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LITERATURE REVIEW
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Psoriasis and Cardiovascular Disease: A Literature Review of Relationships and Causes

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Abstract:

Psoriasis and cardiovascular disease share a complex interrelation mediated by chronic inflammation. Epidemiological data reveal higher cardiovascular risks in psoriasis patients, including diabetes and atherosclerosis. Pathophysiologically, inflammatory cytokines play a pivotal role. Genetic, lifestyle, and psychological factors exacerbate this link. Anti-inflammatory therapies, notably TNF-α inhibitors, demonstrate potential in mitigating cardiovascular risk. However, pharmacotherapy selection necessitates cautious consideration, especially regarding biologic agents' impact on cardiovascular health. Management entails tailored approaches ranging from topical treatments to biologics, adjusted to disease severity and individual response. Understanding this relationship fosters personalized treatment strategies. Further research is imperative for validation and deeper mechanistic insights, enhancing prevention and management paradigms for affected individuals.

Keywords: Psoriasis; Cardiovascular Disease; Skin Inflammation; Atherosclerosis

Introduction

Psoriasis is a chronic, recurrent inflammatory skin disease characterized by hyperproliferation through a faster-than-normal keratinization process.[1] Cardiovascular diseases, on the other hand, are a group of medical conditions that affect the heart and blood vessels, including arteries, veins and capillaries. These conditions include various diseases, such as coronary heart disease, heart failure, coronary artery disease, as well as vascular diseases such as atherosclerosis.[2]

Psoriasis and cardiovascular disease are two medical conditions that, at first glance, may not appear to have a direct relationship. However, this view has changed as recent studies have revealed the link between the two. As a chronic inflammatory skin disease, psoriasis not only affects the physical aspect through its skin symptoms, but can also have serious implications on the health of other organs. Previous discussions regarding the prevalence of psoriasis reaching 1% to 3% of the world's population shows its significant impact on the global society.[1]

Cardiovascular disease is in the spotlight as the leading cause of death worldwide. With the number of deaths from cardiovascular disease reaching more than 17 million in 2005, the increase highlights the need for a deeper understanding of the factors that can exacerbate cardiovascular disease risk.[3] The preceding discussion also provides an overview of how cardiovascular diseases, including heart disease and stroke, have a major impact in the United States and globally, with health costs running into billions of dollars each year.[1,2]

The link between psoriasis and cardiovascular disease is then a major concern. Several studies have shown that psoriasis patients have a higher risk of developing cardiovascular disease compared to the general population.[3] Factors such as the profound psychological impact on psoriasis sufferers, a tendency towards risky behaviors, and intrinsic risks such as high blood lipid levels, are all important considerations in understanding this relationship.[3]

Recognizing the complexity of the relationship between psoriasis and cardiovascular disease, further research is needed to detail the mechanisms underlying this association. This article will detail key findings from current research and delve deeper into how psoriasis may be a risk factor or even a trigger for cardiovascular disease. Understanding this relationship is not only important for providing better care for individuals with psoriasis but also opens the door for more effective prevention strategies against cardiovascular disease in general.

Grand Theory

Epidemiological

The epidemiology of psoriasis has been the focus of research since the early 1970s, with a number of studies confirming a significant association between psoriasis and cardiovascular disease. Involving various research designs, both prospective and large-scale retrospective, a cross-sectional study in 2006 brought 127,706 mild psoriasis sufferers and 3854 severe psoriasis sufferers into the study. The results showed that psoriasis sufferers had a higher *odds ratio* (OR) for developing a number of cardiovascular diseases such as diabetes, hypertension, hyperlipidemia, and obesity compared to the control group. A higher prevalence was also identified in the severe psoriasis group compared to the mild psoriasis group, suggesting that the severity of psoriasis may contribute to the risk of cardiovascular disease.[4] A prospective cohort study involving 130,976 psoriasis patients and 556,995 controls over 5 years showed supportive results. Psoriasis patients in this cohort showed a higher incidence of myocardial infarction attacks compared to the control group, underscoring the correlation between psoriasis and higher cardiovascular risk.[5] A separate UK study involved 3603 severe psoriasis patients and 14,330 healthy control samples. The results showed that there was a 57% increase in mortality from cardiovascular

disease in the severe psoriasis patient group compared to the control group. Using the *Hazard Ratio* as a parameter, the risk of death from cardiovascular comorbidities in patients with severe psoriasis was found to be 1 person per 283 patients per year.[6] These data provide a strong epidemiological foundation to further explore the relationship between psoriasis and cardiovascular disease and detail the factors that may influence the prognosis and management of patients with these two conditions.

Pathophysiologic

The pathophysiology of the association between psoriasis and cardiovascular comorbidities involves a well-documented complexity of inflammatory processes. This process begins when *antigen-presenting cells* (APCs) recognize and capture antigens from the skin of people with psoriasis. *Major histocompatibility complex* (MHC) type II on the surface of the APC then interacts with the antigen, and subsequently, the APC migrates to the lymph node, where a brief interaction with *naive T-cells* via adhesion molecules occurs.[7,8] Upon activation, T cells interact with dendritic cells, macrophages, and keratinocytes, involving also smooth muscle cell binding in the pathogenesis of atherosclerosis. Activated T cells enter the circulatory system, interact with the vascular endothelium, and migrate to the inflammatory skin. Interleukin (IL)-12 and IL-23 play important roles in T cell differentiation and *natural killer* cell activation, and trigger the production of proinflammatory cytokines such as interferon (IFN)-γ, *tumor necrosis factor* (TNF)-α, IL-1, and IL-6.[7,8] The effects of this cytokine production include keratinocyte proliferation, neutrophil migration, potentiation of the Th-1 response, angiogenesis, increased adhesion molecules, and epidermal hyperplasia. These inflammatory cells, if active in an atherosclerotic plaque, can lead to plaque rupture and thrombus formation. In other words, the inflammatory process and increased cytokine cascade by Th-1 is the cause of psoriasis, but it can also cause acute coronary syndrome.[7] It is important to note that in addition to inflammatory factors, genetic risk may also play a role in this relationship, with several gene loci responsible for an increased risk of diabetes and coronary heart disease in psoriasis sufferers. Studies have also highlighted the role of IL-12 and IL-23 in the inflammatory mechanism of psoriasis, where IL-12 induces T cell differentiation, while IL-23 stimulates a subset of T cells (Th17) to produce IL-17, which in turn triggers the production of proinflammatory cytokines from keratinocytes in psoriasis and endothelium in atherosclerosis.[7,8]

Risk Factors

Psoriasis and cardiovascular disease have a complex relationship and understanding the risk factors involved is crucial in designing a holistic approach to prevention and management.

Genetic factors play a significant role, although there is no established genetic association between psoriasis and cardiovascular disease in *Genome-Wide Association Studies* (GWAS). However, elevated homocysteine levels caused by DNA demethylation is a concern with the *methylentetra-hydrofolate reductase polymorphism* identified as a trigger for DNA demethylation and studies suggesting that homocysteine is an independent risk factor in cardiovascular disease.[9]

Lifestyle factors, especially obesity, are identified as key contributors in the development of both diseases. The strong association of high body mass index (BMI) with psoriasis and cardiovascular disease has been supported by robust systematic reviews. Obesity is also associated with metabolic syndrome, which triggers systemic inflammation through several pathological mechanisms, such as abdominal obesity, impaired glucose tolerance, hyper-

triglyceridemia, hypertension, and low HDL cholesterol levels.[10,11]

Psychological factors, particularly stress, have been linked to both diseases through leukocyte catalysis and the release of inflammatory factors. Although initially thought to be a trigger for severe psoriasis *flare-ups*, recent studies have shown a lack of a strong relationship between perceived stress and psoriasis severity.[12]

Social factors, such as smoking, are recognized as strong risk factors for cardiovascular disease and are also involved in the psoriasis disease process. A high prevalence of psoriasis among smokers, even after smoking cessation, as well as a manifold increased risk for severe psoriasis, has been documented.[13,14] Meanwhile, the relationship between alcohol consumption and cardiovascular disease is well established, but complex in the context of psoriasis. Increased alcohol consumption is seen in patients with severe psoriasis, and studies have confirmed an increased risk of cardiovascular disease in this group.[15,16] Taken together, this understanding of risk factors lays the foundation for prevention and holistic management of psoriasis and cardiovascular disease. As further research develops, this understanding may help develop more effective strategies in treating individuals with both conditions.[9]

Immunological Relationships

Inflammation has gained significant attention in the context of cardiovascular disease, particularly in relation to atherosclerosis. Scientific study indicates that long-term inflammation, like the one seen in psoriasis, may have a significant impact on speeding up the development of atherogenesis and raising the likelihood of having heart and vascular disease.[17,18] While traditional risk factors like hypertension and dyslipidemia have been seen in psoriasis patients, there are other cardiovascular concerns that cannot be entirely accounted for by these variables.[19,20]

Upon further investigation, there is an increasing focus on the immunological connection between atherosclerosis and autoimmune illnesses. Psoriasis is regarded as a paradigm for comprehending the involvement of the immune system in cardiometabolic dysfunction.[17,18] Psoriasis not only affects the skin, but also has a notable influence on the whole body, increasing the likelihood of atherosclerosis due to changes in the structure of blood vessels and systemic inflammation.[46] Psoriasis-related chronic inflammation may cause problems with the endothelium, disrupt cholesterol levels, and upset metabolism, all of which increase the risk of cardiovascular complications.[17,18]

In addition to these discoveries, observational studies emphasize the possible beneficial impact of anti-inflammatory treatment in reducing cardiovascular risk in people with psoriasis.[21,22] Biological agents and other therapies have shown correlation with such risk reduction. However, a deeper understanding of the complexity of the relationship between psoriasis and cardiovascular risk requires continued research to identify the specific mechanisms involved.

A better understanding of these interactions may open the door for the development of more sophisticated and focused treatment strategies to protect psoriasis patients from cardiovascular complications. Therefore, there is a need for further research and a holistic approach to integrate this information into relevant clinical practice.[23,24,25,26]

Research Method

Psoriasis is a persistent skin disorder characterized by inflammation, which has been linked to a higher likelihood of developing cardiovascular diseases (CVD). The correlation between psoriasis and cardiovascular disease (CVD) is well proven, with several research emphasizing the link between psoriasis and common

cardiovascular risk factors like hypertension, hyperlipidemia, obesity, and diabetes mellitus. Moreover, psoriasis has been associated with a higher occurrence of cardiovascular risk factors and comorbidities, such as metabolic syndrome, dyslipidemia, and obesity. There is evidence suggesting that psoriasis is a separate risk factor for heart attacks, strokes, and death from heart disease. The severity of psoriasis is linked to a higher chance of experiencing negative cardiovascular events.

The connection between psoriasis and cardiovascular disease (CVD) is based on same immunologic and inflammatory processes that occur in both conditions. Psoriasis is a chronic inflammatory illness that affects the whole body. The ongoing inflammation in psoriasis patients is thought to be directly connected to the development of cardiovascular disease, which is referred to as the "psoriatic march". Furthermore, the persistent inflammation in psoriasis has been linked to the deterioration of vascular health, therefore increasing the susceptibility of persons with psoriasis to cardiovascular disease.

Furthermore, there is epidemiological evidence that supports the connection between psoriasis and cardiovascular disease (CVD). Studies have consistently shown a dose-response relationship between the severity of psoriasis and the likelihood of experiencing negative cardiovascular outcomes, such as all-cause mortality, cardiovascular death, myocardial infarction, stroke, and coronary revascularization. The rising occurrence of cardiovascular risk factors and the distinct correlation between psoriasis and cardiovascular events emphasize the need for thorough evaluation and control of cardiovascular risks in individuals with psoriasis.

The literature review presents compelling data that establishes a strong correlation between psoriasis and cardiovascular disease. The link between psoriasis and cardiovascular disease is complex, including common immunologic and inflammatory mechanisms, along with a greater occurrence of conventional cardiovascular risk factors and comorbidities in persons with psoriasis. Comprehending and dealing with the cardiovascular consequences of psoriasis are essential for the entire treatment of this persistent inflammatory disorder.

Discussion

The management of psoriasis and cardiovascular comorbidities includes various therapies tailored to the severity of the disease. Psoriasis therapy can be divided into several categories such as: topical therapy, phototherapy, systemic therapy, and biological agents.

In the early stages of psoriasis, topical therapies, including the use of corticosteroids, anthracins, tar, vitamin D3 analogs, urea, emollients, and retinoids, are often the main options. Although effective in managing psoriasis symptoms at the skin surface level, topical therapies are usually faced with limitations in addressing the underlying inflammation of psoriasis disease and its potential comorbidities. This factor makes it necessary to pay attention to the selection of additional therapies or changes in treatment approach as the disease progresses. Therefore, comprehensive management of psoriasis at an early stage includes careful evaluation of disease severity and response to topical therapies, while considering additional treatment options to achieve optimal control of inflammation and minimize the risk of psoriasis-related health complications.[1,7]

Several drugs used in the treatment of psoriasis have been the focus of research regarding their potential impact on cardiovascular risk. For example, methotrexate, a systemic agent for psoriasis, was initially thought to be promising in reducing vascular disease, but clinical trial

results, such as in the Cardiovascular Inflammation Reduction Trial (CIRT), showed contradictory findings, necessitating further research.[27,28] Cyclosporine, effective in psoriasis, is associated with increased hypertension, especially in chronic kidney disease, so its use is recommended only for short periods of time, with consideration of replacement after flare-ups improve 24. Acitretin, a compound similar to vitamin A, has a negative effect on the lipid profile.[29-31] Recent studies have examined the impact of tumor necrosis factor inhibitors (TNFi) on decreasing cardiovascular events. The findings from a 5-year study indicate that after 2 years, there was a noteworthy decrease in the risk of such events, with reductions of up to 11%.[32,33] Nevertheless, when comparing TNFi drugs, there were discrepancies in their impact on inflammatory markers and vascular inflammation. This highlights the need for more study to confirm the results and evaluate their efficacy in mitigating the risk of cardiovascular disease.[34-37] While systemic medications like cyclosporine, retinoids, and methotrexate are successful in reducing inflammation in psoriasis, their use comes with the possibility of heightened cardiovascular risk. Cyclosporine and retinoids can trigger hypertension and lipid metabolism disorders, while methotrexate, although beneficial in cardiovascular comorbidities, requires vigilance against the potential to stimulate hyperhomocysteinemia and damage the endothelium.[1,7]

Phototherapy, including NB-UVB (narrow-band ultraviolet B), BB-UVB (broad-band ultraviolet B), PUVA (psoralen ultraviolet A), excimer, and climatotherapy, is an effective alternative for patients with mild psoriasis who do not respond to topical therapy. While offering a solution for some patients, it should be noted that phototherapy is not recommended for pregnant women, nursing mothers, and children, given the potential risks associated with ultraviolet light exposure. After administration of topical therapy or phototherapy, routine side effect evaluation every 2 weeks is an important step to monitor safety and patient response. Patients who respond well to topical therapy, by achieving a PASI of 75, as well as adhering to treatment and not experiencing significant side effects, may continue their topical therapy. However, if the response to topical therapy is less than satisfactory, switching to phototherapy or systemic therapy may be a considered option. In patients receiving phototherapy, evaluation of therapeutic response around 8 weeks after the start of treatment is key. If a good response is achieved, by reaching PASI 75 and the patient remains compliant and does not experience significant side effects, phototherapy can be continued. Conversely, if the response to phototherapy is unsatisfactory, consider seeking alternative systemic therapies. This approach emphasizes the importance of periodic evaluation and adjustment of therapy according to the patient's individual response, providing practical guidance in the management of psoriasis patients with a variety of therapeutic options.[38-42]

Therapy with biologic agents has become the main option in managing moderate to severe psoriasis, especially when conventional systemic therapies cause side effects that can lead to patient non-adherence to treatment. The research demonstrates that biological treatments, including secukinumab, adalimumab, and infliximab, are preferable to traditional systemic medications like methotrexate and cyclosporine due to their superior safety profile.[42,43] While biologic medicines have the potential for enhanced clinical skin results shortly after starting therapy, it is crucial to undertake frequent monitoring to ensure ongoing safety and efficacy of treatment.

Biological therapies are becoming an increasingly emphasized option in the management of psoriasis. They have specific targets, such as T cell inhibitors (efalizumab and alefacept) or TNF-α inhibitors (etanercept, infliximab, and adalimumab).[43] Retrospective cohort studies suggest that the

use of TNF-α inhibitors may potentially reduce cardiovascular risk in psoriasis patients.[40,42,44] For example, the incidence of myocardial infarction in patients receiving TNF-α inhibitors was lower compared to patients receiving other systemic therapies or phototherapy. Biologic therapy promises to be a more specific and effective approach in controlling psoriasis, but still needs to be carefully considered for risks and benefits.[39, 44-47]

On the other hand, the use of steroids in the treatment of psoriasis carries implications for heart disease. Steroids have the potential to cause hypertension through mechanisms that include increased systemic vascular resistance, extracellular volume and cardiac contractility. Similarly, non-steroidal anti-inflammatory drugs also contribute to poor cardiovascular outcomes by causing salt and water retention, exacerbating peripheral vascular resistance, and activating the renin-angiotensin-aldosterone system.[47,48] As the understanding of the cardiovascular impact of different types of therapies increases, careful treatment planning and continuous monitoring are key to providing optimal benefit for patients with psoriasis.

In the cardiovascular health management of psoriasis patients, folate supplementation has been shown to be beneficial when used in conjunction with methotrexate. Folic acid can help prevent hyperhomocysteinemia, which is an increase in blood homocysteine levels above 15 µmol/L. Hyperhomocysteinemia can be induced by methotrexate use. Studies show that the daily intake of folic acid in psoriasis patients receiving methotrexate ranges from 1 mg/day for adults and 300-800 µg/day in children.[38] Folic acid supplementation can reduce plasma total homocysteine levels. Folate has long been used in combination with methotrexate in the management of psoriasis and psoriatic arthritis. Folate can reduce the side effects and toxicity of methotrexate without affecting the effectiveness of therapy.[38]

Conclusions

The association between psoriasis and cardiovascular disease has been the focus of attention in recent decades, with epidemiological studies trying to understand the relationship between these two conditions. Cardiovascular disease, particularly coronary heart disease, is a leading cause of death globally, and risk factors such as high blood pressure, high LDL cholesterol, and smoking have long been recognized as major contributors.

The epidemiology of psoriasis highlights consistent findings from a number of studies, both prospective and retrospective, confirming that psoriasis has associations with a variety of health conditions, including diabetes, hypertension, atherosclerosis, as well as coronary heart disease, myocardial infarction, and stroke. The results of several studies suggest that psoriasis severity can be a significant risk factor, with psoriasis patients tending to have a higher OR for developing cardiovascular disease than control groups.

Pathophysiology outlines the complexity of the inflammatory process involving antigen-presenting cells, T cells, and the production of proinflammatory cytokines. This inflammatory activity is believed to play a role in accelerating atherosclerosis and increasing the risk of developing heart and vascular disease. Risk-causing factors, including genetic, environmental, psychological, and social factors, are all recognized as complex contributors to the link between psoriasis and cardiovascular disease.

In the context of immunology, studies highlight the potential of anti-inflammatory therapies, such as TNF-α inhibitors, in reducing cardiovascular risk in psoriasis patients. Pharmacotherapy, which includes different types of drugs such as cyclosporine, retinoids and methotrexate, warrants careful consideration of their impact on cardiovascular health. Biological therapies,

such as those targeted at T cells or TNF-α, show promise in reducing cardiovascular risk, although more research is needed to validate these findings.

Optimal management includes topical, systemic therapy, phototherapy, and engagement of biological agents, tailored to the severity of the disease. A deeper understanding of the complex relationship between psoriasis and cardiovascular disease paves the way for the development of more sophisticated and personalized treatment strategies in treating individuals with both conditions.

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