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REVIEW ARTICLE

Bridging Dermatology and Cardiology: The Link between Skin Lesions and Cardiovascular Risk

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Abstract: ***Introduction*:** Dermatological disorders are emerging as important indicators of systemic health and have drastic implications for cardiovascular disease (CVD). Skin and cardiovascular diseases share common pathophysiological mechanisms, including chronic inflammation, oxidative stress, and endothelial dysfunction. These overlapping pathways contribute to the increased cardiovascular (CV) risk observed in patients with inflammatory and genetic dermatological conditions, such as psoriasis, atopic dermatitis, and systemic lupus erythematosus.

***Methods*:** This narrative review was conducted by evaluating current evidence from peer-reviewed literature on the association between dermatological disorders and cardiovascular risk. Particular attention was given to pathophysiological mechanisms and therapeutic implications relevant to both specialties.

***Results and Discussion*:** Since systemic inflammation is a major risk factor for CVD, treatments that reduce the inflammatory burden represent promising strategies to prevent or mitigate cardiovascular complications in patients with dermatological conditions. Traditional therapies (*e.g.*, methotrexate and statins) remain the gold standard to reduce CV risk. In addition, advances in the field of inflammation—such as inhibitors targeting IL-17 and IL-23 pathways—along with new systemic biomarkers and the development of targeted therapies, are paving the way for improved patient stratification and personalized approaches.

***Conclusions*:** This review highlights the importance of interdisciplinary collaboration in optimizing patient outcomes and emphasizes the need for closer integration of dermatological and cardiological expertise. Future research should focus on clarifying molecular mechanisms, identifying therapeutic targets, and refining shared clinical guidelines. By bridging dermatology and cardiology, this review underscores the potential for earlier detection, better risk prediction, and integrated management of coexisting dermatological and cardiovascular conditions.

Keywords: Cardiovascular risk, inflammatory skin disorders, dermatological markers, systemic inflammation, metabolic dysfunction, oxidative stress, cardio-dermatology.

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1. INTRODUCTION

Dermatological disorders are emerging as significant markers of systemic health and are strictly related to cardiovascular disease (CVD). Indeed, several inflammatory and non-inflammatory skin disorders have been associated with classical and atypical cardiovascular (CV) risk factors [1, 2].

Emerging evidence highlights a crosstalk between dermatological and CV conditions, in which systemic inflammation, immune dysregulation, and metabolic pathways play pivotal roles. As an example, inflammatory skin disorders such as psoriasis (PS) and eczema have been associated with increased risk of myocardial infarction (MI), stroke, and major adverse cardiovascular events (MACE). These associations have been attributed to canonical risk factors, including chronic low-grade inflammation, endothelial dysfunction, and dyslipidemia [3-5]. On the other hand, non-inflammatory skin conditions – including age-related disorders and genodermatoses- have been linked with metabolic syndrome and other CV risk factors [2].

In this review, we examined the interconnections between dermatology and cardiology, with a particular focus on CV risk in inflammatory and non-inflammatory skin disorders and the impact of inflammation and metabolic dysfunction on the estimated risk score. Additionally, the review highlights areas for future interdisciplinary research, emphasizing the need for collaboration between dermatologists and cardiologists in both clinical and basic science.

2. METHODOLOGY

To conduct this review, we carried out a systematic search of articles using PubMed and Google Scholar as our main sources. The search was conducted through the aforementioned keywords. Each selected article was carefully reviewed and critically analysed, and the useful key elements were summarised. In the case of special issues, we also considered and analysed the other articles included in the same issue, in addition to those previously identified through PubMed searches. No articles were excluded from the search *a priori*.

3. SHARED MECHANISMS BETWEEN INFLAMMATORY SKIN DISORDERS AND CARDIOVASCULAR DISEASES

3.1. Systemic Inflammation and the Cytokine Cascade

Systemic inflammation can be considered the strongest link between inflammatory skin diseases and CVD. In PS and atopic dermatitis (AD), an overactivation of the innate immune system, mediated by keratinocytes and antigen-presenting cells, leads to the production of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and IL-17, which in turn propagate the pro-inflammatory signal to other tissues, thus spreading a systemic inflammation [6-7]. Among those pro-inflammatory factors, IL-23 plays a pivotal role in fueling systemic inflammation, especially in PS. In particular, IL-23 promotes differentiation and maintenance of lymphocytes T-helper 17 (Th17) cells, which in turn secrete IL-17 and IL-22, promoting keratinocyte hyperproliferation. Furthermore, IL-17 has been shown to promote vascular inflammation, endothelial activation, and atherosclerotic plaque instability [6, 8].

The activation of toll-like receptors (TLRs), expressed on keratinocytes and vascular endothelial cells, also represents another trigger of pro-inflammatory pathways, including nuclear factor kappa light chain enhancer of activated B cells (NF-kB) and MAPK, resulting in the production and release of pro-inflammatory cytokines that promote local and systemic inflammation [9, 10].

Considering all the shared risk factors between dermatological and CV diseases, systemic inflammation represents the most significant one. Other factors include oxidative stress, endothelial dysfunction, and autophagy dysregulation [2, 11, 12].

The knowledge of the shared mechanisms that link dermatological and CV conditions may lead to the development of targeted therapies with a dual effect: treating the specific dermatological disorder and reducing CV risk in dermatological patients. Fig. (**1**) gives a schematic and summarized representation of all these interconnected pathways and their systemic effect, serving as a potential visual guide for clinicians.

3.2. Oxidative Stress and Immune Activation

Oxidative stress is both a trigger and a consequence of chronic inflammation and is characterized by increased levels of reactive oxygen species (ROS). ROS can interact with and damage different cellular components, including lipids, proteins, and DNA. Damaged components, also called damage-associated molecular patterns (DAMPs), act as signaling molecules able to boost inflammation and activate the immune system by acting on TLRs [13, 14]. ROS levels are elevated in PS and correlate with markers of subclinical CV damage [15, 16].

3.3. Endothelial Dysfunction and Cardiovascular Implications

Endothelial dysfunction represents the first event in the development of atherosclerosis, and it is characterized by reduced nitric oxide (NO) production, increased vascular permeability, expression and release of pro-inflammatory and pro-apoptotic markers, and ROS production.

Endothelial exposure to cellular stressors, such as chronic systemic inflammation and ROS, leads to the exposure on cell membrane of the endothelial adhesion molecules ICAM-1 and VCAM-1, which trigger the recruitment of leukocytes to the vascular endothelium, starting the atherogenic process [17, 18].

4. INFLAMMATORY SKIN DISORDERS AND CARDIOVASCULAR RISK

Inflammatory skin disorders such as PS, AD, systemic lupus erythematosus (SLE), and hidradenitis suppurativa (HS) are characterized by increased CV risk. This is because inflammatory skin disorders and CVD share common risk factors, including systemic inflammation, endothelial dysfunction, and immune dysregulation [2]. The molecular mechanisms at the base of these dermatological disorders and their associated CV risk factors are summarized in Table **1**.

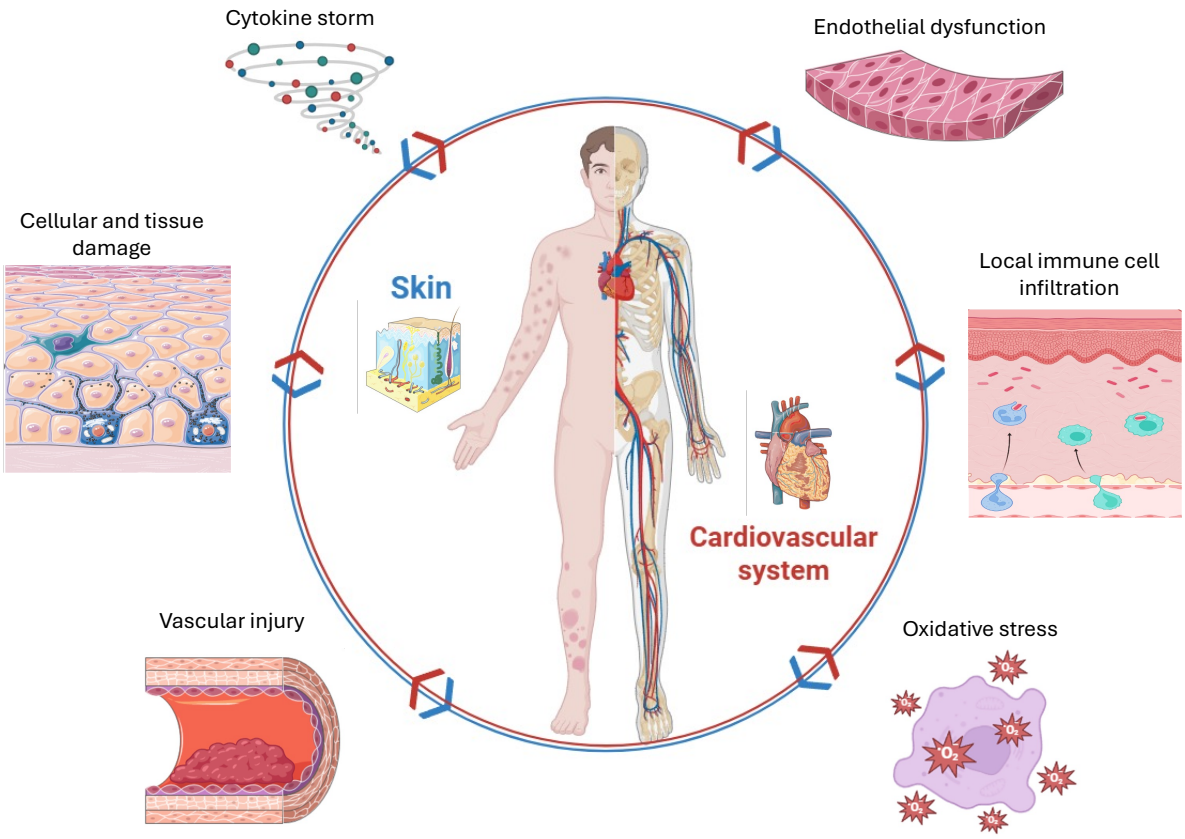

Fig. (1). Summary of shared pathophysiological mechanisms linking skin and cardiovascular conditions. The diagram highlights how systemic inflammation leads to endothelial dysfunction and oxidative stress, which causes vascular injury, cellular and tissue damage. The process is mediated by factors such as cytokines (*e.g.*, TNF-α, IL-6) and reactive oxygen species (ROS). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Summary of the afore-mentioned dermatological disorders, their associated CV risk factors, and the molecular mechanisms.

Dermatological Disease	Associated CV Risk Factors	Mechanisms of Damage
Psoriasis	Increased incidence of MACE, MI, and stroke	Excessive IL-17, IL-23 and IgE production
Atopic Dermatitis	Increased incidence of CVD, heart failure, and venous thromboembolism	Excessive IL-4 and IL-13 production. Increased CRP levels
Systemic Lupus Erythematosus	Endothelial dysfunction, vasculitis, and atherosclerosis	Production of antinuclear antibodies and immune complex deposition
Hidradenitis Suppurativa	Metabolic syndrome, diabetes, and atherosclerosis. Increased incidence of MI and cerebrovascular accidents	Marked systemic inflammation

Among these, PS is an inflammatory skin disorder characterized by an overactivation of T cells, which brings an excessive production of IL-17 and IL-23, thus causing systemic inflammation [19-20]. PS is often associated with psoriatic arthritis, diabetes, depression, and CVD. CVD represents the main cause of death in psoriatic patients [21]. It has been shown that patients with moderate-to-severe PS are characterized by a drastic increase in risk of MACE, MI, and stroke [5]. On top of IL-17/IL-23 effect, recent evidence suggests an involvement of IgE in the crosslink between PS and CVD [19], since high serum levels of IgE in patients with PS correlate with increased CV risk [22-24]. Representative clinical features of plaque psoriasis are shown in Fig. (**2A**).

Similarly, AD is a common chronic inflammatory disease driven by a Th2-skewed immune response involving IL-4 and IL-13 [25-26]. A direct correlation between the levels of C-reactive protein (CRP) and the severity of the disease has been proven in patients with AD [27]. Furthermore, several recent studies suggest a strong association between AD and CVD, heart failure, and venous thromboembolism [28-31]. Fig. (**2B**) illustrates typical eczematous lesions of atopic dermatitis.

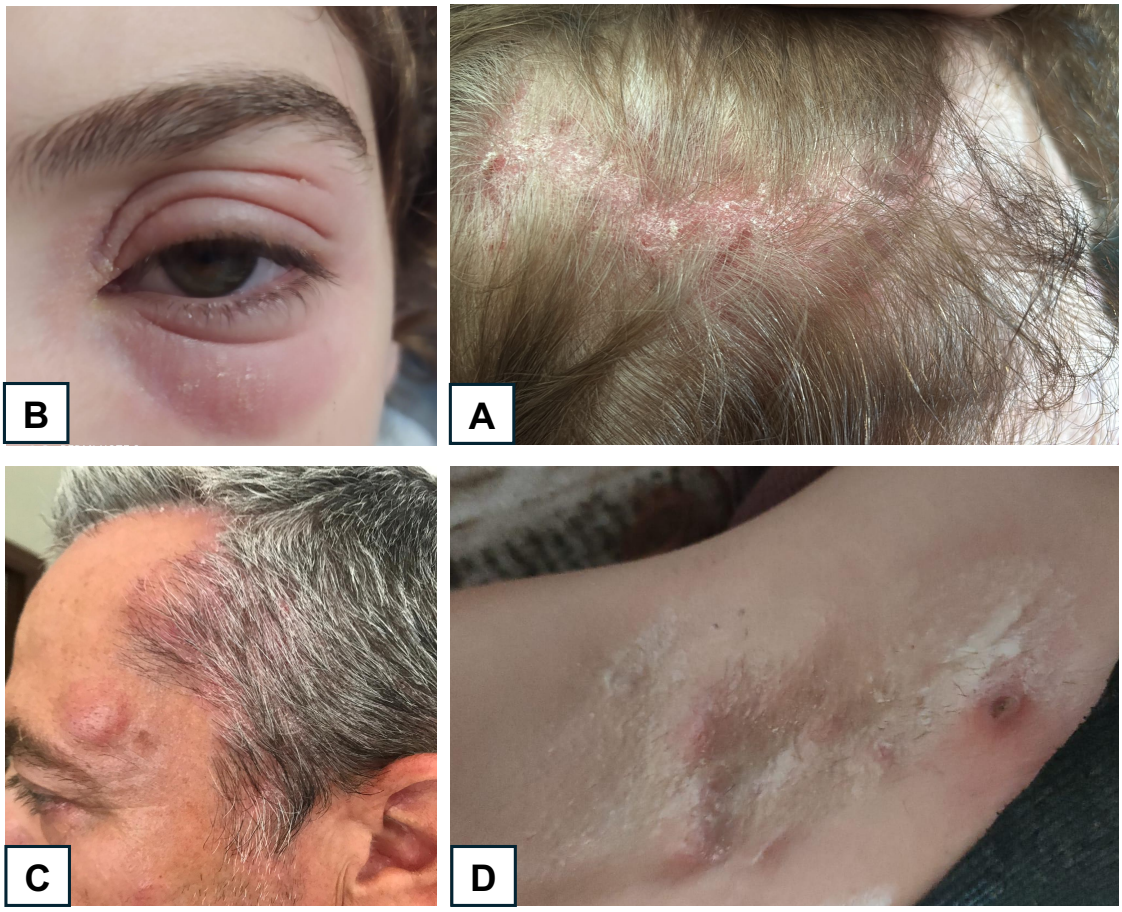

Fig. (2). Representative clinical images of dermatological conditions associated with increased cardiovascular risk. (**A**) Psoriasis (PS): erythematous plaques with scaling involving the scalp. (**B**) Atopic dermatitis (AD): eczematous and lichenified lesions with periorbital involvement. (**C**) Systemic lupus erythematosus (SLE): malar erythema extending to the temples and forehead. (**D**) Hidradenitis suppurativa (HS): inflamed nodules and sinus tracts with scarring in the axillary region. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Finally, SLE is a prototypical autoimmune disorder that markedly increases CV risk. It has been shown that the risk of MI in patients with SLE is up to 50-fold higher than in the general population [32-34]. Furthermore, patients with SLE display several canonical and atypical CV risk factors that confer to them an increased atherosclerosis and coronary artery disease (CAD) predisposition [35]. The etiology of SLE has been attributed to the production of antinuclear antibodies that lead to immune complex deposition and vasculitis, thus promoting endothelial dysfunction and atherosclerosis [36, 37]. Clinical examples of SLE-associated cutaneous manifestations are presented in Fig. (**2C**).

5. EMERGING INFLAMMATORY DERMATOSES WITH CARDIOMETABOLIC IMPLICATIONS

Recent studies suggest that acne, especially in severe or persistent cases, may be linked to increased cardiovascular risk through shared inflammatory and metabolic pathways. Elevated cytokines (IL-1, IL-6, TNF-α), dyslipidemia, and insulin resistance are common in both acne and CVD. In women with polycystic ovary syndrome (PCOS)—where acne is a frequent symptom—cardiometabolic risk is further amplified. The Mediterranean diet shows a protective effect, with Skroza *et al*. reporting an inverse correlation between dietary adherence and acne severity. Acne may thus represent an early marker of cardiometabolic vulnerability [38].

In a similar context, HS is a skin disorder that primarily affects apocrine gland-bearing regions and is associated with marked systemic inflammation that predisposes patients to an increased risk of metabolic syndrome, diabetes, and atherosclerosis [39-43]. Recent evidence suggests that patients with HS are characterized by a 23% incidence of myocardial infarction or cerebrovascular accidents [44]. This may be due to increased circulating inflammatory markers that promote endothelial dysfunction and oxidative stress, thus predisposing the patient to cardiovascular events [45-47]. Typical clinical manifestations of HS are illustrated in Fig. (**2D**).

6. DERMATOLOGICAL MARKERS OF CARDIOVASCULAR DISORDERS

Cutaneous manifestations are often the read-out of more severe systemic conditions, including CVD. These dermatological "red flags" can serve as non-invasive diagnostic tools for clinicians in the identification of cardiovascular diseases, thus speeding up the diagnosis and the initiation of the treatment. A variety of distinct skin findings can reflect un-

derlying structural, infectious, autoimmune, or thrombotic cardiac conditions, and their recognition may provide critical clinical insight.

Among these, cardiac myxoma is a benign cardiac tumor frequently associated with Carney complex, an autosomal dominant syndrome characterized by pigmentation abnormalities—such as lentigines and blue nevi localized on the face, lips, and mucosa—and endocrine dysregulation. Cutaneous manifestations may include petechiae, itchy skin lesions, hyperpigmentation, and Raynaud's phenomenon [48-49]. In some rare cases, skin findings—particularly myxomatous emboli—are the key determinants for the diagnosis of cardiac myxoma [50, 51].

Infective endocarditis, on the other hand, represents a life-threatening condition due to the rapid degeneration of the heart valves caused by microbial infections. Here, specific cutaneous signs—such as Janeway lesions, Osler's nodes, and Roth spots—along with systemic symptoms like fever and fatigue, may be crucial for early clinical suspicion and diagnosis [52, 53].

Similarly, rheumatic fever is a systemic immune-mediated condition that typically arises following a streptococcal infection and predominantly affects cardiac valves. In these patients, early identification of characteristic cutaneous signs—namely erythema marginatum and subcutaneous nodules—allows for timely initiation of antibiotic prophylaxis, reducing the risk of chronic valvular damage [54-56].

Another important dermatological marker is livedo reticularis, which results from impaired microvascular flow and appears as a mottled, violaceous reticular pattern on the skin. This manifestation is frequently associated with atheroembolic disease or autoimmune vasculitis, both of which elevate the risk of arterial thrombosis and systemic cardiovascular events [49, 57]. Moreover, livedo reticularis has been linked to elevated levels of lipoprotein(a) [Lp(a)], an independent cardiovascular risk factor whose pathogenicity is attributed to its ability to activate plasmin and increase PAI-1 and tissue factor expression [58, 59].

6.1. AMYLOIDOSIS AS A CASE STUDY

Amyloidosis is the perfect example of the important interplay between dermatological and CV conditions. Amyloidosis is caused by the accumulation of amyloid fibers in the myocardium, leading to diastolic dysfunction, conduction system diseases, and heart failure with preserved ejection fraction (HFpEF) [60-61]. As the early detection of the accumulating amyloid fibers is almost impossible, the recognition of specific clinical dermatological features, such as purpura (especially around the eyes) and waxy papules on the face and neck, can really speed up the diagnosis of amyloidosis, preventing cardiac complications [62-63].

Based on the type of protein that creates amyloid depots, cardiac amyloidosis can be divided into abnormal transthyretin amyloidosis (ATTRv) and immunoglobulin light-chain (LC) amyloidosis. In ATTRv, accumulation of transthyretin causes the activation of caspase 3/7 and mitochondrial dysfunction. In LC amyloidosis, instead, cytotoxicity is mediated by the induction of p38 and the increase in oxidative stress [64].

6.2. Implications for Clinical Practice

The identification of dermatological red flags for CV disorders can sometimes be crucial to drive the clinician towards a rapid and accurate diagnosis. Nevertheless, the detection of dermatological symptoms must be coupled with CV ones. For this reason, the tandem work of dermatologists and cardiologists is crucial to optimizing the diagnosis and treatment, improving patients' quality of life.

7. GENETIC LINK BETWEEN CARDIOLOGY AND DERMATOLOGY: THE EXAMPLE OF RASOPATHIES

RASopathies are a group of rare genetic syndromes characterized by a germline mutation in the RAS/MAPK pathway. This group includes Noonan, Leopard, Costello, and cardiofaciocutaneous (CFC) syndrome. Even though these syndromes are not exclusively dermatological disorders, cutaneous manifestations are essential to bypass their common phenotypical characteristics and, thus, to have an early and precise diagnosis [65-67]. On top of that, congenital heart defects and hypertrophic cardiomyopathies are present in up to 90% of the patients with RASopathies [68-70]. In particular, pulmonary valve stenosis, atrioventricular septal and atrial septal defect represent the most common congenital heart defects [71].

Among RASopathies, Noonan syndrome is an autosomal dominant developmental disorder characterized by facial dysmorphism, short stature, congenital heart defects, and other anomalies, including chest deformities and lymphatic vessel dysplasia [72]. Dermatological features of Noonan syndrome have been largely underestimated but are emerging as key discriminators for the diagnosis of this disease [73, 74]. In particular, recent findings demonstrated that cutaneous manifestations are associated with specific genetic mutations. A high prevalence of keratinization disorders and hair abnormalities has been found in the majority of patients with Noonan syndrome carrying SOS1 mutations [74]. Furthermore, patients with mutations in genes directly involved in the cell proliferation kinase cascade (*i.e.*, SOS1, RAF1, BRAF, and KRAS) have a higher frequency of hyperkeratosis lesions—including xeroderma, nevi, follicular and palmoplantar hyperkeratosis, and café-au-lait spots—compared to those with mutations in genes indirectly involved in the pathway, such as PTPN11 [75].

A closely related entity is Leopard syndrome—also known as Noonan syndrome with multiple lentigines—which exemplifies the importance of dermatological lesions for the diagnosis of RASopathies. As the name suggests, it is characterized by multiple lentigines and melanocytic nevi, often accompanied by ECG abnormalities. This dermatological phenotype is strictly associated with PTPN11 mutations and is critical in distinguishing Leopard from Noonan syndrome [76-77]. Patients with Leopard syndrome also display several cardiac abnormalities, the most common being left ventricular hypertrophy [78].

Another rare but clinically significant RASopathy is Costello syndrome, which is defined by distinctive craniofacial features, congenital heart defects, neurodevelopmental delay, and a variety of dermatological abnormalities [79]. Due to

Table 2. Summary of therapeutic strategies of overlapping dermatological and cardiovascular conditions.

Therapeutic Strategy	Key Agents/Approaches	Benefits
Biologic Therapies (IL-17 inhibitors, IL-23, TNF-α inhibitors)	Secukinumab, Guselkumab, Infliximab, Adalimumab	Reduced systemic inflammation, stabilizes plaques, decreases MACE
Methotrexate	Methotrexate, corticosteroids	Lower systemic inflammation; reduce CRP levels
Corticosteroids	Systemic corticosteroids	Effective for acute flares; short-term use only due to CV risks
Lipid Lowering Agents (statins, PCSK-9 inhibitors)	Statins, Alirocumab, Evolocumab	Improves lipid profile; anti-inflammatory properties
Colchicine	Colchicine	Suppresses vascular inflammation; potential dual benefit for heart and skin
Anticoagulation (DOACs, Warfarin)	Apixaban, Dabigatran, Rivaroxaban, Edoxaban, Warfarin	Reduced thrombotic risk in autoimmune conditions
Lifestyle modifications (Mediterranean Diet, Exercise)	Dietary changes, smoking cessation, and physical activity	Improves systemic inflammation; reduces CV risks
Regular Cardiovascular Screening and Early Intervention	CAC scoring, vascular ultrasound, and inflammatory markers	Early detection of subclinical atherosclerosis: tailored interventions
Interdisciplinary Collaboration	Multidisciplinary clinics integrating dermatology and cardiology	Comprehensive and individualized patient care
Educational Initiatives	Training programs for healthcare providers	Improves early detection and patient outcomes

the rarity of this condition, the importance of skin manifestations has historically been underappreciated [80]. However, recent clinical findings have revealed that excessive hairiness of the eyebrows, keratotic papules, acanthosis nigricans, 'cobblestone' papillomatous papules of the upper lip, and acral excess skin are common signs. These findings are essential to distinguish Costello syndrome from CFC and Noonan syndrome [80-83]. Moreover, some of these dermatological lesions warrant clinical attention not only for diagnostic purposes but also to improve patients' quality of life and to prevent complications such as tumor development [84].

Lastly, CFC syndrome is a RASopathy characterized by a triad of features: congenital heart defects, distinctive facial traits, and skin abnormalities. These dermatological features are central to its clinical recognition. The most frequent lesions include xerosis and keratosis pilaris—particularly on the arms, legs, and face—along with pigmented nevi and palmoplantar hyperkeratosis [85, 86]. Among the RASopathies, CFC presents the most complex and diverse dermatological profile [87].

8. THERAPEUTIC PERSPECTIVES AND INTERDISCIPLINARY APPROACH

8.1. Biologic Therapies

Biologic therapies aimed at targeting inflammatory pathways are emerging as promising tools to treat chronic inflammatory skin disorders like PS, contextually reducing CV risk (Table **2**).

8.1.1. IL-17 and IL-23 Inhibitors

IL-17 and IL-23 inhibitors, such as secukinumab and guselkumab, respectively, have been proven to effectively reduce systemic inflammation and to improve psoriatic skin lesions [88]. Furthermore, results from the *Canakinumab Anti-Inflammatory Thrombosis Outcome Study* (CANTOS) showed that targeting inflammatory pathways, such as IL-1β, is effective in reducing CV risk and the rate of recurrent CV events in patients predisposed to CVD [89, 90]. However, results from this trial are controversial, and further studies are needed to address the long-term safety and efficiency of these drugs. Collectively, these data support the effectiveness of this class of drugs on both dermatological and cardiac disorders.

8.1.2. TNF-α Inhibitors

TNF-α inhibitors, such as infliximab and adalimumab, have shown dual benefits by alleviating severe dermatological symptoms and improving endothelial function, thereby mitigating CV risk [91, 92]. Their use in psoriatic arthritis and HS highlights their systemic benefits across specialties [93-96].

8.2. Traditional Systemic Treatments

Even though new innovative therapeutic options are starting to emerge, traditional treatments like methotrexate and corticosteroids still remain essential to manage most of the inflammatory dermatological diseases.

8.2.1. Methotrexate

Methotrexate is a folate agent largely used for PS and psoriatic arthritis. Its effect in lowering systemic inflammation and circulating levels of CRP, on top of its dermatological effect, may lead to CV protection [97-99].

8.2.2. Corticosteroids

Even though this class of drugs is very effective for acute flares, precaution has to be taken in the use of systemic corticosteroids due to their association with hypertension, dyslipidemia, and increased CV risk [100-103].

8.3. Cardiovascular Effect of Dermatological Treatments

In addition to the aforementioned ones, dermatological treatments like retinoids or JAK inhibitors also influence CV risk in dermatological patients.

Retinoids are derivatives of retinoid (vitamin A) that explicit their function by binding retinoid acid receptors (RARs) and retinoid X receptors (RXRs). The binding of RAR/RXR with its ligand allows the transcription/repression of genes involved in cell homeostasis [104-105]. Retinoids are particularly effective in treating acne and PS due to their ability to regulate keratinocyte homeostasis and turnover, their anti-inflammatory effects, and their ability to reduce sebaceous gland size and secretion [106-107]. Retinoids, in particular, all-trans retinoic acid (ATRA), are generally beneficial for the CV system. In particular, the use of ATRA *in vivo* has been shown to reduce vascular smooth muscle cell proliferation and migration by inhibiting metalloproteases, to increase NO production from endothelial cells, and to prevent heart failure by inhibiting the renin-angiotensin pathway [108-110]. Nevertheless, oral retinoid treatments, such as isotretinoin and acitretin, lead to dyslipidemia by increasing triglyceride levels and reducing high-density lipoprotein levels. Although the molecular mechanisms at the base of retinoid-induced dyslipidemia are unknown, these changes are dose-dependent and usually reversible [111-113].

JAK inhibitors are a class of drugs that interfere with the pro-inflammatory JAK-STAT pathway, which is dysregulated in several chronic inflammatory and autoimmune skin disorders, including AD, PS, and vitiligo [114, 115]. Although very promising, the use of JAK inhibitors has raised concerns regarding their side effects on the CV system. Clinical trials on rheumatoid arthritis found a notable increase in MACE, deep vein thrombosis, and pulmonary embolism in patients treated with the JAK inhibitor tofacitinib compared with the TNF-α inhibitor-treated group [116, 117]. However, short-term trials on specific dermatological use of JAK inhibitors have shown no increase in MACE, deep vein thrombosis, and pulmonary embolism [118]. As in the case of retinoids, JAK inhibitors have been associated with transient dyslipidemia [119].

8.4. Cardiovascular Risk Reduction

8.4.1. Lipid-lowering Agents

Statins are the first-line drugs to combat dyslipidemia and to reduce CV risk. PCSK9 inhibitors such as alirocumab and evolocumab are emerging as potential therapeutic approaches for patients with refractory dyslipidemia or familial hypercholesterolemia [120-122]. Recently, another therapeutic approach based on increasing high-density lipoprotein cholesterol levels rather than reducing low-density lipoprotein levels has been proposed. For this reason, CETP inhibitors - such as evacetrapib, dalcetrapib, and torcetrapib – have been developed, with no or scarce results in terms of CV risk reduction [123, 124]. In terms of dermatological side effects, tolerability and safety tests showed no collateral events for dalcetrapib, while evacetrapib seems to cause skin rash and itching [125, 126].

8.4.2. Blood Pressure Control

ACE inhibitors and angiotensin-receptor blockers (ARBs) are classes of drugs that aim to reduce blood pressure. On top of their main effect, ACE inhibitors and ARBs have been proven to improve endothelial function and systemic inflammation, thus opening the path for their use to counteract CV risk in patients with inflammatory skin disorders [127-129].

8.4.3. Colchicine

Colchicine is a well-known anti-inflammatory agent that has recently been recognized for its potential CV benefits beyond traditional indications. In this regard, the landmark *Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease* trial (LoDoCo2) demonstrated a significant reduction in MACE in patients with stable CAD primarily through its ability to suppress vascular inflammation [130-131].

In the context of inflammatory dermatological conditions, colchicine holds promise as a therapeutic agent targeting systemic inflammation—a key shared mechanism underlying both cardiovascular and dermatological diseases. By modulating neutrophil activation and reducing pro-inflammatory cytokine production, colchicine may mitigate the chronic low-grade inflammation implicated in atherosclerosis, as well as in conditions like PS, HS, and vasculitis [132, 133].

8.4.4. Anticoagulation and Thrombotic Risk Management

Patients undergoing treatments for autoimmune and inflammatory disorders have an increased risk of thrombotic events due to hypercoagulability. Although very effective, anticoagulants and anti-thrombotic drugs are characterized by an elevated risk of adverse skin reactions, such as warfarin-induced necrosis and heparin-induced thrombocytopenia. New classes of direct oral anticoagulants (DOACs) like apixaban and rivaroxaban have been proven to be a safer option compared to warfarin for long-term anticoagulant administration therapies [134, 135].

9. CUTANEOUS MANIFESTATIONS OF CARDIOVASCULAR DRUGS

CVD treatments are essential for improving patient outcomes. Nevertheless, most CVD treatments display dermatological side effects that range from mild and reversible to severe and life-threatening ones. These side effects can drastically reduce the compliance of the patients with the therapy. The most used treatments for CVD and their dermatological side effects are listed in Table **3**.

9.1. Clinical Implications

The management of cutaneous side effects derived from the use of CV drugs is essential for the success of the treatment. At the same time, it is important to clearly educate patients on the possible dermatological side effects of these

Table 3. Summary of cutaneous manifestations of CV drugs.

Drug Class	Common Cutaneous Reaction	Severe Reactions	Management
Statins	Rash, eczema-like dermatitis	Steve-Johnson Syndrome/Toxic Epidermal Necrolysis	Discontinuation; systemic therapy for severe cases
Beta-Blockers	Psoriasiform eruptions, alopecia	Lichenoid reactions	Dose adjustment or alternative therapy
Calcium Channel Blockers	Photosensitivity, gingival hyperplasia	Purpura	Symptomatic care; dental management for hyperplasia
Anticoagulants	Ecchymoses, petechiae, injection-site necrosis (EBPM)	Warfarin-induced skin necrosis	Discontinuation; vitamin K or alternative anticoagulant
ACE inhibitors/ARBs	Angioedema	Erythema multiforme	Immediate discontinuation; supportive care
Amiodarone	Photosensitivity, blue-gray discoloration	Severe dermatitis exacerbation	Sun protection; dose reduction
Diuretics	Photosensitivity, hyperpigmentation	Lupus-like syndrome	Symptomatic care; drug substitution

treatments, as awareness allows patients to partially prevent the onset of skin manifestations, ensure better compliance, and fast recognition of early signs of adverse events. As an example, informing patients that statins or amiodarone may cause photosensitivity can prompt them to use preventive measures such as using sunblock or wearing protective clothing [136-138].

9.2. Early Recognition and Management

Dermatological side effects can be a red flag of drug intolerance. In this regard, an immediate identification of warfarin-induced skin necrosis or ACE-inhibitor-driven angioedema can allow a fast change of the therapy, preventing more severe and life-threatening complications [139-141].

An early detection of dermatological side effects of CV drugs would allow an adjustment of the dosage, the substitution of the drugs with equivalent treatments, or the introduction of supportive drugs (*i.e.*, corticosteroids or antihistamines) to mitigate the symptoms. Furthermore, new biotechnological drugs have been developed to manage drug-induced skin reactions. Nevertheless, consultation with a dermatologist remains the most effective strategy to rapidly plan the most suitable and personalized therapy for the patient, especially in cases of severe or atypical reactions.

10. FUTURE DIRECTIONS AND PERSPECTIVES IN TRANSLATIONAL RESEARCH

The intricate interplay between dermatological and CV conditions necessitates a paradigm shift in both basic research and clinical practice, moving toward a translational approach in which different professionals should be involved. As our understanding of shared pathophysiological mechanisms continues to evolve, several promising avenues for future exploration emerge.

10.1. Unveiling Molecular Pathways

High-throughput "omics" technologies (*i.e.*, genomic, transcriptomic, proteomic, and metabolomic) provide valuable tools for the identification of new molecular pathways and predictive biomarkers shared between skin and CV diseases. On top of that, it is essential to deepen our knowledge of the function and regulation of the already-known pathways that bridge dermatological and DV conditions. For instance, research into the NF-κB signaling axes offers insights into the regulation of chronic inflammation and immune dysregulation [142, 143]. Additionally, understanding the role of inflammasomes, particularly the NLRP3 inflammasome, in linking PS to CV dysfunction may open the path to the development of alternative therapeutic strategies [144-146].

10.2. Biomarker Development

As mentioned above, *omics* techniques can allow the identification of new biomarkers, which may drastically improve the diagnosis and stratification of CV risk in patients with dermatological disorders. As an example, emerging evidence suggests a pivotal role of small non-coding RNAs miR-146 and miR-21 in systemic inflammation and may act as biomarkers to predict both PS severity and CV risk [147-150]. Furthermore, it has been proven that IL-17 and TNF-α levels on psoriatic lesions positively correlate with endothelial dysfunction and subclinical atherosclerosis [20, 151, 152].

10.3. Longitudinal Studies

Long-term cohort studies are indispensable for clarifying the causal relationship between dermatological conditions and CV events. For example, the tracking of subclinical atherosclerosis progression in patients with severe PS or Lupus could yield insights into temporal dynamics and therapeutic opportunities [153, 154].

CONCLUSIONS

In conclusion, the intricate relationship between dermatological disorders and CVD underscores the necessity of an interdisciplinary approach to patient care.

Dermatological manifestations of CV disorders are useful red flags that provide clinicians with a non-invasive indi-

cation of the CV conditions of the patient, speeding up the diagnosis and the start of the treatment. The strong association between dermatological manifestations and increased CV risk may serve as an early biomarker to identify asymptomatic or high-risk individuals for subclinical or yet undiagnosed CV diseases, allowing the utilization of preventive treatments to mitigate this risk.

This evidence also points out the importance of incorporating dermatological evaluation into cardiovascular checkups as a complementary, non-invasive screening tool. Such an integrated approach could improve early identification of subclinical disease and enhance the accuracy of cardiovascular risk stratification, particularly in patients with chronic inflammatory skin disorders.

Shared pathophysiological mechanisms- including chronic inflammation, oxidative stress, and endothelial dysfunction - illustrate the complex biological pathways that link the skin and CV systems. This recognition has led to the development of innovative therapeutic strategies aimed at addressing both dermatological and CV conditions simultaneously. Nevertheless, most of the knots of this intricated interconnected network are still largely unknown. For this reason, further research aimed at identifying new biomarkers and therapeutic targets is needed. Furthermore, collaborative efforts between dermatologists, cardiologists, and basic scientists are paramount in pushing the boundaries of this interdisciplinary field in the way of a translational approach.

By bridging the gap between dermatology and cardiology, in this review, we seek to provide a comprehensive understanding of the interconnections between these systems and their implications for clinical practice.

Looking ahead, dedicated multicenter and multidisciplinary prospective studies are warranted to validate the complex bidirectional relationship between dermatological and cardiovascular diseases. These trials should integrate standardized diagnostic criteria, shared biomarker panels, and harmonized follow-up protocols, fostering effective collaboration between cardiologists and dermatologists. Addressing the ethical and logistical challenges inherent to such interdisciplinary designs will be essential to translate mechanistic insights into meaningful clinical advances.

STUDY LIMITATIONS

This narrative review was conceived to offer a comprehensive and integrated perspective on the complex interplay between dermatological diseases and cardiovascular conditions, with particular emphasis on cutaneous signs as possible early red flags of cardiovascular risk. However, some limitations should be considered. First, the non-systematic nature of the review may have introduced selection bias. Although we carefully selected the most relevant and recent literature, it is possible that some important or emerging studies were unintentionally excluded. Overall, we attempted to prioritize the selection of articles with strong clinical relevance or translational potential. Furthermore, much of the evidence cited is based on observational or retrospective research, which does not allow for conclusions about causality and may be affected by confounding factors. Considerable variability in diagnostic definitions, population characteristics, and outcome measures across the studies also limits the generalizability of the findings. Although we have discussed several shared biological mechanisms, including chronic inflammation, endothelial dysfunction, and altered autophagy, most of the supporting evidence still comes from experimental data or preclinical models, and translational confirmation in humans remains limited, as does actual relevance to clinical practice.

Finally, despite growing interest in the relationship between skin and cardiovascular health, clinical trials specifically designed to assess this connection are still limited. These considerations highlight the need for further research to confirm the biological links discussed and to guide future clinical applications.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: Writing - reviewing and editing: GS, MEG, MF, VP, ER, LS, MB, LS, SS, LD, DV, VV, SS, EDF, MP, EG, GF, IP and CP; draft manuscript: BS and ED. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AD	=	Atopic dermatitis
ARBs	=	Angiotensin-receptor blockers
ATTRv	=	Abnormal transthyretin amyloidosis
CAD	=	Coronary artery disease
CFC	=	Cardiofaciocutaneous
CRP	=	C-reactive protein
CV	=	Cardiovascular
CVD	=	Cardiovascular disease
DAMPs	=	Damage-associated molecular patterns
DOACs	=	Direct oral anticoagulants
HFpEF	=	Heart failure with preserved ejection fraction
HS	=	Hidradenitis Suppurativa
IL	=	Interleukin
LC	=	Light chain
Lp(a)	=	Lipoprotein (a)
MACE	=	Major Adverse Cardiovascular Events
MI	=	Myocardial infarction
NF-kB	=	Nuclear factor kappa light chain enhancer of activated B cells
NO	=	Nitric oxide
PCOS	=	Polycystic ovary syndrome
PS	=	Psoriasis
ROS	=	Reactive oxygen species
SLE	=	Systemic Lupus Erythematous
Th	=	T-helper

TLRs = Toll-like receptors

TNF-α = Tumor Necrosis Factor alpha

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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CLINICAL IMAGES DISCLAIMER

All clinical images presented in this manuscript are original and were obtained from patients treated at our institution. Informed consent for the use of their images in this publication was obtained from all individuals in accordance with institutional and ethical guidelines.

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