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REVIEW

Cardiovascular Disease-Associated Skin Conditions

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Abstract: According to data from the American Heart Association and the World Health Organization, cardiovascular disease (CVD) is the most frequent cause of premature death. Several inflammatory and non-inflammatory skin diseases have been associated with metabolic syndrome and cardiovascular risk (CVR). Here, we classified these conditions into traditionally CVR-associated and those that have been linked to a lesser degree. Psoriasis and hidradenitis suppurativa are commonly associated with CVD, sharing common inflammatory pathways and a higher prevalence of traditional cardiovascular risk factors. Many other diseases could be associated indirectly – with no common pathogenic features with the atheromatous disease – but share a higher prevalence of standard cardiovascular risk and chronic inflammatory state. This review aims to highlight the associated cardiovascular risk that exists for some dermatologic diseases and sensitize cardiologists, dermatologists, and first care providers to implement risk factor control promptly.

Keywords: skin diseases, cardiovascular risk, cardiovascular disease, atheromatosis

Introduction

According to data from the American Heart Association and World Health Organization, cardiovascular disease (CVD) is the most frequent cause of premature death. Incidence and prevalence are rising.[1] Traditional risk factors such as increased systolic pressure, low HDL cholesterol, diabetes, and smoking are used to calculate the 10-year risk for cardiovascular events (CVE) with specially designed scales. Also, non-traditional risk factors have been proven to predict CVE even when they are not included in those specific scales like Carotid intima-media Thickness (cIMT) and homocysteine levels[2] Several inflammatory and non-inflammatory skin diseases have been associated with metabolic syndrome, and some of this traditional or non-traditional cardiovascular-risk (CVR) factors.[3–5] Historically, psoriasis has been the most studied and accepted condition with increased CVR prompting dedicated study and active recommendations from dermatologists to patients to prevent CVE.[6] Hidradenitis suppurativa and atopic dermatitis have also been linked to CVE; nevertheless, many other inflammatory and non-inflammatory diseases are also directly or indirectly associated with CVR in terms of its etiopathogenesis. Herein, we present a comprehensive and concise description of prevalent skin diseases associated, to different degrees, with a higher CVR, pointing out shared features with atheromatosis. If these pathophysiological similarities are taken into account, better prevention strategies can be planned. We classified skin diseases into those with evidence of common pathogenic features with CVD – namely directly related diseases – and those that have increased traditional cardiovascular risk factors and chronic inflammation, named indirectly related diseases (Table 1).

Traditionally CVD-Associated Skin Diseases

These diseases have been thoroughly studied and related to increased CVR, and the condition shares pathophysiological mechanisms with CVD.

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Table 1 Broad Characteristics of Skin Diseases According to Cardiovascular Risk Association

	Common Pathogenic Features	Cardiovascular Risk Factors	Non-Specific Inflammation
Traditionally CVD-associated diseases	Demonstrated or widely accepted	Increased or more prevalent traditional or non-traditional cardiovascular risk factors, Framingham Score or European Score demonstrated high	Widely accepted chronic inflammation as a part of the pathogenic process
Emergent CVD-associated diseases	None or poorly studied	Increased in one or more traditional or non-traditional cardiovascular risk factors	Chronic inflammation described as a part of the pathogenic process

Psoriasis

Psoriasis is a chronic systemic inflammatory disorder that can present with or without articular involvement during its course.[7] Recently, psoriasis has been frequently associated with several inflammatory and non-inflammatory comorbidities. CVE and diabetes mellitus 2 are the top causes of mortality in these patients.[8] The relationship between CVR and psoriasis is linked mainly through a higher prevalence of traditional CVR factors like obesity and diabetes.[9] Since poorly controlled diabetes favors flares-up of psoriasis, both conditions have been proposed to have a common pathway of immune-mediated features.[6] Activation of 3 specific pathways has been associated with this matter through the pro-inflammatory role of the adipose tissue.[10] Both psoriasis and psoriatic arthritis are linked to CVR and CVE through three main elements: a chronic inflammatory state that stimulates atheroma plaque formation,[11] typical serum and local activated pathways,[6] and increased traditional and non-traditional CVR factors, all explained below.[12]

Psoriasis and psoriatic arthritis are directly related to CVR.[13] Besides unspecific chronic inflammation, the axis IL-12/Th1 and IL-23/Th17 have been described as part of common immunological mechanisms leading to skin and endovascular plaque formation.[12] A decrease in peripheric regulatory T lymphocytes allows proliferation and activation of Th1 and Th17 lymphocytes with higher endovascular activity promoting pro-angiogenic and innate immune cell recruiting to the plaque.[10] It has been shown that patients with carotid atherosclerosis have higher serum levels of IL-23 than healthy controls. Also, carotid plaques of surgically treated patients showed higher IL-23 and IL-23R mRNA levels than control group.[14] The plaque is mainly formed because of the active participation of monocytes and macrophages, which are crucial to its development and expansion.[15] Monocytes are recruited to the plaque and then differentiate to foam cells phagocyting oxidated LDL cholesterol and producing cytokines and chemokines that favor changes in the microenvironment leading to the matrix and neo-intima formation.[16] Circulating inflammatory monocytes (called M1) have been shown to correlate with CVE;[17] moreover, M1 are active cells producing IL-23 suggesting that an M1-predominating setting could raise circulating IL-23 levels.[18] Traditional CVR factors like obesity, hypertension, and diabetes are also markedly prevalent in psoriatic patients and grow in severity with the disease.[10] Obese patients have a chronic low-grade inflammatory state that favors the production of pro-inflammatory peptides.[19]

Interestingly, higher serum levels of IL-23 and IL-12 in obese patients have been reported, supporting shared pathogenic processes.[20] Adipokines are a particular mediator that participates both in the skin and articular involvement of the disease and in metabolic dysregulation, including insulin resistance and non-alcoholic fatty liver disease.[21] Arterial hypertension has been reported with odds ratios (OR) of 1.58,[9] with psoriatic patients being almost 20 times more likely to use three or more anti-hypertensive drugs than non-psoriatic patients.[22] Finally, there is a higher risk of diabetes and insulin resistance, and psoriatic patients are more prone to use antidiabetic drugs.[9] It has been postulated that the difficulty in achieving well-controlled diabetes is related to immunological effects of Th1 and Th17-produced cytokines.[23]

With the advent of biological drugs, there is a new dimension to take into account regarding CVR in psoriasis.[24] Briefly, anti-TNFα agents seem to exert a positive effect on CVR as observed in relation to reduction in risk of myocardial infarction when compared to topical treatment[25] or to methotrexate[26] whereas the effect of anti-IL17 and anti-IL12/23 drugs is less clear. The CVD effects anti-IL-17 drugs are controversial because the latter can exert pro or anti-atherogenic effects

depending on the cellular, tissue, and immune context.[27] Nonetheless, there are new findings showing secukinumab might have a beneficial impact on CVR by improving the endothelial function of patients with psoriasis,[28] which contrasts with a cohort study that shows a higher risk of CVE in psoriatic patients that initiate an anti-IL-17 versus an anti-TNF drug.[29] More studies are warranted on this subject. The effect of anti-IL12/23 drugs is unclear, although it seems to be that there is a significant association between initiation of ustekinumab and the occurrence of a severe CVE in patients with high CV risk. No association was found in low CV risk patients.[30] In a cohort study, there was a significantly higher CVE risk in patients initiating an anti IL-12/23 versus an anti-TNF drug,[29] however, larger studies and studies aimed to explain the pathophysiologic mechanisms of this increased risk are needed.

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic suppurative inflammatory skin disease affecting apocrine gland-bearing intertriginous areas. Its prevalence varies widely between 0.03% and 8% depending mainly on the classification methodology used[31,32] Crohn's disease and spondylarthritis have a higher prevalence of HS; therefore, metabolic features associated with these diseases are also shared with HS.[33]

Many cardiac parameters underlying CVE have been found altered in HS patients: Heart rate and QRS duration are higher and shorter, respectively, features commonly found in CVE patients. These variables also correlate directly with cIMT values, which also are increased.[34] IL-32 levels are higher both in serum and lesions of HS patients. IL-32 is found to be higher in tissue after myocardial infarction, and its serum levels are inversely correlated with the prognosis of cardiac failure after CVE.[35] Interestingly, IL-32 is not a traditional inflammatory cytokine but an angiogenic stimulator and metalloproteinase activator, which are essential pathogenic features of atheromatous plaque growth.[36]

The influence of the metabolic state in progression and response to treatment in HS patients is widely accepted.[37] Diabetes, a coronary risk equivalent of CVD, has been strongly associated with HS, with an OR of 1.69 for diabetes mellitus 2.[38] Systematically analyzed CVR factors in HS patients found that obesity and central obesity had a significant association with HS and active and non-active smoking, hypertriglyceridemia, low HDL, diabetes, and metabolic syndrome.[39] Even when the odds ratio ranged from 2 to 6, causality could not be assessed.[39] In another study, carotid intima-media thickness (cIMT), and accepted non-traditional CVR factor and marker of early atheromatosis, has been studied in HS patients. When analyzed versus age and sex-matched healthy controls, HS patients had significantly higher cIMT suggesting a more active atheromatous disease versus controls.[40] The analysis of almost 6000 patients was able to demonstrate that HS patients had an Incidence Risk Ratio (IRR) of 1.57 for myocardial infarction adjusted for modifiable and non-modifiable risk factors.[37] HS has been associated with a higher incidence of spondylarthritis, inflammatory bowel disease (IBD), and psoriasis, diseases previously associated with increased CVR due to a higher incidence of CVR factors and systemic inflammation.[41] In a small study, using Assessment of SpondyloArthritis international Society (ASAS) criteria, an OR of 11 for spondyloarthritis was found, being axial the most prevalent form.[33] In 2019, in a meta-analysis of 8 studies, a higher prevalence of IBD with OR ranging from 2 to 10 was found, showing a well-founded association between both conditions.[41] Spondylarthritis and IBD have been associated with CVR, supporting the relation between HS and CVR in the presence of companion diseases already associated with CVE.[42]

Emergent CVD-Associated Skin Diseases

In this section, diseases that have been recently related to CVD are presented. These conditions share a plausible common pathophysiologic mechanism with CVD but lack the acumen of knowledge that the former conditions have.

Rosacea

Rosacea is an inflammatory disease affecting 5% to 6% of the population.[43] It is characterized by chronic erythema, papules, pustules, telangiectasia, affecting mainly centrofacial and ocular areas.[44] Its etiopathogenesis is complex with a broad interplay of influences, including immune, vascular and infectious, plus environmental factors such as UV light and alcohol consumption.[45] Many comorbidities have been associated with rosacea, including a higher incidence of CVE.[46] There is no consensus about whether this relation is actual comorbidity or just the coexistence between two prevalent diseases.[46]

A possible explanation for those who advocate that rosacea has higher CVR is that pro-atherogenic vascular changes and inflammatory pathways are coincidental at some points.[47] Vascular endothelial growth factor (VEGF) has been associated with inflammation and vascular permeability. In rosacea, the prevalence of a specific +405C/G polymorphism of VEGF is increased by 1.7-fold.[48] This same polymorphism has been described in systemic inflammatory conditions widely associated with higher CVR like rheumatoid arthritis.[49] Moreover, higher VEGF levels have been found when metabolic risk factors like high body mass index (BMI) and smoking are present.[48] When Framingham Risk Score (FRS) or European CVR (SCORE) are applied to rosacea, no risk increase was found even when systolic blood pressure (SBP) and reactive C Protein (CRP) show higher levels in this group of patients.[50]

In the formation of the atheromatous plaque, macrophages and monocytes are essential and participate actively in the expansion of the plaque and cytokine microenvironment.[51] Cathelicidins are innate immune cell-produced proteins that participate as defensins in response to infections.[52] These peptides are overexpressed in rosacea lesions versus healthy skin in the same subject.[44] Moreover, atheromatous plaque-infiltrating macrophages also overexpressed this protein, suggesting that they could be part of the same pathogenic process.[53] Also, since *D.folliculorum* and *S.aureus* are well-known agents in rosacea etiopathogenesis, their relation with LL-37 (cathelicidin microbial peptide) and kallikrein-5 production support a common inflammatory dysregulation process.[54] As macrophages and their M1 phenotype are important in atheromatous plaque growth, their behavior in rosacea lesions could be the next step in the analysis. Recent studies show that in rosacea mouse model LL-37 cathelicidin-stimulated lesions, overexpress Desintegrin Metalloprotease ADAM-Like Decysin-1 (ADAMDEC1) protein which is also overexpressed in a culture of M1 macrophages suggesting a possible common response in both tissues.[55]

Cutaneous Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) is a skin-limited form of systemic lupus (SLE). SLE is a chronic inflammatory disease with a complex physiopathology including genetic predisposition, environmental elements such as UV light and trauma, and exposure to medications and hormones.[56] These factors, or some of them, interacting in a susceptible patient, can trigger an autoimmune response involving B and T lymphocytes and target-tissue damage.[57] CLE can occur in conjunction with SLE or independently, evolving as a unique disease without secondary tissue damage. In SLE, CVR is well known and widely accepted as a fundamental cause of morbidity and mortality in these patients.[58] Multiple reasons have been described, including a chronic inflammatory state associated with disease flare-ups, higher prevalence of traditional CVR factors, and treatment-associated complications.[59] CLE patients have a Hazard ratio (HR) of 1.31 for CVE versus general population;[60] in other studies, no significant differences have been found in CVE of any kind between CLE and control subjects.[61] CLE forms that are usually associated with SLE are more prone to show CVR features and better correlated with CVE in large studies.[61]

Metabolic syndrome features are increased in CLE patients, and its prevalence is two times higher in these patients.[62] In some case-control studies, active smoking has an increased rate among CLE patients.[60]

Many elements that are part of the plaque growing process like monocyte-recruiting, neointimal formation, and extracellular matrix production are linked with pathogenic changes observed in CLE lesions and the atheromatous process.[51] In CLE biopsies, a CXCL10 overexpression has been found, which leads to T cell recruitment and higher levels of Interferon-α (IFN-α) and Tumor Necrosis Factor α (TNF-α).[63] Some of the effects of these local and systemic cytokines are endothelial permeability and prothrombotic changes, characteristic and necessary features of atheromatosis.[51] Since monocytes are important in the expansion and microenvironment of the atheromatous plaque, changes in phenotype and recruiting could be an essential link between CLE and CVR.[64]

Atopic Dermatitis

Atopic Dermatitis (AD) is a chronic inflammatory skin disease more prevalent in children. Nevertheless, the prevalence in adults has been reported to be 5% to 15%.[65] In all-cause mortality association studies, AD patients have a higher CVR risk than the healthy population.[66]

Obesity, diabetes, and smoking habit are the most frequent CVR factors associated with AD.[67] It has been demonstrated that AD patients have an OR of 1.85 for obesity and 1.13 for diabetes. Also, as described before, arterial

hypertension is more prevalent in the adult AD population.[68] In 2018, a systematic review and meta-analysis of 19 studies, including case-control and cohort studies, showed that myocardial infarction and other CVE are significantly higher in AD patients.[66] Subsequent studies showed that mainly obesity and diabetes are associated with AD diagnosis.[67]

Early studies showed that AD patients had higher levels of platelet activation peptides than healthy subjects,[69] which relates to the inflammatory nature of the disease. In these studies, β-tromboglobulin, platelet factor 4, platelet-derived microparticles, and p-selectin were found to be increased in plasma of atopic patients; however, this relative "procoagulant" state never showed correlation with clinical findings.[69,70] In newer studies, AD has been associated with autoimmune diseases like IBD, which has been associated with CVR due to a systemic inflammatory state.[71] A direct association between an inflammatory condition in AD and atheromatosis cannot be sustained at this point.

Other Emergent CVD-Associated Skin Diseases

Acne

It is the most common skin disease and many times a feature of systemic and metabolic diseases.[72] It can present as primary acne or as a part of adrenal hyperplasia, polycystic ovary syndrome, hyperandrogenism, or insulin resistance.[72] Some of these latter have higher cardiometabolic risk due mainly to progression to diabetes and obesity.[73] Besides traditional CVR factors, the chronic low-grade inflammatory response has been associated with higher CVR.[74]

Xanthelasma Palpebrarum

Xanthelasma palpebrarum (XP) is the most common xanthoma type consisting of yellowish plaque over eyelids. It is formed by phagocytic foam cells that infiltrate perivascular territory invading superficial reticular dermis.[75] A clear correlation between CVR and XP diagnosis does not exist. Most of the studies are dedicated to finding the association between XP and circulating lipids profiles. In a systematic review studying 15 case-control studies gathering 854 patients with the diagnosis of XP, total cholesterol, low-density lipoproteins, ApoB, and cIMT were increased, suggesting higher indirect CVR.[76]

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) is characterized by wheals and angioedema for at least six weeks without an apparent stimulus.[77] CSU shares inflammatory features with metabolic syndrome, arising the idea of common pathogenic elements. Traditional risk factors have been described in a case-control study involving 9798 patients with chronic urticaria, who have 65% more risk of hyperlipemia and 35% more arterial hypertension versus healthy controls.[78] In another study, both in CSU as well as in metabolic syndrome, adipokines are augmented.[79] Adiponectin was decreased, and lipocalin-2 was increased in CSU patients versus control subjects.[80] This imbalance has been associated with a pro-inflammatory and prothrombotic metabolic state in metabolic syndrome and CSU.[81]

Male Androgenetic Alopecia

Male androgenetic alopecia (MAG) is a common type of alopecia affecting men. Its central etiopathogenic feature is an increased sensitivity of the follicle to dihydrotestosterone; however, both inflammatory and environmental factors have contributed.[82] In the last 20 years, several studies have shown a correlation between MAG and CVR.[83] Early on, small case-control studies showed a higher prevalence of traditional and non-traditional CVR factors like obesity, diabetes, low HDL cholesterol, and cIMT.[84] Metabolic syndrome was five times more frequent on MAG patients and the presence of atheromatous plaques was four times more frequent than in control subjects. In a small prospective study, 50% of MAG patients fulfilled the criteria for metabolic syndrome versus 15% in the control group.[84] Possible explanations for these findings are related to testosterone levels and metabolic changes associated with these increased levels.[85]

Calciphylaxis

This is a life-threatening condition characterized by calcification of microvessels in the subcutaneous tissue and dermis. It presents preferably in end-stage renal disease patients with a poor prognosis and life expectancy of about one year.[86]

Given this noticeably short survival, long-standing outcomes as cardiometabolic complications are challenging to assess.[87] Through an indirect connection, calciphylaxis has inflammatory features stimulated by the deposit of calcium hydroxyapatite in between muscular cells, triggering local inflammatory and deregulatory responses.[88] This dysregulation could interact with diseases like diabetes which facilitate activation of transcriptional factor Runt-related transcription factor 2 (RUNX2), leading to calcium deposit in muscular and intimal vascular layers, with subsequent endothelial disfunction and local thrombosis.[89]

Seborrheic Dermatitis

Seborrheic Dermatitis (SD) is a chronic inflammatory disease characterized by desquamative inflammatory lesions with frequent recurrences and remissions.[90] As an inflammatory disease, it has been associated with metabolic disturbances. Obese and metabolic-dysregulated patients have a higher prevalence of SD between their comorbidities.[91] Also, SD patients had significantly lower HDL levels and a higher rate of relatives with arterial hypertension, suggesting a relation between both diseases sustained by a higher prevalence of CVR.[92]

Vitiligo

Vitiligo is a depigmenting autoimmune disease. Recent studies suggest a subset of vitiligo patients, those with more chronic and severe diseases, are at higher risk of developing dyslipidemia and atherosclerosis, with the potential increase of CVR.[93,94] Interestingly, the use of narrowband UVB phototherapy treatment correlated with a significant decrease in CV and cerebrovascular events.[95] Also, simvastatin, a statin drug, has been tried as a vitiligo treatment, showing beneficial effects, attributed to its antioxidant and immunomodulating effect.[96] Despite these findings, further studies are needed.

Discussion

Many inflammatory conditions are associated with CVR. In autoimmune diseases like rheumatoid arthritis, spondylarthritis, and psoriatic arthritis, this is the first cause of mortality and morbidity. Among physio-pathological explanations are chronic inflammation, higher prevalence of traditional CVR factors, and specific pathogenic features that participate in the disease and the atheromatous process. It is uncommon for dermatologists to assess and treat CVR factors in their patients. Many skin diseases have localized involvement and do not affect other organs or tissues. Maybe the most emblematic case is psoriasis, where cardiovascular mortality has been well documented and widely accepted as an important consequence of the disease. Here, we presented skin conditions highlighting those traditionally associated with CVD and mentioning possible elements in other emerging diseases in which CVR could rise. Some disorders seem to directly relate to their pathogenic processes and the atheromatous plaque formation that is measurable both in plasma and tissue. These include common pathway activation and inflammatory cytokine overexpression, higher prevalence of traditional CVR factors, and systemic chronic inflammatory state. Other emerging and less studied skin conditions sometimes show epidemiological analysis positively correlating with CVD, in which, beyond chronic inflammation, there is no other molecular plasma or tissue link between skin disease and atheromatosis. Some systemic skin diseases are susceptible to the metabolic state like psoriasis and hidradenitis suppurativa; cardiovascular risk is higher and associated with the inflammatory condition of the disease. In these cases, it is essential to pursue remission as a target to cardiovascular risk reduction, but also traditional risk factors must also be assessed thoroughly. In other diseases, where the association is linked mainly by local or systemic inflammatory state, exhaustive treatment strategies must be implemented; moreover, when the presence of the skin disease is expected to be for life. This low-grade inflammatory state has been frequently related to the atheromatosis process, primarily associated with chronic systemic inflammatory diseases and altered metabolic states. Still, we cannot forget that dermatologic inflammatory conditions are sometimes locally detected but systemic and chronic and need to be treated as a part of the integral management of our patients.

Conclusions

Re acknowledging traditional and emerging related skin diseases should prompt dermatologists, cardiologists, and primary care providers to include and manage modifiable risk factors, with particular consideration in these patients. It

Table 2 CVD-Associated Skin Diseases

Skin Disease	Common Features	Cardiovascular Risk Factors	Non-Specific Inflammation	Management Key Points	References
Psoriasis	IL-23/Th17 pathway, M1 monocyte phenotype	Especially important*	Especially important	Disease treatment, avoid flares-up, treat, and assess cardiovascular risk, achieve remission	[7–30]
Hidradenitis Suppurativa	IL-32, Neo-angiogenesis	Especially important	Important	Disease treatment, avoid flares-up, treat, and assess cardiovascular risk, achieve remission	[31–42]
Cutaneous Lupus	INFα, TNFα and Th1 Lymphocytes, M1 monocyte phenotype	Especially important	Important[#]	Assess and treat cardiovascular risk factors, continuously assess for SLE	[56–64]
Rosacea	ADAMDEC1 (1 study)	Especially important	Mildly important[°]	Assess and treat cardiovascular risk factors	[43–55]
Atopic Dermatitis	b-thromboglobulin, platelet factor 4 (1 study)	Mildly important	Important	Control inflammatory state, assess and treat cardiovascular risk factors	[65–71]
Acne	Non-specific features	Important	Important	Assess and treat cardiovascular risk factors, control infection and inflammatory state	[72–74]
Xantelasma Palpebrarum	High total cholesterol and ApoB (1 study)	Especially important	Non-Important	Assess and treat cardiovascular risk factors, especially lipid profile	[75,76]
Chronic Spontaneous Urticaria	Non-specific features	Mildly important	Important	Assess and treat cardiovascular risk factors, control inflammatory state	[77–81]
Male Androgenetic alopecia	Non-specific features	Especially important	Non-Important[&]	Assess and treat cardiovascular risk factors	[82–85]
Calciphylaxis	Non-specific features	Important	Especially important	Assess and treat cardiovascular risk factors, control inflammatory state	[86–89]
Seborrheic Dermatitis	Non-specific features	Important	Mildly important	Assess and treat cardiovascular risk factors	[90–92]
Vitiligo	Non-specific features	Important	Mildly important	Assess and treat cardiovascular risk factors	[93–96]

Notes: *Especially important: Referred to a critical aspect of the cardiovascular risk; [#]Important: Referred to an essential element of cardiovascular risk but without enough data available; [°]Mildly important: Some reports are mentioning this point as a possible feature in cardiovascular risk; [&]non-important: there is no data available of this feature in current literature.

is imperative to achieve the best possible control of the related skin conditions in patients with a higher baseline CVR, mainly in those traditionally associated diseases (Table 2). Finally, in skin diseases with a shared molecular mechanism between skin damage and atheromatous process formation, achieving remission of the skin disease could be significant in CVD risk management. More studies are needed, especially on emerging CVD-associated skin diseases, to understand better common pathogenic pathways that could lead to new treatment strategies.

Author Contributions

All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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