not have these comorbidities. However, there was no difference in the values of both CIMT and PWV between psoriasis patients with and without hyperlipidemia ($P = 0.09$ and 0.11, respectively).

Discussion

Atherosclerosis and psoriasis are two distinct pathological conditions. However, recent evidence has indicated a link between the two diseases.[5,6] People with psoriasis are at an increased risk of developing atherosclerosis, which can lead to several cardiovascular events, such as myocardial infarction.[8]

This link between psoriasis and atherosclerosis can be attributed to several factors. First, psoriasis is associated with a chronic state of systemic inflammation, which can promote the progression of atherosclerosis.[9,10] Second, the same cytokines and signaling pathways that drive inflammation in psoriasis, such as tumor necrosis factor (TNF)-α and Notch signaling, have also been linked to angiogenesis and the progression of atherosclerosis. In addition, high levels of VEGF, an important factor in psoriasis, have also been found in lesions of atherosclerosis and are linked to increased inflammation and plaque instability.[11,12] The poor platelet-derived growth factor (PDGF) B/PDGF receptor (PDGFR) signaling seen in psoriasis may also cause a reduction in the pericyte covering of the blood arteries, which can result in plaque rupture and subsequent cardiovascular events.[5]

In our study, the levels of the cytokine VEGF were found to be significantly higher in patients with psoriasis than in healthy controls and were even higher in those with moderate-to-severe psoriasis. Additionally, a strong positive correlation was observed between the severity of psoriasis and the levels of VEGF and cutaneous angiogenesis. The results showed that patients with psoriasis have a higher risk of developing cardiovascular ischemia due to the excessive angiogenesis associated with the disease. These findings were statistically significant, with *P* values less than 0.001, supporting the hypothesis that excessive angiogenesis is a cause of cardiovascular ischemia in psoriasis patients.

Our findings also suggest that psoriasis patients with comorbidities such as diabetes, hypertension, and obesity are at a higher risk of developing cardiovascular disease, as indicated by higher CIMT and PWV values. Interestingly, there was no significant difference in CIMT and PWV values between psoriasis patients with and without hyperlipidemia. These results highlight the importance of considering the impact of confounding factors when assessing cardiovascular risk in psoriasis patients. The

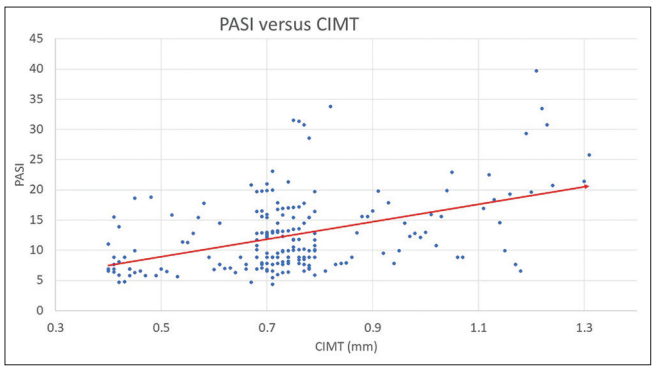

Figure 1: Correlation between PASI and CIMT

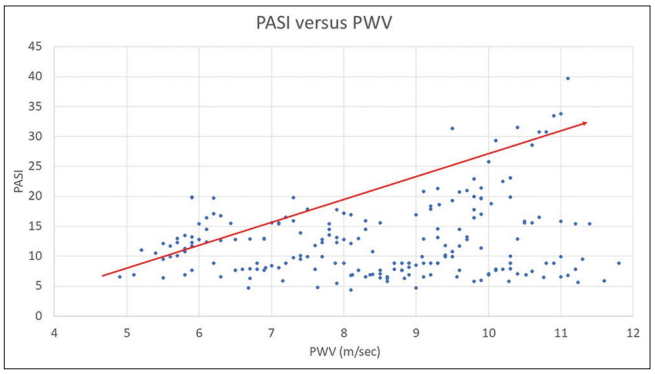

Figure 2: Correlation between PASI and PWV

recruitment of healthy controls for comparison and the internal subgroup analysis help to account for the influence of these confounding factors on the results.

These findings also underscore the need for comprehensive management of psoriasis patients, including regular cardiovascular risk assessments and lifestyle modifications to address comorbidities such as diabetes, hypertension, and obesity.

Our results from the Indian population showed that patients with psoriasis have significantly higher values of CIMT and PWV than healthy controls. Similar results have been reported from other parts of the world.[13,14] However, there is still a dearth of literature on this topic. The results showed a significant positive correlation between the severity of psoriasis and the levels of VEGF and cutaneous angiogenesis. The arterial vasa vasorum evaluation results also showed that the vasa vasorum density was significantly higher in patients with severe psoriasis. These findings suggest that excessive angiogenesis associated with psoriasis may be a cause of cardiovascular ischemia and place patients with psoriasis at a higher risk of cardiovascular disease.

Inflammatory cells such as T lymphocytes and macrophages infiltrate the skin and blood vessel wall, causing the release of pro-inflammatory cytokines that have pro-angiogenic effects. Atherosclerosis and psoriasis have similar molecular mechanisms underlying their development, including hypoxia that triggers the release of pro-angiogenic factors, namely hypoxia-inducible factor-1 (HIF-1) and cytokines such as VEGF.[15,16] There is also a commonality between both conditions in oxidative stress, which is a key metabolic determinant for reactive oxygen species (ROS) production.[17] Additionally, Wnt and Notch signaling pathways are involved in both conditions and modulate various aspects of their development.[18]

The relationship between VEGF-mediated angiogenesis and the development of psoriasis has been widely studied. However, its association with atherosclerosis in the context of psoriasis is still underexplored. In a similar report, Nofal *et al*. also discovered that psoriasis patients had considerably higher mean blood levels of VEGF than control volunteers.[19]

The formation of new blood vessels or angiogenesis is regulated by the VEGF/VEGF receptor (VEGFR)-2 pathway. Hence, controlling pathological angiogenesis via regulation of inappropriately upregulated VEGF/VEGFR-2 is a potential strategy for managing vascular diseases. According to various studies, the amount of VEGF in psoriasis plaques corresponds with the severity of the skin disease condition, and plasma levels of VEGF can predict unfavorable cardiac events in individuals with established atherosclerosis. TNF-α, an upregulator of various pro-angiogenic pathways, also contributes to the development of psoriasis and atherosclerosis. Anti-TNF-α therapy downregulates various inflammatory and angiogenic cytokine levels within psoriasis plaques.[20]

VEGF inhibitors, including anti-VEGF monoclonal antibodies, VEGF receptor antagonists, and tyrosine kinase inhibitors, have been developed to target the VEGF pathway. There have been reports of improvement in psoriasis in patients receiving treatment with these inhibitors for other conditions and in animal models. Antiangiogenic gene therapy and a novel small-molecule inhibitor of VEGF/VEGFR-2 have also been shown to be effective in reducing the number and size of microvessels in the skin and inhibiting angiogenesis in psoriasis.[21]

Based on the results of this study, future studies could aim to explore the underlying mechanisms behind this correlation further and determine whether interventions targeting the regulation of VEGF levels or angiogenesis could help reduce the risk of cardiovascular disease in patients with psoriasis. Additionally, larger and more diverse patient populations could be studied better to understand the relationship between psoriasis and cardiovascular disease and to validate the findings of this study.

Conclusion

In conclusion, VEGF-mediated angiogenesis is central to developing psoriasis and atherosclerosis. Assessing cutaneous vascularity in psoriasis could be important for disease prognosis and personalized treatment regimens for patients. Based on the results of the study, there is a significant positive correlation between the severity of psoriasis and the levels of VEGF and cutaneous angiogenesis. This suggests that patients with psoriasis have a higher risk of developing cardiovascular ischemia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given consent for their clinical information to be reported in the journal. The patients understand that their name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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