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REVIEW

Inflamed Skin, Burdened Heart: A Multidisciplinary Perspective on Atopic Dermatitis and Cardiovascular Health

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Abstract: The diseases of both skin and cardiovascular are the most significant global medical challenges for their high rates of morbidity and mortality. Although not life-threatening, skin diseases significantly impair patients' quality of life and affect a large proportion of the population due to their chronic and persistent nature. Cardiovascular diseases are characterized by both a widespread prevalence and a high risk of mortality, posing a significant public health burden. As both skin diseases and cardiovascular diseases fall under the umbrella of inflammatory disorders, a degree of pathophysiological connection exists between them. Historically, the potential interplay between these seemingly unrelated conditions was largely overlooked. However, accumulating evidence in recent years has suggested that inflammatory skin diseases—particularly Atopic Dermatitis (AD)—may be associated with an elevated risk of adverse cardiovascular outcomes. This review therefore not only examines the emerging interdisciplinary links between AD and cardiology, but also highlights ongoing controversies, the limitations of current evidence, and outlines future research directions needed to clarify their shared inflammatory pathways and clinical implications.

Keywords: atopic dermatitis, inflammation, skin, cardiovascular, heart

Introduction

Cardiovascular diseases represent a major global health challenge due to their high incidence and substantial mortality. Likewise, skin diseases are highly prevalent worldwide. Despite their lower fatality rates, the lack of objective diagnostic tools necessitates the involvement of experienced dermatologists for accurate diagnosis and effective management. A substantial proportion of both cardiovascular and dermatological diseases are rooted in chronic inflammation. Cardiovascular mortality, in particular, frequently arises from the cumulative burden of various comorbid chronic inflammatory disorders.

The skin, as the largest organ of the human body, contains a wide array of immune cells and plays a crucial role in immunological defense. In inflammatory skin diseases, this immune balance is disrupted, leading to immune dysregulation at the cutaneous level. In conditions such as atopic dermatitis, immune cell infiltration across skin layers has been observed, and such paracrine immune activity may inevitably contribute to systemic inflammatory responses affecting distant organs.[1] Atopic dermatitis represents the most prevalent chronic inflammatory dermatosis, with a protracted clinical course that is commonly divided into three stages: infantile, adolescent, and adult phases. A significant proportion of patients experience persistent symptoms throughout life, with diseases frequently occurring in early infancy. The triphasic classification of atopic dermatitis reflects the markedly different clinical features seen across its

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infantile, pediatric, and adult stages, with the contrast between the pre-adulthood and adulthood being especially notable This clinical heterogeneity necessitates tailored, phase-specific approaches to diagnosis and treatment.[2–5]

Although the precise pathogenesis of atopic dermatitis has yet to be fully elucidated, it is currently regarded as a multifactorial condition. A complex interplay between genetic susceptibility, environmental exposures, immune imbalance, skin barrier impairment, and chronic inflammation contributes to both the onset and progression of the disease. In atopic dermatitis, inflammation is primarily initiated by epidermal barrier disruption, which facilitates the activation of skin-resident immune cells and their interaction with infiltrating Th2 lymphocytes, ultimately contributing to disease development.[6] Notably, persistent low-grade inflammation is a common pathophysiological feature in atherosclerosis and a wide range of cardiovascular disorders.[7]

Recent evidence suggests that Th2-mediated cytokines such as IL-4 and IL-13—central to the pathogenesis of atopic dermatitis—may also play a role in atherosclerosis by promoting endothelial dysfunction and immune cell infiltration into the arterial wall.[8] In addition, chronic dermatitis may predispose to cardiovascular risk via impaired skin barrier function, platelet hyperactivity, and reduced fibrinolysis, suggesting possible mechanistic overlap.[9] One important axis involves the epithelial alarmins IL-33 and TSLP. IL-33, released from multiple tissues including endothelial cells upon injury, and TSLP, produced in both CAD and AD, can shape immune responses across organs. Those make this axis a critical focus when discussing shared inflammatory origins.[10] Beyond single mediators, a broader framework of epithelial barrier dysfunction, type 2 immunity, and microbial dysbiosis has been proposed as a systemic inflammatory foundation underlying multi-organ comorbidities. This perspective situates AD not as an isolated skin disorder but as part of a wider systemic inflammatory state that may contribute to vascular complications.[11] In addition, clinical and translational evidence suggests that vascular inflammation is enhanced in patients with moderate-to-severe AD, and this process correlates with augmented Th2 immune responses. Such findings provide direct bridging evidence that skin-driven type 2 inflammation may extend to the vasculature, supporting the hypothesis of a shared inflammatory substrate.[12]

The growing recognition of inflammation as a central mechanism in numerous diseases has prompted intensified research efforts in recent years. Future studies should aim to further elucidate the inflammatory links between seemingly distinct conditions.[13] Given the chronic nature of cardiovascular diseases and the lifelong inflammatory course of atopic dermatitis, their potential interrelationship deserves heightened attention from the clinical community.[14,15] This review aims to elucidate the connection between atopic dermatitis and cardiovascular diseases by addressing their shared immunoinflammatory features, summarizing current epidemiological evidence, evaluating the potential cardiovascular effects of atopic dermatitis therapies, and providing recommendations for clinical management.

Inflammation in AD and Cardiovascular Disease

Inflammation in AD

In atopic dermatitis, inflammation is primarily orchestrated by inflammatory dendritic cells and activated T lymphocytes. A key component of this process is the differentiation of naïve CD4+ T cells into Th2 cells, which subsequently produce type 2 cytokines that drive disease pathogenesis. These cells secrete a range of cytokines, most notably interleukin (IL)-4, IL-13, and IL-31, which contribute to skin inflammation, barrier dysfunction, and pruritus. Interleukins such as IL-4 and IL-13 promote the activation of B cells and plasma cells, thereby intensifying the inflammatory cascade.[2,6,7] These cytokines also induce pruritus and enhance the production of antigen-specific IgE. Furthermore, they activate downstream signaling pathways, notably the Janus kinase (JAK) pathway, which plays a key role in mediating cytokine signaling in atopic dermatitis.[16–19]

Pruritus represents one of the most burdensome and persistent symptoms of atopic dermatitis. While it is not fatal, its chronicity can severely compromise patients' quality of life. Mechanistically, itch in atopic dermatitis is mediated by various pruritogenic factors secreted by keratinocytes, mast cells, T cells, and eosinophils. Major pruritogenic mediators in atopic dermatitis include Th2 cytokines such as interleukin (IL)-4, IL-13, IL-31, histamine, and thymic stromal lymphopoietin (TSLP). TSLP exerts its immunomodulatory effects by binding to the TSLP receptor (TSLPR) on dendritic cells, leading to their activation and the maturation of antigen-presenting cells.[20,21] Furthermore, TSLP facilitates eosinophil recruitment and amplifies type 2 inflammation by upregulating the expression of IL-4 and IL-13.

These molecules activate itch pathways by binding to their corresponding receptors on keratinocytes, dermal immune cells, and peripheral sensory neurons, ultimately transmitting pruritic signals to the central nervous system.[22]

Beyond the well-established role of Th2 cells, emerging evidence suggests the involvement of additional T helper cell subsets in atopic dermatitis, with distinct patterns observed across ethnicities. In Asian populations, both Th2 and Th17-mediated pathways contribute to disease pathogenesis, while European patients primarily exhibit Th2-dominated inflammation. Conversely, in African populations, Th1 and Th17 responses appear to be less involved.[23,24] While Th2-mediated inflammation remains the hallmark of atopic dermatitis, other T helper subsets have been implicated in modulating disease progression. Th1 cells, in concert with cytokines such as IL-2, IL-12, and interferon-gamma (IFN-γ), are thought to contribute to the chronic phase of inflammation. Moreover, Th17 and Th22 cells play a pathogenic role through the production of IL-17, IL-19, and IL-22. Emerging evidence underscores the significance of these non-canonical T cell subsets in shaping the immunopathology of atopic dermatitis.[25–27]

Inflammation in Cardiovascular System

In recent years, inflammation-induced endothelial senescence has emerged as a critical factor in cardiovascular research. Inflammatory processes impair endothelial function and promote arterial stiffness—two key mechanisms underlying vascular injury. These pathological alterations contribute to the onset of hypertension and atherosclerosis, thereby increasing the risk of various cardiovascular conditions. Currently, endothelial dysfunction is recognized as a hallmark of early vascular aging and is predictive of the development of hypertension and atherosclerosis. Cardiovascular inflammation is typically associated with increased levels of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α), primarily secreted by activated immune cells.[28–32] However, emerging evidence suggests that non-immune cardiac cells, including cardiomyocytes, cardiac fibroblasts, and endothelial cells—also play an active role in propagating inflammation through cytokine production.[33–36]

Myocardial infarction (MI) is a pathological event predominantly triggered by coronary artery occlusion, resulting in ischemia and subsequent myocardial cell death. Acute cardiac inflammation following MI is mediated by innate immune cells, including neutrophils, macrophages, and mast cells, which release a range of pro-inflammatory mediators. Notably, during the first 24 hours post-MI, neutrophils initiate an inflammatory cascade by activating the S100A8/A9–TLR4 axis,[37] leading to the release of interleukin-1β (IL-1β) and stimulation of emergency granulopoiesis, ultimately exacerbating cardiac dysfunction.[38,39] Mast cells exacerbate local cardiac inflammation by releasing histamine, which acts as a potent mediator of immune activation.[39] Meanwhile, macrophages promote the inflammatory response through the production of pro-inflammatory cytokines such as TNF-α and IFN-γ, further contributing to myocardial injury.[40,41] Post-infarction cardiac remodeling is largely driven by the infiltration and sustained activity of immune cells and their secreted mediators. As a result, a growing body of research is exploring therapeutic strategies that target the reduction of immune cell recruitment and activation within the injured myocardium, representing a potential approach to mitigate ischemic cardiac damage and improve long-term cardiac function.

Heart failure is largely attributed to pathological cardiomyocyte hypertrophy and the accumulation of fibrotic tissue. In the context of non-ischemic heart failure, immune cell infiltration and the activity of pro-inflammatory cytokines have been shown to contribute significantly to cardiac dysfunction and remodeling.[42] Dilated cardiomyopathy is characterized by elevated levels of pro-inflammatory cytokines, including IL-1α, IL-2, and IL-6. Experimental studies have shown that treatment of cardiomyocytes with isoproterenol induces upregulation of tumor necrosis factor-alpha (TNF-α), whereas co-treatment with the anti-inflammatory cytokine IL-10 markedly attenuates the expression of these inflammatory mediators.[43] During cardiac remodeling, inflammatory cell infiltration significantly contributes to tissue damage, fibrotic remodeling, and progressive deterioration of cardiac function.

Cardiac inflammation is orchestrated by a multifaceted interplay of immune cells, pro-inflammatory cytokines, and receptor-mediated signaling pathways. The severity of inflammation correlates with the extent of immune cell infiltration within myocardial tissue.[44,45] Inflammatory processes have been implicated in the pathogenesis of various cardiovascular disorders, such as atherosclerosis, hypertrophic cardiomyopathy, and other forms of structural heart disease.[46]

Shared Immune and Inflammatory Pathways Linking Skin and Heart

Inflammatory Pathways in AD

Atopic dermatitis is characterized by a multifaceted pathophysiological landscape, with numerous interconnected upstream and downstream pathways contributing to disease progression. These mechanisms are broadly classified into pruritogenic and pro-inflammatory pathways, both of which involve a wide range of mediators. Despite significant advances in recent years, our current understanding remains incomplete, and additional molecular pathways are actively being explored and validated.[47]

From an inflammatory perspective, a central pathogenic mechanism in atopic dermatitis is the skewing of CD4+ T lymphocytes toward the Th2 phenotype, leading to an excessive Th2 immune response. This is accompanied by elevated secretion of key cytokines such as IL-4, IL-5, and IL-13, which promote inflammation and directly impair epidermal barrier integrity—one of the defining clinical features of the disease.[48] Persistent epidermal damage and inflammatory cell infiltration in atopic dermatitis often led to secondary manifestations such as infection and tissue injury. In response, keratinocytes become activated and secrete key pro-inflammatory cytokines, including TSLP, IL-25, and IL-33. These epithelial-derived cytokines further enhance the Th2-driven immune response, thereby perpetuating the inflammatory cycle. IL-33 and TSLP further potentiate the production of IL-4, IL-5, and IL-13, reinforcing the Th2-skewed inflammatory environment. This establishes a self-sustaining positive feedback loop that perpetuates chronic inflammation in atopic dermatitis.[49] As atopic dermatitis transitions into its chronic phase, there is a notable shift in the immune profile marked by increased activity of Th1, Th17, and Th22 cell subsets. The pro-inflammatory cytokines secreted by these cells—previously considered peripheral to disease pathogenesis—have gained considerable attention in recent years. These emerging pathways are now recognized as potential contributors to chronic disease persistence and severity.[25,27]

Beyond the inflammatory damage to the skin barrier, pruritus constitutes a defining and distressing symptom of atopic dermatitis. While it may not significantly restrict daily physical activity, its persistent and often severe nature substantially compromises patients' quality of life, leading to sleep disturbances, psychological distress, and social impairment. Despite ongoing research, the exact pathophysiological mechanisms of pruritus remain elusive. It is widely accepted that itch is primarily mediated by sensory neurons located in the dorsal root ganglia, which relay pruritic stimuli to the central nervous system, ultimately eliciting the scratching response as a behavioral reflex.[50–53] A hallmark of pruritus in atopic dermatitis is the involvement of IL-31, a Th2-derived cytokine that has emerged as a central mediator of itch. IL-31 is considered one of the most disease-specific pruritogenic factors, linking type 2 inflammation with sensory neuronal activation.[53] In addition to IL-31, both IL-4 and IL-13 have been shown to exert pruritogenic effects in atopic dermatitis and are also critically involved in disease pathogenesis.[50] TSLP, released by keratinocytes, is another important itch-inducing cytokine. Scratching-induced damage to the skin barrier leads to further injury of keratinocytes, which in turn triggers the release of additional inflammatory mediators and promotes ongoing Th2 cell activation. These cytokines act on sensory neurons, perpetuating the itch-scratch cycle and establishing a self-reinforcing inflammatory loop[52,54] (Figure 1).

Inflammatory Pathways in Cardiovascular System

In contrast to keratinocytes—which are pivotal in mediating inflammatory and immunological responses in atopic dermatitis—endothelial cells serve as the primary targets and regulators in the cardiovascular system. Chronic inflammation, immune dysregulation, and senescence-related changes impair endothelial function, ultimately resulting in vascular damage and contributing to the pathogenesis of a broad spectrum of cardiovascular diseases.[55] T cells are among the most extensively studied immune cells in cardiac inflammation, highlighting a striking parallel with the immunopathogenesis of atopic dermatitis, in which T cells also play a central role.[56,57] Notably, emerging evidence has demonstrated that activated T cells in atopic dermatitis are capable of penetrating the epidermal barrier and entering systemic circulation, suggesting a potential immunological link between cutaneous and cardiovascular inflammation.[1]

Age-related changes in immune function significantly influence T cell behavior. In older adults, activated CD4+ T cells tend to acquire a Th17-skewed pro-inflammatory phenotype, which is closely associated with mitochondrial dysfunction and defective autophagy. Conversely, CD4+ T cells from younger individuals exhibit preserved mitochondrial function and autophagic capacity, contributing to a more regulated immune response. Th17 polarization has been

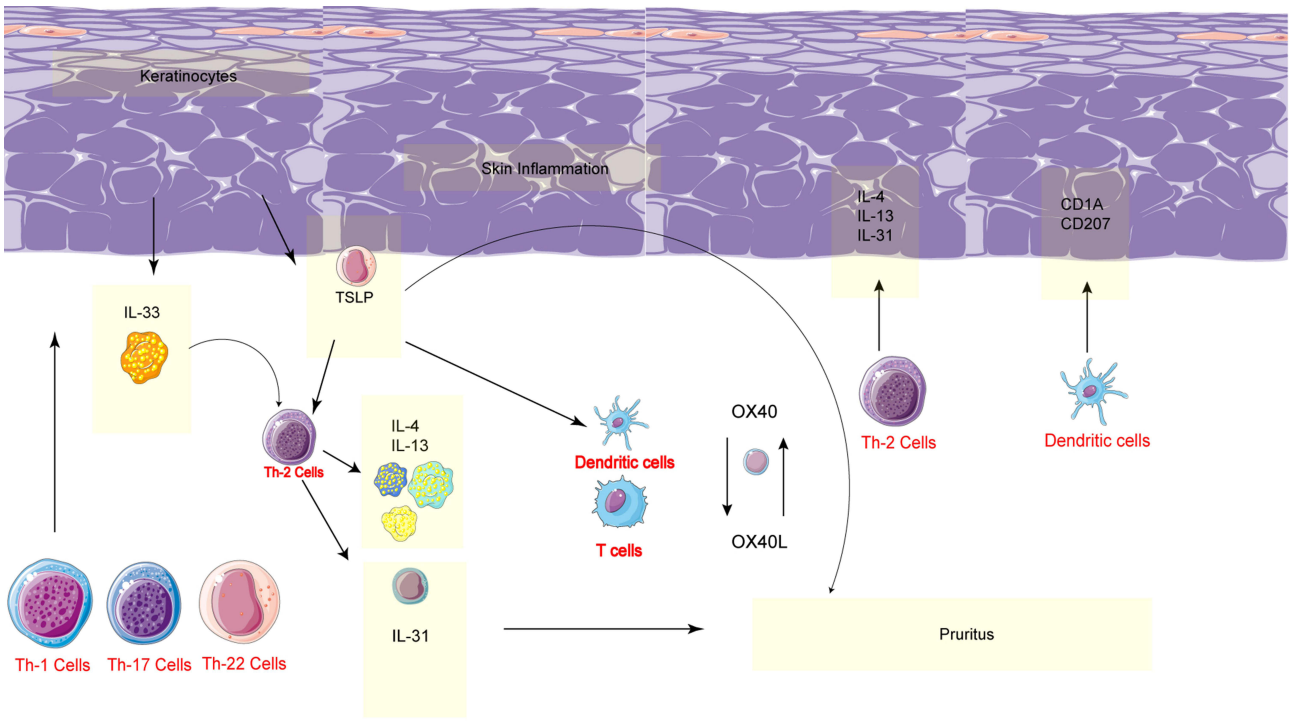

Figure 1 Key inflammatory and pruritic pathways in atopic dermatitis. Keratinocytes release IL-33 and TSLP, as indicated by the arrows pointing toward dendritic cells and Th2 cells. These mediators activate dendritic cells and promote the differentiation of Th2 cells. Th2 cells, in turn, secrete IL-4, IL-13, and IL-31 (arrows from Th2 cells), which drive skin inflammation and pruritus. The arrows from IL-31 and TSLP highlight their action on neurons, triggering itch. Additionally, the bidirectional arrows between OX40 and OX40L emphasize their role in enhancing Th2 responses, thereby establishing a self-amplifying inflammatory loop.

linked to impaired mitochondrial energy metabolism and altered oxidative stress responses. However, current evidence remains limited, and further validation in patient-derived studies is still needed.[58] Experimental studies have demonstrated that adoptive transfer of senescence-like CD4+ T cells into immunodeficient NSG-DR1 mice leads to enhanced cardiac inflammation and fibrosis. This is accompanied by increased activation of inflammatory signaling cascades, most notably the IL-17 pathway. These findings highlight the emerging role of immunosenescent T cells in cardiovascular pathology and suggest that immune-mediated mechanisms may become a critical focus in the future investigation of cardiac inflammation and tissue remodeling.[59] The inflammatory landscape of myocardial infarction is characterized by a biphasic response, with an initial surge of pro-inflammatory cytokines followed by the delayed induction of anti-inflammatory and reparative mediators. By day seven following myocardial infarction, an increased infiltration of CD4+ and CD8+ T cells have been observed in cardiac tissue. Among the CD4+ T cell population, Th1 and Th17 subsets are particularly involved in driving post-infarction cardiac inflammation.[60] This temporal shift is essential for effective tissue remodeling and recovery.[61,62] For instance, a significant post-MI increase in CD45+ leukocyte infiltration has been observed, underscoring the coordinated immune involvement in both injury and repair processes.[60]

IL-6 has been identified as a key inflammatory cytokine in both dermatological and cardiovascular disorders. In atopic dermatitis, its levels rise significantly during the acute phase, serving as a biomarker of disease activity. In the cardiovascular setting, IL-6 has long been recognized for its involvement in ischemia-induced myocardial inflammation, where it contributes to tissue damage and adverse remodeling. The prominent role of IL-6 in both conditions underscores its potential as a shared therapeutic target across inflammatory diseases.[63] IL-6 has emerged as a predictive biomarker for recurrent heart failure, as elevated levels have been consistently associated with acute ischemic events.[64,65] Increased serum IL-6 concentrations are also correlated with endothelial dysfunction, reflecting its role in vascular injury.[30] In elderly patients, chronic inflammation–driven elevations in IL-6 have been identified as a major contributor to morbidity and mortality.[66] Therapeutic strategies targeting IL-6 have shown efficacy in alleviating vascular inflammation and preserving vascular integrity.[67] The consistent elevation of IL-6 in various cardiovascular conditions suggests that this

Table 1 Comparative Inflammatory Mechanisms in Atopic Dermatitis and Cardiovascular Diseases

Disease	System	Immune Cells	Tissue Target	Pathophysiological Outcome	Key Factors
Atopic Dermatitis	Immune Axis	CD4+ T cells (Th2), eosinophils, mast cells	Skin (epidermis)	Inflammation, skin barrier dysfunction	Th2 (IL-4, IL-5, IL-13)
	Pruritogenic	Keratinocytes, sensory neurons	Epidermis-nerve junction	Chronic pruritus, itch-scratch cycle	IL-31, TSLP, IL-33
Cardiovascular	Endothelial Inflammation	Endothelial cells, macrophages	Vascular endothelium	Endothelial dysfunction, atherosclerosis	IL-6, IL-1β, TNF-α;
	Immune Cell Infiltration	Neutrophils, macrophages, CD8+ T cells	Ischemic myocardium	Acute inflammation, ischemic injury	Th1/Th17 (CD4+, CD8+), IL-6, IL-17;
	Post-MI Remodeling	CD4+ T cells (Th1/Th17), fibroblasts	Heart muscle (post-infarct)	Fibrosis, cardiac remodeling	Th1, Th17, CD45+ leukocytes

cytokine may play a central role in disease progression. As such, its mechanistic contributions to cardiovascular pathology warrant further exploration, both as a biomarker and as a potential therapeutic target (Table 1) (Figure 2).

While atopic dermatitis and cardiovascular disease each exhibit complex and partly distinct inflammatory landscapes, a key unresolved question is whether these immune pathways act as shared drivers of both conditions or represent parallel phenomena occurring independently within different tissues. For example, Th2-skewed inflammation and IL-33/TSLP signaling dominate in AD, whereas endothelial dysfunction and Th17/IL-17 responses are prominent in cardiovascular disease. The convergence around mediators such as IL-6, which is consistently elevated in both disorders, raises the possibility of a common mechanistic link. However, much of the current evidence remains associative, and it is equally plausible that skin-driven inflammation and vascular inflammation progress in parallel but distinct trajectories. Clarifying whether these represent shared root causes or coincidental inflammatory patterns will be crucial for determining the extent to which therapies can be integrated across dermatological and cardiovascular domains.

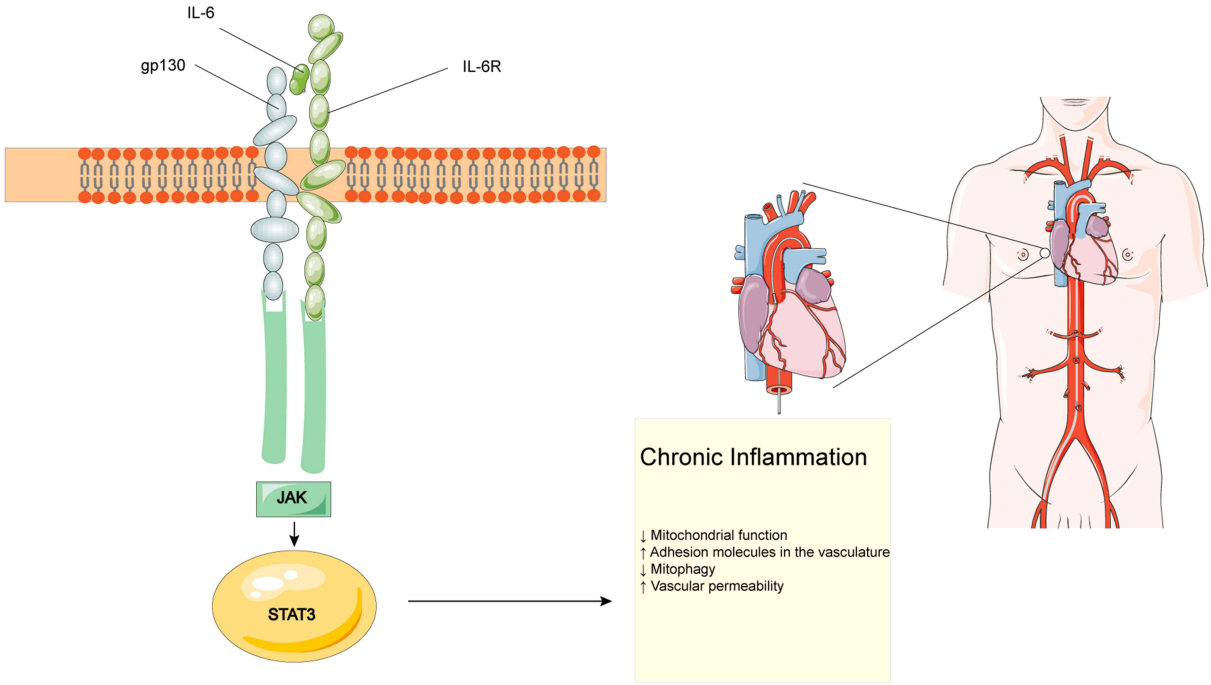

Figure 2 IL-6/IL-6R signaling and its role in chronic cardiovascular inflammation. Interleukin-6 (IL-6) binds to its receptor (IL-6R) and the co-receptor gp130, as shown by the arrows indicating receptor engagement, which activates the JAK/STAT3 signaling pathway (arrow pointing downward to STAT3). In the cardiovascular system, the arrow from STAT3 points toward chronic inflammation, highlighting its downstream effects. As illustrated by the arrows: ↓ mitochondrial function and ↓ mitophagy (downward arrows), and ↑ adhesion molecule expression and ↑ vascular permeability (upward arrows), these changes collectively represent hallmarks of endothelial dysfunction and vascular injury.

Cardiovascular Implications of Systemic Therapies for Skin Diseases

In the past, the therapeutic management of atopic dermatitis was largely confined to symptomatic treatments, such as topical corticosteroids and antihistamines. While these agents provide temporary relief, their efficacy in achieving long-term disease remission has been limited, underscoring the unmet need for more targeted and effective therapies. With the growing elucidation of the immunological mechanisms underlying atopic dermatitis, treatment strategies have evolved beyond symptomatic control into a new era of targeted immunomodulation. The development of therapies that specifically inhibit critical disease-driving pathways—such as type 2 cytokines—has led to markedly enhanced therapeutic efficacy, surpassing that of conventional topical agents.[3,6,7] Despite the substantial therapeutic advances in atopic dermatitis, it is essential for dermatologists to consider the potential implications of treatment in the context of systemic comorbidities. Cardiovascular disease, as a leading global health burden, warrants particular attention in this regard. A more integrated clinical approach is needed to ensure that the management of atopic dermatitis does not overlook or exacerbate coexisting cardiovascular risks in the future.

Biologic treatment strategies for atopic dermatitis are currently divided into systemic and topical modalities. Dupilumab, which targets the interleukin-4 receptor alpha (IL-4Rα) and inhibits both IL-4 and IL-13 signaling, remains the cornerstone of systemic therapy.[2] In recent years, additional biologics targeting specific cytokines such as IL-13 (eg, Tralokinumab) and IL-31 (eg, Nemolizumab) have been developed and approved. For topical therapy, JAK inhibitors have emerged as a key therapeutic class, enabling targeted suppression of downstream inflammatory signaling at the site of disease.[68] Among these agents, Dupilumab was the first biologic approved for the treatment of atopic dermatitis and remains the most well-established in terms of clinical efficacy (Table 2).

Many of the currently approved targeted therapies for atopic dermatitis exert downstream effects on IL-6 signaling, either directly or indirectly. Considering the established role of IL-6 as a major pro-inflammatory mediator in both atopic dermatitis and cardiovascular diseases, it is reasonable to hypothesize that these therapies may offer ancillary cardiovascular benefits, at least from the standpoint of systemic IL-6 modulation. However, this potential remains to be substantiated by dedicated clinical studies.[69,70]

Although research on inflammation in cardiology has increased in recent years, the clinical application of biologic agents in this field remains limited. One of the few biologics currently in use is evolocumab, a monoclonal antibody targeting proprotein convertase subtilisin/kexin type 9 (PCSK9).[71] By inhibiting the interaction between PCSK9 and low-density lipoprotein receptors (LDLR), evolocumab increases the number of LDLRs available to clear circulating low-density lipoprotein cholesterol (LDL-C), thereby significantly reducing LDL-C levels.[72,73] Administered subcutaneously, this biologic has been shown to lower the risk of various cardiovascular diseases and is particularly effective in the management of hyperlipidemia.[74]

While biologic agents have not yet been widely adopted in clinical cardiology, the growing awareness of inflammation role in cardiovascular pathology has brought renewed interest in the anti-inflammatory effects of conventional pharmacologic treatments.[75] Drugs originally developed for lipid-lowering or antihypertensive purposes are increasingly being re-evaluated for their immunomodulatory potential, indicating a broader therapeutic relevance within inflammation-driven cardiovascular disease. Emerging evidence indicates that many conventional cardiovascular drugs possess previously underappreciated anti-inflammatory properties. For instance, enalapril, a widely used angiotensin-converting enzyme (ACE) inhibitor, has demonstrated anti-inflammatory effects in experimental mouse models by attenuating the recruitment and secretion of inflammatory cells.[76] Simvastatin has been shown to reduce cardiac inflammation, improve left ventricular ejection fraction, decrease left ventricular mass, and attenuate T cell–mediated fibrosis. These cardioprotective effects are thought to be mediated, at least in part, by an increase in circulating levels of the anti-inflammatory cytokine interleukin-10 (IL-10), thereby alleviating cardiac stress.[77] Azithromycin has also been found to reduce cardiac inflammation and attenuate adverse cardiac remodeling following myocardial infarction in murine models.[78] At present, most studies investigating the anti-inflammatory effects of cardiovascular drugs remain limited to murine models. Further research involving human subjects is essential to validate the clinical relevance and therapeutic feasibility of these findings (Table 3).

Taken together, the therapeutic landscapes of atopic dermatitis and cardiovascular disease illustrate a growing convergence around inflammation as a shared pathogenic driver. In AD, biologics such as dupilumab, tralokinumab, and

Table 2 Summary of Targeted Therapies for Atopic Dermatitis

Drug Name	Target	Approved By	Age Group	Key Feature	Targeted Pathway	Potential Cardiovascular Relevance
Dupilumab	IL-4Ra	FDA / EMA	≥6 months	First approved biology for AD	Type 2 inflammation	May improve endothelial function and reduce vascular inflammation
Tralokinumab	IL-13	FDA / EMA	≥12 years	Systemic IL-13 blockades	Type 2 inflammation	Blockade may indirectly lower vascular risk
Lebrikizumab	IL-13	FDA / EMA	≥12 years	Newer IL-13 targeted therapy	Type 2 inflammation	
Nemolizumab	IL-31	FDA	≥12–13 years	Anti-pruritic cytokine target	Pruritus pathway	IL-31 associated with systemic inflammation; potential indirect CVD relevance
Telazorlimab	OX40			Phase 2b only, systemic OX40 blockade	T cell co-stimulation	
Rocatinlimab	OX40			Late-phase OX40 inhibition	T cell co-stimulation	
Amlitelimab	OX40L			Targeting OX40 ligand	T cell co-stimulation	
Abrocitinib	JAK1	FDA / EMA	≥12 years	Oral JAK1 inhibitor	JAK-STAT signaling	JAK/STAT implicated in both skin and vascular inflammation; possible dual benefit in AD and CVD
Upadacitinib	JAK1	FDA / EMA	≥12 years	Selective JAK1 inhibitor	JAK-STAT signaling	
Baricitinib	JAK1/JAK2	EMA	≥2 years	Dual JAK1/2 inhibitor	JAK-STAT signaling	
Ruxolitinib	JAK1/JAK2	FDA	≥12 years	Topical JAK inhibitor	JAK-STAT signaling	
Tapinarof	Aryl hydrocarbon	FDA	≥2 years	Topical immune modulator	Aryl hydrocarbon receptor pathway	
Roflumilast	Phosphodiesterase 4	FDA	≥6 years	Topical PDE4 inhibitor	PDE4-cAMP pathway	PDE4 inhibition shown to reduce systemic inflammation; potential cardiovascular protective effects

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Table 3 Summary of Anti-Inflammatory Mechanisms and Evidence for Cardiovascular Therapeutics

Drug	Class	Anti-Inflammatory Effect	Evidence Source	Potential Relevance to AD
Enalapril	ACE Inhibitor	Reduces inflammatory cell recruitment and secretion	Murine model	May attenuate Th2-driven vascular inflammation; indirect relevance via reduced systemic inflammation
Simvastatin	Statin (lipid-lowering)	Reduces cardiac inflammation, improves LV function, decreases LV mass, reduces T cell–mediated fibrosis	Murine model	Shown to modulate IL-10 and T cell responses, pathways also implicated in chronic AD inflammation
Azithromycin	Macrolide antibiotic	Reduces cardiac inflammation, limits post-MI remodeling	Murine model	
Evolocumab	PCSK9 Inhibitor (Monoclonal Antibody)	Lowers LDL-C, reduces cardiovascular disease risk	Human clinical studies	Mainly lipid-lowering, but systemic reduction in inflammation could intersect with AD-related cardiovascular risk

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nemolizumab, as well as topical JAK inhibitors, achieve their efficacy through targeted suppression of type 2 inflammation and downstream mediators, including indirect effects on IL-6 signaling. Given the pivotal role of IL-6 in both cutaneous and cardiovascular pathology, these therapies may theoretically confer ancillary cardiovascular benefits, although this hypothesis awaits confirmation in clinical studies. Conversely, in cardiology, agents such as PCSK9 inhibitors and conventional drugs including ACE inhibitors, statins, and even certain antibiotics have demonstrated immunomodulatory and anti-inflammatory properties, reducing vascular and myocardial inflammation beyond their primary indications. These reciprocal findings underscore a potential overlap in therapeutic strategies, suggesting that interventions developed for one disease area may hold translational value for the other. More importantly, they reinforce the view that AD and CVD should not be managed in isolation, but rather within an integrated framework that recognizes their common inflammatory underpinnings and the need for cross-disciplinary approaches in both research and clinical care.

Clinical Perspectives: Risk Stratification and Multidisciplinary Management

While the immunological connections between atopic dermatitis and cardiovascular diseases have been discussed extensively, their clinical correlation remains poorly defined. Both disorders are common, chronic, and associated with substantial morbidity, yet the intersection between dermatologic and cardiovascular care has been largely overlooked. In recent years, a growing number of studies have explored the relationship between atopic dermatitis and cardiovascular disease risk. While the overall volume of research remains modest, the emerging evidence has raised important concerns and highlights the need for heightened awareness and further investigation into this potentially overlooked comorbidity.[79]

A previous study utilizing data from the Korean National Health Insurance Service investigated the potential association between atopic dermatitis (AD) and cardiovascular disease risk in comparison to healthy controls. Based on data collected from 2005 to 2016, the study revealed that patients with AD exhibited significantly higher risks for several cardiovascular conditions, including hyperlipidemia (hazard ratio [HR] = 33.02, $p < 0.001$), hypertension (HR = 4.86, $p < 0.001$), myocardial infarction (HR = 9.43, $p < 0.001$), angina (HR = 5.99, $p < 0.001$), and peripheral vascular disease (HR = 2.46, $p < 0.001$).[80] A Mendelian randomization study investigating the potential causal relationship between atopic dermatitis and cardiovascular diseases was also conducted using European population data. Interestingly, the findings did not support a significant association between AD and cardiovascular outcomes, suggesting that shared genetic predisposition may not fully explain the observed epidemiological correlations.[81] An analysis based on the National Health and Nutrition Examination Survey (NHANES) revealed a significant association between atopic dermatitis (AD) and myocardial infarction (MI). However, this association was no longer statistically significant after adjusting for traditional cardiovascular risk factors, suggesting that the observed relationship may be mediated or confounded by shared risk profiles.[82] In addition to myocardial infarction, earlier epidemiological studies have identified a significant positive correlation between atopic dermatitis and angina. These findings add to the growing body of evidence suggesting that chronic systemic inflammation in AD may contribute to certain cardiovascular manifestations, even if not uniformly across all endpoints.[83,84]

Although existing evidence on the association between atopic dermatitis (AD) and cardiovascular diseases occasionally presents conflicting results, the overall body of research increasingly supports the potential existence of a meaningful link. Given the growing number of studies suggesting an elevated cardiovascular risk in patients with AD, there is a compelling need for future prospective clinical trials to further validate this hypothesis and clarify the nature and directionality of the relationship.

In summary, the emerging evidence suggests that atopic dermatitis and cardiovascular disease may share overlapping inflammatory pathways, with mediators such as IL-6, IL-33, and TSLP providing plausible mechanistic links between cutaneous and vascular inflammation. Therapeutic insights further reinforce this connection, as targeted biologics for AD and conventional cardiovascular agents both exhibit immunomodulatory properties that may transcend their primary indications (Figure 3). Nonetheless, the epidemiological findings remain inconsistent, with some studies reporting strong associations between AD and adverse cardiovascular outcomes, while others find no significant causal relationship after adjusting for cofounders.

From an epidemiological perspective, however, findings remain inconsistent. Some large population-based studies, such as analyses from the Korean National Health Insurance Service, have demonstrated significantly increased risks of

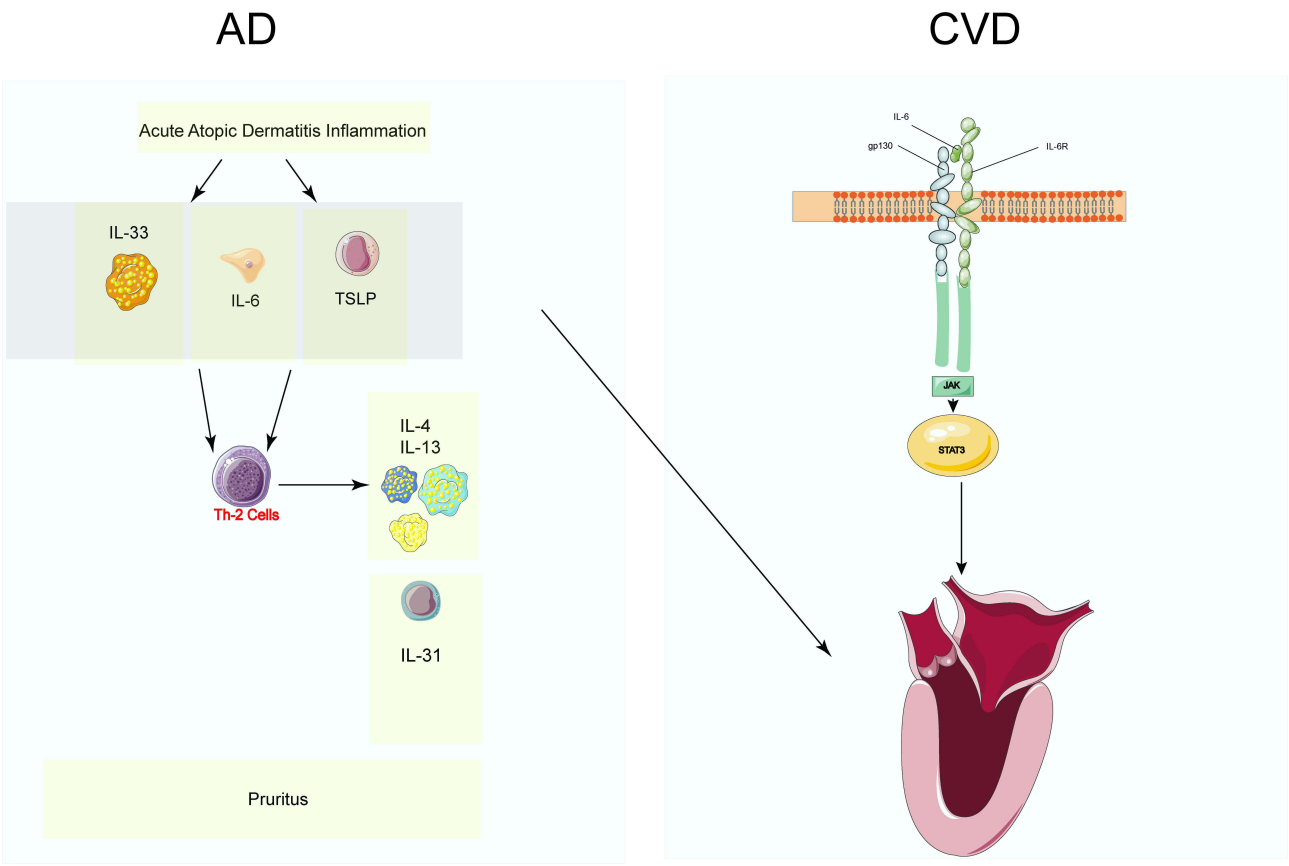

Figure 3 Shared inflammatory pathways between atopic dermatitis (AD) and cardiovascular disease (CVD). In AD, cytokines such as IL-33, IL-6, and TSLP activate Th2 cells, leading to secretion of IL-4, IL-13, and IL-31, which drive skin inflammation and pruritus. IL-6 links AD to CVD by activating the IL-6R/gp130–JAK/STAT3 pathway in vascular cells, contributing to cardiovascular inflammation. Arrows indicate signaling directions and increased cytokine activity.

hypertension, myocardial infarction, angina, and peripheral vascular disease among patients with AD, while Mendelian randomization studies in European cohorts have failed to confirm a causal relationship. Data from NHANES similarly indicate an association with myocardial infarction that disappears after adjustment for traditional cardiovascular risk factors. These discrepancies may be explained by confounding variables (eg, obesity, metabolic syndrome, smoking), differences in population characteristics, and variation in AD severity, all of which influence cardiovascular outcomes. Taken together, these observations highlight a substantial potential for a meaningful clinical link, but also underscore the need for well-designed, prospective clinical trials to clarify causality, delineate shared mechanisms, and ultimately inform integrated strategies for cardiovascular risk stratification and multidisciplinary management in patients with AD.

Conclusion

Atopic dermatitis (AD) is increasingly recognized as a condition potentially associated with cardiovascular disease, with accumulating evidence pointing to overlaps in immunopathogenesis and inflammatory signaling pathways (eg, IL-6, IL-33, and TSLP). Therapeutic insights further support this link, as targeted biologics for AD and conventional cardiovascular agents both demonstrate immunomodulatory effects that may transcend their primary indications. From an epidemiological standpoint, although findings remain mixed, several large-scale cohort studies and meta-analyses indicate a modestly increased cardiovascular risk among patients with AD. Taken together, these three lines of evidence—mechanistic, therapeutic, and epidemiological—suggest that AD may represent more than a coincidental comorbidity. Importantly, clinicians should consider routine screening of AD patients for cardiovascular risk factors as part of integrated care. Nevertheless, the causal relationship has not yet been definitively established, and well-designed prospective clinical trials are urgently needed to clarify the extent of this association and to guide tailored interventions for this patient population.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas, took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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