Platelet Dysfunction and Its Role in the Pathogenesis of Psoriasis

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Keywords

Psoriasis · Platelets · Thrombosis · Inflammation

Abstract

Background: Psoriasis is an immune-mediated inflammatory skin disease in conjunction with the systemic inflammatory process. It appears to be related to increased risks of cardiovascular disease events, especially in severe cases. The hemostatic balance is disrupted due to the prothrombotic bias in psoriasis, which might be mainly preserved by platelet hyperactivity. Platelets are also immune cells that initiate and regulate immune and inflammatory processes, except as the principal mediator of hemostasis and thrombosis, and platelet dysfunction is deeply involved in the pathogenesis of psoriasis. **Summary:** The aim of this study is to perform a review that expounds abnormal platelet function in psoriasis and explains the important role of platelets in the pathogenic mechanism of psoriasis in order to provide new targets for comprehensive medical treatment.

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Introduction

Psoriasis is a common chronic immune-mediated skin disorder recurrently characterized by local and systemic inflammation the prevalence of which ranges widely from 0.51 to 11.43% in the world [1]. In China, the prevalence of psoriasis was from 0.12% in 1987 [2] to 0.47% in 2012 [3] by a large-scale, population-based study which showed an apparent upward trend. The quality of patients' life is affected by their physical discomfort, psychological burden, and impaired social functioning.

Besides, much of the previous literature has revealed that there are close relationships between psoriasis and adverse cardiovascular diseases. Patients with psoriasis have been assumed to exhibit higher incidence rates of metabolic syndrome as the essential indicator of cardiovascular events, across the severity degree of diseases. And patients with severe psoriasis were in general associated with more comorbidities than patients with mild psoriasis, such as angina pectoris or myocardial infarction [4–11]. Therefore, patients with severe psoriasis have also been highly predisposed to increased vascular morbidity and mortality [11–13].

The detailed pathological mechanisms by which psoriasis could develop vascular events are still not well understood; however, uncontrolled inflammation and persistent platelet activation might be involved.

Platelets are circulating anucleate cell fragments derived from bone marrow megakaryocytes, and this is one of the key effectors in the pathogenesis of cardiovascular diseases. Recent cumulative studies have demonstrated that psoriasis exhibits an elevated incidence rate of venous thromboembolism accompanied by platelet activation compared to controls [14, 15]. Platelets have also been engaged in inflammation and regulating immune responses in addition to the quintessential roles in hemostasis and thrombosis. Activated platelets could help to foster an inflammatory environment by the release of biologically active molecules in some skin disorders, such as systemic sclerosis and systemic lupus erythematosus [16, 17].

It has been increasingly recognized that platelet activation seems to be a major pathogenic factor in psoriasis, while the specific effect that platelets exert on the patient population remains unclear.

In this review, we summarize the past and the current information to clarify the relationship between platelet dysfunction and psoriasis and determine the additional utility of these stable platelet activation parameters in assessing the pathomechanism of psoriasis.

In the Role of Psoriasis Thrombosis

Platelet Aggregation

Platelet hyperaggregation has been detected in psoriatic patients for some time which could promote the formation of a thrombus.

Kragballe and Fallon [18] noted that platelet aggregation induced by thrombin, adenosine diphosphate, and ristocetin was enhanced in psoriasis, as compared with healthy subjects in the 1980s. Later studies confirmed the phenomenon that platelets from psoriatic patients showed a significantly increased percentage of platelet aggregation and might present a thrombophilic state. And platelet aggregation in vitro was assessed by various aggregating agents, such as adenosine diphosphate, arachidonic acid, or collagen [19–23].

Platelet aggregation was positively correlated with disease severity [19], and subjects with minimal disease activity after receiving treatment in psoriatic arthritis were comparable to controls, while subjects with poorly controlled disease still showed platelet hyperaggregation [20].

Alteration of arachidonic acid metabolism in psoriasis was found to be able to stimulate platelet aggregation as the increased production of prostaglandins G_2 and H_2 , and especially thromboxane A_2 in the platelet plasma membrane, was strongly involved in the platelet aggregation process [23]. Vila et al. [22] also detected that elevated cyclooxygenase activity in psoriasis resulted in a higher amount of thromboxane A_2 . So increased platelet aggregation is more likely to lead to thrombosis in psoriasis.

Platelet-Derived Microparticles

Platelet-derived microparticles (PDMPs) are membrane vesicles of 0.1–1 μm in diameter generated from activated or apoptotic platelets in an exocytotic budding process, as the most plentiful microparticles subtypes in the circulation [24].

Since the first report of Tamagawa-Mineoka et al. [25] that PDMPs were significantly elevated in patients with psoriasis compared with healthy individuals, other scholars have come to similar conclusions [19, 24, 26–29]. It was also positively related to the clinical severity of the disease [19, 24, 25], and different size classes of PDMPs with different active components were analyzed to help to clarify the role of PDMPs in psoriasis [24, 30].

Moreover, some researchers compared the level of PDMPs after drug treatment, while conclusions were inconsistent due to different medications. The mean number of circulating PDMPs significantly decreased in patients treated with anti-tumor necrosis factor- α agents upon disease remission [31], and in concordance with topical therapy with 0.05% clobetasol propionate and 0.005% calcipotriol [25]. Despite the clinical improvement of psoriasis after interleukin (IL)-12/13 blockages, the levels of circulating CD41a and CD31 microparticles did not significantly decline in parallel [26]. Therefore, whether antipsoriatic treatments could reduce cardiovascular risks by decreasing the production of PDMPs remains to be further studied.

Higher PDMPs in psoriasis could be considered as a risk factor prone to cardiovascular events. The arachidonic acid fraction of platelet microparticle incubation with platelets could be used to evoke a dose-dependent increase in thromboxane formation, intracellular calcium movement, and platelet aggregation. And incubation with endothelial cells and platelet microparticles could also induce expression of cyclooxygenase and prostacyclin production to exert procoagulant activity [32].

Besides, the membrane glycoprotein (GP) section of platelet microparticles also seems to be of great importance in thrombosis. Platelet GPIIb/IIIa, also known as

Table 1. Studies reporting on mean platelet volume in psoriasis

Study	N	Disease type	MPV levels	PASI correlation
Korkmaz [46], 2018	76	PV	Higher levels in PV with Mets when compared with other groups	No correlation
Farag et al. [36], 2018	70	NR	Higher levels when compared with healthy controls	Positive correlation
Mahrous [37], 2018	40	NR	Higher levels when compared with healthy controls	Positive correlation
Raghavan et al. [38], 2017	50	NR	Higher levels when compared with healthy controls	Positive correlation
Kılıç et al. [39], 2017	157	PV, PSA	Higher levels when compared with healthy controls	Positive correlation
Unal [47], 2016	320	PV	Higher levels when compared with healthy controls	Negative correlation
Chandrashekar et al. [19], 2015	62	NR	Higher levels when compared with healthy controls	Positive correlation
Kim et al. [40], 2015	176	PV	Higher levels when compared with healthy controls	Positive correlation
Capo et al. [41], 2014	59	PV, PSA	Higher levels at baseline when compared with controls and patients after biological therapy	Negative correlation
Ahmad et al. [42], 2014	30	NR	Higher levels when compared with healthy controls	NR
Saleh et al. [63], 2013	25	NR	No significant difference when compared with healthy controls	No correlation
Canpolat et al. [44], 2010	106	PV, PSA	Higher levels in PSA when compared with PV and healthy controls	Positive correlation

N, number of patients; MPV, mean platelet volume; PASI, Psoriasis Area and Severity Index; PV, psoriasis vulgaris; Mets, metabolic syndrome; NR, not reported; PSA, psoriasis arthritis.

platelet CD41/CD61 complex, is involved in the regulation of platelet aggregation by serving as the receptor for fibrinogen and von Willebrand factor. The study suggested that PDMPs increased binding with the active platelets in the presence of soluble fibrinogen to promote platelet adhesion and aggregation in a GPIIb/IIIa-dependent mechanism [33]. And PDMPs could also bind to the sub-endothelial matrix at sites of endothelial damage to initiate thrombus formation [34]. What is more, the procoagulant property of PDMPs was 50- to 100-fold higher than that of activated platelets, and PDMP membranes were enriched with phosphatidylserine and P-selectin [35].

Taken together, elevated levels of PDMPs observed in psoriasis patients may be conducive to the development

of thrombus and predictive of the cardiovascular outcomes by triggering a cascade of events.

In the Role of Psoriasis Inflammation

Mean Platelet Volume

Mean platelet volume (MPV) is an approved marker of platelet activation and has a fatal role in the pathological mechanism of cardiovascular complications. An increased level of MPV, as an indicator of larger, more reactive platelets resulting from an elevation in platelet turnover, represents platelet morphological changes including both the spherical shape and pseudopodia formation.

The rapidly expanding evidence of research in various populations supports that the value of MPV was significantly increased in patients with psoriasis compared with that of controls [19, 36–45] (Table 1). An elevated MPV level was found in psoriasis as well as psoriatic arthritis [39, 41, 44], and there was also a higher expression of MPV in patients with arthritis [44]. We could conclude that higher MPV values may be relevant to more inflammation.

Besides, higher MPV levels were dramatically demonstrated among psoriatic patients with atherosclerosis and metabolic syndrome compared to psoriatic patients without atherosclerotic changes and metabolic syndrome [36, 37, 46]. MPV could be an early predictor to diagnose premature atherosclerosis more accurately and sensitively in psoriasis.

Most studies have shown that elevated MPV values are positively correlated with disease severity measured by the psoriasis area and severity index (PASI) score [36–40, 43–45]. However, the experimental data are rather controversial, and there is no general agreement about the positive relationship between MPV and disease severity. On the contrary, Unal [47] and Capo et al. [41] found an inverse correlation between them. Thus, the relationship needs to be more deeply studied to assess whether MPV could be used as an appropriate marker of disease severity.

Given the clear evidence that MPV values were higher in psoriasis, researchers also reported that MPV levels significantly decreased after improvements with biological therapy [40, 41].

Simultaneously, platelet distribution width was also significantly elevated in patients when compared to controls [19, 40]. Higher platelet distribution width means heterogeneity of platelet volume that increases the number of deformed platelets with pseudopodia in different sizes.

As previously reported, sustained consumption of platelets due to increased platelet coagulation in psoriasis might stimulate platelet production and cause the release of larger and more immature platelets into the peripheral blood circulation.

Larger platelets may be related to the inflammatory reactions in psoriasis:

(1) Large-volume platelets can release more chemokines, cytokines, and so on.

Platelet factor 4 (PF4) and β -thromboglobulin (β -TG) are the most abundantly expressed CXC chemokines in platelet α -granules that could be released in high concentrations following activated platelets [48]. Significant dif-

ferences in plasma levels of PF4 or β -TG were found between many inflammatory skin diseases and normal controls, such as systemic sclerosis [49], allergic contact dermatitis [50], and atopic dermatitis [51], elevated expression indicating the critical role of platelet activation. β -TG together with PF4 levels in psoriasis was also reported to be higher than in healthy controls, and PF4 levels were correlated with PASI [51]. On the one hand, PF4 with a high affinity to heparin could induce the formation of antibodies against the PF4/heparin complexes to enhance platelet activation and aggregation by binding the receptor Fc γ RIIa and triggering cross-linking reactions [52]; β -TG could inhibit prostacyclin production by binding to adjacent vascular endothelium and accelerate thrombosis [53]. On the other hand, they could be implicated in the regulation of leukocyte adhesion and migration, especially neutrophil granulocytes and monocytes [54]. Besides, IL-17-producing cells are pivotal in the development of psoriasis [55], while PF4, as the key upstream driver, could differentiate naive CD4⁺ T cells into Th17 cells and induce elevated secretion of proinflammatory cytokines, especially IL-17 which affected leukocyte proliferation and led to leukocyte infiltration in psoriasis [56].

Cytokines released by activated platelets are also available to play a key role in psoriasis. Platelets are the major source of the cytokine IL-1 β , and an increased IL-1 level is believed to be involved in the development and progression of inflammation in psoriasis, and serotonin derived from platelet dense granules is also expressed in the psoriatic skin to modulate the immune response [57].

(2) Large-volume platelets can express more adhesion molecules and immune receptors on the surface to participate in the immune responses, including integrin, CD40 ligand, and so on.

The platelet CD40 ligand which is stored in α -granules could be released in soluble form into the extracellular space with activation. The serum concentrations of the soluble ligand of CD40 (sCD40L) have been declared to increase in patients [58, 59], and sCD40L was positively correlated with the C-reactive protein level [60]. CD40 ligation facilitated interactions between platelets and leukocytes contributing to the initiation and progression of proinflammatory reactions like atherogenesis [61].

P-Selectin

P-selectin (CD62P), as the specific marker of irreversible platelet activation, is an integral membrane GP that is stored in the α -granules of platelets and the Weibel-Palade bodies of endothelial cells. On activation, P-selec-

Table 2. Studies reporting on P-selectin in psoriasis

Study	N	Testing index	P-selectin levels	PASI correlation	Levels after treatment
Kwiek et al. [68], 2017	27	sP-selectin	No significant difference when compared with healthy controls	No correlation	Decrease
Chandrashekar et al. [19], 2015	62	sP-selectin	Higher levels when compared with healthy controls	Positive correlation	NR
Ataseven et al. [66], 2014	24	sP-selectin	Higher levels when compared with healthy controls	No correlation	NR
Fathy Agamia et al. [65], 2014	70	sP-selectin	Higher levels at baseline when compared with healthy controls and after therapy	Positive correlation	Decrease
Saleh et al. [63], 2013	25	P-selectin	Higher levels when compared with healthy controls	Positive correlation	NR
Tamagawa-Mineoka et al. [25], 2010	21	sP-selectin	Higher levels at baseline when compared with healthy controls and after therapy	No correlation	Decrease
Garbaraviciene et al. [64], 2010	47	sP-selectin, P-selectin	Higher levels when compared with healthy controls	Positive correlation	Decrease
Long et al. [67], 2010	58	sP-selectin	Higher levels when compared with healthy controls	No correlation	No difference

PASI, Psoriasis Area and Severity Index; sP-selectin, soluble P-selectin; NR, not reported.

tin will be translocated to their membranes or secreted into plasma as soluble P-selectin (sP-selectin) [62], and sP-selectin originates from platelets only.

It has been increasingly recognized that the level of CD62P expression is greatly enhanced in psoriasis, particularly in those with moderate or severe disease when compared with healthy individuals, including platelet P-selectin and sP-selectin in multiple studies [19, 25, 63–67] (Table 2). What is more, P-selectin expressed on platelets was correlated closely with sP-selectin in patient plasma [64]. Furthermore, many studies showed a significant correlation between the PASI score and P-selectin expression [19, 63–65].

Saleh et al. [63] found increased atherosclerosis risks in patients with psoriasis especially in those with severe conditions, as evidenced by increased expression of CD62P which was positively correlated with atherosclerotic markers.

Some studies supported the significant correlation of CD62p expression with improvement after treatment. Tamagawa-Mineoka et al. [25] revealed that sP-selectin levels were markedly reduced and then returned to normal values after clinical improvement by clobetasol propionate and calcipotriol. This finding was similarly in

agreement with other studies in this area like Garbaraviciene et al. [64], Fathy Agamia [65], and Kwiek et al. [68] who reported that effective therapy such as narrow-band phototherapy and biological drugs could significantly reduce the level of CD62P and control platelet activation in patients who had increased CD62P expression when untreated.

It is well known that selectins generate the first step to the tethering and rolling of leukocytes which is crucial for the formation of an inflammatory infiltrate [69]. P-selectin expressed on platelets can support leukocyte rolling via the interaction between P-selectin and leukocyte P-selectin GP ligand-1, increasing the formation of leukocyte-platelet aggregates with regional recruitment of massive leukocytes from blood to the inflamed tissue and secretion of chemokines at inflamed sites [64, 65, 69, 70].

As we all know, P-selectin is also associated with the inflammatory processes, and this essential role of P-selectin is a potential target for the development of novel treatments besides traditional drugs.

Platelet-Leukocyte Complexes

The interaction between activated platelets and leukocytes gradually increases in psoriasis. The level of platelet-

monocyte complexes in psoriatic arthritis patients is considerably elevated, and in psoriasis patients it was higher than in healthy controls, but the difference was not statistically significant, maybe because of the limited number of study subjects [60]. Apart from platelet-monocyte complexes, the expression of platelet-specific markers on neutrophils was found to be higher due to the increased formation of platelet-neutrophil complexes in psoriasis patients [71]. Further research found an upregulated interaction between low-density granulocytes and platelets of particular interest [72].

A recent study reported that activated platelets in psoriasis increased adhesion to damaged endothelium for initiating inflammation by the release of proinflammatory cytokines [73]. So, increased platelet activation might favor platelet-leukocyte association which directly and indirectly mediates leukocyte incorporation into plaques to cause vascular complications and which promotes extravasation of leukocytes from skin proximal blood vessels to cause inflammatory changes in the skin, in case of a damaged endothelium.

Platelet-to-Lymphocyte Ratio

The platelet-to-lymphocyte ratio (PLR), easily calculated from the platelet and lymphocyte counts, has been currently used in many diseases [74–77] to predict inflammatory responses and guide the follow-up of diseases as a new biomarker. Accumulating evidence has shown that PLR is closely associated with disease course in psoriasis.

PLR values were significantly higher in patients with psoriasis [78], especially in psoriatic arthritis; significant differences were found as the PLR increased in parallel with an increase in PASI and C-reactive protein [78–81]. The PLR decreased after treatment with different biologics, and the greater the improvement of the PASI score, the better the reduction rate of PLR [81].

Blood cell count ratios appear more stable and informative than blood cell parameters per se. Maybe the PLR becomes the strong predictor for the presence of arthritis among patients with psoriasis.

For all these findings, platelet dysfunction does exist in psoriasis and shows a strong connection with disease severity and vascular complications. It is very critical to find the relevant mechanism about platelet activation and to target platelet-specific pathways to slow down the progress of psoriasis.

Oxidative Stress and Platelet Activation

Oxidative stress has been considered to be a key factor in the pathogenesis of psoriasis, which represents an imbalance between the production of reactive oxygen species (ROS) and the capacity of the intrinsic antioxidant system [82].

On one hand, research data suggested that the production of oxidative-free radicals such as nitric oxide (NO) and superoxide anion were significantly increased in psoriatic patients which caused damage to cellular constituents [83, 84]. More ROS produced owing to the inflammatory process may lead to the formation of lipid oxidation products such as malondialdehyde. Increased serum malondialdehyde was correlated with disease severity [85], and ROS also elevated the levels of protein oxidation products such as pyrrolized protein, protein carbonyl compounds, and advanced oxidation protein products [86].

On the other hand, patients with psoriasis exhibit an impaired antioxidant status as the endogenous antioxidant system fails to catalyze the reaction of ROS scavenging. The antioxidant system is mainly comprised of some enzyme complexes including glutathione peroxidase enzyme, superoxide dismutase, and catalase. A significant decrease in antioxidation ability was measured by reduced glutathione peroxidase, superoxide dismutase, and catalase levels in different groups of psoriasis patients when compared with a normal group [83, 85]. Lower levels of plasma thiols containing sulphhydryl (–SH) groups were found and thereby indicated the insufficient antioxidant system to neutralize the effects of prooxidants in the patients [87]. Other free-radical-scavenging systems, such as lipophilic antioxidant paraoxonase 1 and vitamin E, were also significantly lower in psoriasis [88].

While mounting evidence has indicated that platelet function could be regulated by platelet-derived ROS or induced oxidative stress [89, 90], the enzymatic activity of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is considered to be a major source of ROS in platelets [91].

ROS could adjust the changes in platelet adhesion and aggregation [92]. ROS generation could be involved in the process of agonist-induced (collagen, thrombin, or calcium ionophore [A23187]) GPIIb/IIIa ectodomain shedding [93]. By detecting a direct correlation between either P-selectin or sCD40L and ROS, ROS generation could augment the production and expression of P-selectin and sCD40L which may cause further proinflammatory responses [94]. So, is it possible that oxidative stress in psoriasis

riasis could result in platelet dysfunction. Our research group is now working on it.

It is well known that ROS could modulate platelet function via calcium mobilization, NO inactivation and the formation of isoprostanes.

One of the redox-dependent regulatory mechanisms for platelet activation is principally via protein tyrosine phosphatases, especially SH2 domain-containing phosphatase-2 which could be reversibly oxidatively inactivated by ROS and potentially increase the phosphorylation response of tyrosine substrates. Then, these changes could eventually cause activation of phospholipase C γ_2 , release of cytosolic calcium, and platelet aggregation [95].

ROS could also regulate the NO signal transduction pathway. The NO pathway is believed to be negatively associated with platelet activation. NO generated by possibly platelet NO synthases activates the heme-containing soluble guanylyl cyclase resulting in cyclic guanosine-3',5'-monophosphate generation, thereby increasing activation of cGMP-dependent protein kinase (cGK/PKG I β), phosphorylation of vasodilator-stimulated phosphoprotein, and ultimately inhibition of platelet activation [96]. Bioactive NO could be inactivated and impaired through the rapid reaction with ROS to form peroxynitrite, resulting in a reduced role of the NO inhibitory and increasing platelet activation [97].

Besides, the 8-iso-prostaglandin F 2α (8-iso-PGF 2α) is a stable isoprostane with biologic functions including modulating platelet activation and thrombus formation. Increased GPIIb/IIIa activation and platelet recruitment induced by 8-iso-PGF 2α suggested that 8-iso-PGF 2α production may be relevant in a more complex scenario such as the process of platelet activation [98]. Platelet ROS could contribute to the formation of 8-iso-PGF 2α by upregulation of NOX2, the catalytic core of NADPH oxidase [99, 100].

Although ROS could regulate platelet function by different pathways, it remains to be further studied whether there is a corresponding mechanism that oxidative stress state in psoriasis could induce platelet activation and thereby increase the cardiovascular complication risks.

Conclusion

The abnormal immune system in psoriasis may lead to the release of various inflammatory mediators to induce concomitant platelet activation, and in turn platelet activation could further aggravate the inflammatory re-

sponse, thus triggering a vicious circle to worsen the condition. Much more systematic research that could identify how psoriasis interacts with platelet dysfunction will be extremely important.

Platelet activation indexes as described above generally suggest abnormal platelet function and are given an additional role in the diagnosis of psoriasis. Taking into account the diverse effects of biological markers, their combination could help to predict psoriasis severity and characterize the subgroup of patients who are at high risk to develop long-term vascular complications. Furthermore, these biomarkers could also be used to monitor the effect of antipsoriatic therapeutic strategies. Of note, they could be readily measured and are widely available in clinical practice.

Antipsoriasis treatment needs to be improved in order to decrease the incidence of complications. Whether existing drugs could fight platelet activation will have to attract more attention. Despite the notably increased risk of cardiovascular diseases, there are currently no antiplatelet guidelines for primary prevention in psoriasis patients. The significance of antipsoriasis drugs in combination with antiplatelet medications for reducing both psoriasis activity and the occurrence of comorbidities is worthy of further investigation. Further clinical trials are still required to explore an integrated treatment of psoriasis.

Key Message

The review seems to confirm that abnormal platelet function could be involved in the pathogenesis of psoriasis.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by a grant from the National Natural Science Foundation of China (grant 81673080).

Author Contributions

All authors contributed equally to the manuscript and were accountable for the content and writing of the article.

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