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LEADING ARTICLE

Risk of Cardiovascular Disorders in Psoriasis Patients

Current and Future

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Abstract Psoriasis is an inflammatory autoimmune disease that affects the skin. Recently, psoriasis and its consequential lifestyle and dietary habits have been associated with increased risks for cardiovascular diseases. This article discusses the connection between cardiovascular disorders and psoriasis and the effects of available treatment options on cardiovascular risk. A PubMed search revealed 11 articles that were analyzed for information regarding this association, its effects, and potential courses of treatment. Both the presence and severity of psoriasis increases the risk for cardiovascular disorders and co-morbidities. Forty percent of psoriasis patients met metabolic syndrome criteria as compared with 23 % of non-psoriasis control subjects. Rate ratios for atrial fibrillation are correlated with the severity of psoriasis; patients with severe and mild psoriasis produced rate ratios of 1.63 and 1.31, respectively. Studies also show an increase in the risks for myocardial infarction, atherosclerosis, ischemic stroke, and other cardiovascular disorders. The exact mechanisms behind this affiliation are still uncertain; however, the psychological and physiological effects of psoriasis and the overlapping pathogenesis behind atherosclerosis and psoriasis may play a role. Since the risk for cardiovascular disorders increases with the presence and severity of psoriasis, psoriasis treatment should not only address the disease and its symptoms, but also its co-morbidities. Recent National Psoriasis Foundation (NPF) guidelines have provided recommendations for psoriasis patient care. Histories of co-morbidities, screenings for potential diseases, increased exercise, decreased alcohol consumption, and smoking cessation should be implemented. Unfortunately, while there are data for the increased risk for cardiovascular diseases within psoriasis patients, there are presently no data stating that increasing cardiovascular screening rates in patients produces a significant difference.

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1 Introduction

Psoriasis is an autoimmune inflammatory skin disease that forms itchy, red, scaly plaques.

Inflammatory diseases such as psoriasis are connected to cardiovascular disorders [1]. Similar to psoriasis, effector T lymphocytes are pathologically altered in common cardiovascular disorders such as atherosclerosis and metabolic syndrome. This modification of T helper-1 (T_h1) and T helper-17 (T_h17) cytokines produces inflammatory cells responsible for the formation of psoriasis and cardiovascular plaques and also induces other co-morbidities such as impaired endothelial function, hypertension, increased arterial stiffness, atrial fibrillation, and ischemic stroke.

We reviewed key articles to provide a short balanced assessment of the association between psoriasis and cardiovascular co-morbidities.

2 Literature Search Methods

The key phrases 'cardiovascular disease psoriasis,' 'cardiovascular risk psoriasis,' 'psoriasis treatment,' and 'psoriasis ustekinumab' yielded 21,156 results. Based on the quality of the evidence presented, 11 articles were analyzed. This small representative group of articles provided a short, balanced overview of the association between psoriasis and the risk for cardiovascular disorders. Review articles, case reports, cohort studies, and cross-sectional studies comparing patients with mild and/or severe psoriasis with non-psoriasis individuals were included. Seventeen relevant articles found in the references of the original 11 articles were also included. Altogether, these articles provided study populations ranging from 65 to 25,553 psoriasis patients and from 52 to 4,478,926 other individuals. Publication dates extended from 1997 to 2012. Articles concentrating on the effects of psoriatic arthritis rather than psoriasis were excluded to limit results to the direct connection between psoriasis and cardiovascular disease.

Table 1 Evidence for increased risk of cardiovascular disease and Framingham score for psoriasis patients [1, 5, 9, 26]

Evidence for increased risk of cardiovascular disease	Control	Psoriasis	
Prevalence of metabolic syndrome (%)	23	40	
Average body mass index	25.67	27.72	
		Mild	Severe
Rate ratios for ischemic stroke	Reference	1.25	1.69
Rate ratios for atrial fibrillation	Reference	1.31	1.63
Incidence rates per 1,000 observational years for ischemic stroke	3.06	4.54	6.82
Incidence rates per 1,000 observational years for atrial fibrillation	3.03	4.67	5.96
Framingham score calculated for psoriasis patients	Intermediate risk	High risk	
Coronary heart disease (% of patients)	30.5	11.4	

3 Results

3.1 Evidence for Association Between Psoriasis and Cardiovascular Risks

The rates for hypertension, dyslipidemia, diabetes mellitus, smoking, excessive alcohol consumption, obesity, and depressive symptoms are increased for psoriasis patients [2–4]. These co-morbidities predispose patients to an increased risk for other cardiovascular disorders. A study of 2,456 American men and women revealed a higher prevalence of metabolic syndrome for psoriasis subjects as compared with controls; 40 % of psoriasis patients, compared with 23 % of non-psoriasis patients, met metabolic syndrome criteria (Table 1) [5]. Another study of 3,236 psoriasis patients and 2,500 non-psoriasis patients found psoriasis patients with a nearly doubled probability of developing atherosclerosis as compared with non-psoriasis patients [6]. However, a recent study discovered a lack of evidence to support the relationship between increased duration of psoriasis and increased cardiovascular risk [7]. Although a study of 3,471 subjects found no significant difference between the waist circumferences of psoriasis and non-psoriasis patients, the majority of the literature advocates an increased cardiovascular risk in psoriasis patients [8].

Both the presence and severity of psoriasis are linked to the increased risk of ischemic stroke, atrial fibrillation (a predominant cardiac arrhythmia related to stroke), heart failure, and cardiovascular mortality. In a Danish cohort study of 36,765 mild psoriasis patients, 2,793 severe psoriasis patients, and 4,478,926 other individuals, rate ratios for atrial fibrillation and ischemic stroke increased with psoriasis severity. Disregarding age, rate ratios for psoriasis patients with the risk of ischemic stroke ranged from 1.25 (attributable risk [AR] percentage: 20.0 %) to 1.69 (AR: 40.8 %) in mild to severe psoriasis, respectively. As for atrial fibrillation, the rate ratios varied from 1.31 (AR: 23.7 %) to 1.63 (AR: 38.7 %). Furthermore, the incidence rates for atrial fibrillation and ischemic stroke were greater for psoriasis patients as compared with reference patients. Atrial fibrillation incidence rates were reported as 3.03 per 1,000 observational years for reference patients, 4.67 for mild psoriasis patients, and 5.96 for severe psoriasis patients. Similarly, ischemic stroke incidence rates were reported as 3.06, 4.54, and 6.82 per 1,000 observational years for reference patients, mild psoriasis patients, and severe psoriasis patients, respectively [9]. An additional study also compared the relative risk for ischemic stroke through rate ratios and reveals a similar conclusion. Mild psoriasis patients were found with a rate ratio of 1.97, while severe psoriasis patients were found with a rate ratio of 2.80 [10].

The prevalence of other cardiovascular diseases such as ischemic heart disease, cerebrovascular disease, and peripheral vascular disease also increases. The odds ratio of each disease was found to be 1.78 (with a 95 % confidence interval [CI] of 1.51–2.11), 1.70 (95 % CI 1.33–2.17), and 1.98 (95 % CI 1.32–2.82), respectively [6]. The Framingham score, calculating the risk of coronary heart disease

development within the next 10 years, was used in an analysis of 395 patients aged 18–86 years. 344 of these patients had never experienced any previous major cardiovascular events and were monitored. Of these patients, 30.5 % were found with a Framingham score of 10–20 %, indicating an intermediate risk for suffering a major cardiovascular event in the next 10 years, while 11.4 % were found with a score of at least 20 %, indicating a high risk for future cardiovascular disorders [1].

3.2 Possible Mechanisms

The precise mechanisms behind the association between psoriasis and cardiovascular disease are still uncertain; however, there are several possibilities. On a molecular level, the importance of effector T lymphocytes, such as T_h1 and T_h17, to the pathogenesis and development of both psoriasis and atherosclerosis could potentially lead to this affiliation [11–15]. In both atherosclerosis and psoriasis, regulatory T cells that produce significant anti-inflammatory effects are pathologically altered [16, 17]. In psoriasis, these modified T_h1 cells activate keratinocytes that stimulate the production of chemokines, antimicrobial peptides, and inflammatory cytokines such as tumor necrosis factor (TNF)-α [18]. In turn, increased T_h1 cytokines lead to endothelial dysfunction and T-cell removal from vascular compartments to atherosclerosis plaques [12].

Furthermore, the altered increase in T_h17 cells leads to the secretion of cytokines interleukin (IL)-17 and IL-22. In psoriasis, this secretion leads to the activation of keratinocytes and the production of proteins that propagate the inflammatory cycle [18]. These keratinocytes induce the increased secretion of proteins like LL37-cathelicidin that are able to form complexes with self-DNA entering plasmacytoid dendritic cells that will present self-antigens to skin and lymph node T cells [19]. As a result, T-cell activation and proliferation is increased and the skin is once more inflamed. These IL-17 cytokines are also able to stimulate dendritic cell maturation and macrophages that produce more proinflammatory cytokines [20]. As for atherosclerosis, increased T_h17 cells increase IL-17 cytokine receptors on endothelial cells and vascular smooth muscle cells, and consequently, enhance proinflammatory predisposition of arteries [21].

Moreover, endothelial injury caused by the increases in T_h1 and T_h17 cells leads to the release of more proinflammatory cytokines. These cytokines then convert more T cells into the T_h17 phenotypes that are able to move through endothelial cell tight junctions. Within these cells, the T_h17 phenotypes produce more IL-17 that will stimulate local endothelial cells, smooth muscle cells, and macrophages, and subsequently, secrete further chemokines, adhesion molecules, and inflammatory cytokines such as TNF-α. This cycle continuously occurs, increasing local oxidative stress and decreasing plaque stability [22]. The combination of increased inflammation and oxidative stress stimulates and sustains symptoms of atrial fibrillation [23]. The multiple effects of T_h17 cells links the production of IL-17 cytokines to the plaque instability found in atherosclerosis, thus potentially explaining the increased risk for myocardial infarctions (MIs) found in psoriasis patients [22].

The altered levels of folate and homocysteine found in psoriasis patients also propagate atherosclerosis and other atherothrombotic events. The elevated homocysteine levels of psoriasis patients directly relate to disease severity and inversely relate to plasma folate levels [24]. Increased homocysteine levels damage endothelial cells. In turn, clot formation is intensified, flexibility of blood vessels is decreased, aortic stiffness is increased, and blood flow velocity is reduced [25]. As the severity of psoriasis increases, the amount of folate consumed increases as well. This then reduces the breakdown of homocysteine, thus increasing homocysteine levels and stimulating the increased injury to endothelial cells [25].

The psychological and physiological effects of psoriasis may also explain the association between psoriasis and an increased risk for cardiovascular disease [26]. Patients with psoriasis uphold poorer overall nutrition. Rapid Eating Assessment for Patient (REAP) scores are a tool used by primary care providers for evaluating a patient's diet and physical activity [27]. A case-control pilot study of 65 psoriasis and 52 control subjects found psoriasis patients with a REAP score 0.15 less than controls (mean REAP scores for psoriasis and controls were 2.23 and 2.38, respectively) [$r = 0.86$, $p < 0.0001$]. This decrease in REAP scores could then explain the increase in body mass index (BMI) for psoriasis patients. While controls had a BMI average of 25.67, psoriasis patients had an average of 27.72 [26]. This increase in BMI can easily lead to obesity and eventually induce symptoms of metabolic syndrome. Similarly, psoriasis symptoms, including psoriasis plaques, increased fatigue, and increased discomfort, may lead to an impairment of exercise habits prompting obesity and again, an increase in cardiovascular disorders. Psoriasis symptoms may also lead to a sense of embarrassment for one's appearance and result in reduced social interaction, increased depressive symptoms, and generation of other co-morbidities [28].

3.3 Changes in Psoriasis Treatments as well as Dietary/Lifestyle Habits

The effect of psoriasis on the risk for cardiovascular disorders should encourage early diagnosis and treatment for other naturally accompanying diseases [1]. According to

National Psoriasis Foundation (NPF) guidelines, the following recommendations for psoriasis patient care should also be adopted. First, the diagnosis of psoriasis should lead to recommendations for the screening and management of psoriasis co-morbidities. Second, a history of diabetes mellitus, dyslipidemia, and hypertension should be investigated and blood pressure, BMI, and waist circumference should be evaluated every 2 years. Third, risk factors, such as the presence of a family history of diabetes, should lead to the screening of serum lipoproteins, blood glucose, and glycosylated hemoglobin every 2–5 years. Fourth, patients should also be encouraged to stop smoking, to moderate alcohol consumption, and to exercise at least three times a week for at least 30 min [29]. The management of associated risk factors should lead to a decrease in the possibility of obesity, dyslipidemia, and hypertension [24]. Unfortunately, the lack of treatment and/or compliance for the treatment of psoriasis leads to a lack of improvement, and possibly, an increase in psoriasis symptoms. The patients' capacities for physical activity are reduced by psychological hindrances, such as increased embarrassment for their appearance and increased depressive symptoms, leading to a decline in their general quality of life. Obesity and other co-morbidities then recur, and again, the risk for cardiovascular disease increases [4]. Modifications in psoriasis treatments, including early psoriasis co-morbidity screenings, consistent evaluations for potential cardiovascular risks, and successful psoriasis treatment will reduce the risk for cardiovascular diseases.

3.4 Potential Novel Drugs or Therapies

Topical treatments such as corticosteroids and vitamin D analogs are the most common form of treatment for mild psoriasis. For moderate to severe psoriasis, treatments may range from phototherapy and systemic anti-inflammatories to TNF-α inhibitors. A psoralen and UVA (PUVA) treatment cohort study found a 26 % reduction in cardiovascular mortality for patients accepting more than the average number of PUVA treatments. Such results suggest that more assertive psoriasis treatments may improve psoriasis co-morbidities [30]. The alterations in folate and homocysteine levels also suggest a potential benefit in favor of folate supplementation. Folate is effective in reducing gastrointestinal adverse effects as well as liver function test abnormalities in patients taking methotrexate [24]. In addition, other oral medications, such as the immunosuppressant methotrexate, have reduced the prevalence of other co-morbidities. A cohort study of over 7,000 psoriasis patients revealed a reduction in the prevalence of vascular disease for those administered methotrexate. This reduction was further enhanced with the addition of a folic acid supplementation [31]. Methotrexate and TNF-α inhibitors reduce the risk for MIs and other cardiovascular mortalities [6]. However, in observing the effectiveness of varying psoriasis treatments, systemic treatments appeared to reduce MI risk less effectively than phototherapy treatment. A study of 25,554 psoriasis patients included 5,460 patients receiving phototherapy and 21,334 receiving systemic anti-inflammatories. 9,110 of these 21,334 patients received traditional anti-inflammatories and 16,038 received biologics. Results suggest an increase in the possibility of MIs for patients receiving systemic anti-inflammatories as compared with patients receiving phototherapy. The MI incidence per 1,000 person-years for systemic anti-inflammatories and phototherapy was 4.64 (95 % CI 4.02–5.33) and 4.03 (95 % CI 2.93–5.41), respectively [32]. Furthermore, the increase in TNF-α in psoriasis and atherosclerosis indicates the possible success of TNF-α inhibitors such as infliximab, adalimumab, and etanercept. These TNF-α inhibitors have improved the treatment of psoriasis and could potentially advance atherosclerosis treatment due to their ability to normalize endothelial function [33]. However, these agents have adverse effects including formation of anti-drug antibodies and severe infections, which are not uncommon [34].

Newer drugs that target several ILs have recently been introduced for treatment or are under study. Ustekinumab and briakinumab (ABT-874) are human monoclonal antibodies that target the p40 subunit common to both IL-12 and IL-23 [35–37]. By neutralizing these cytokines and blocking their interaction with receptors, these agents inhibit the signaling cascade that triggers differentiation and cytokine production essential to inflammatory diseases [35, 38]. IL-12 and IL-23 are critical in the pathogenesis of psoriasis; IL-12 stimulates T_h1-cell differentiation and the resultant production of interferon and TNF-α while IL-23 activates IL-17 producing T cells or T_h17 cells [39–41]. These agents are efficacious at treating psoriasis, and ustekinumab is now used in practice for resistant psoriasis [37, 42–44]. Apilimod mesylate (STA-5326) is another IL-12/23 inhibitor under development that differs from the abovenamed agents by its mechanism; it is an oral drug that inhibits IL production at a transcriptional level [35]. Ustekinumab and other IL-12/23 inhibitors can increase the risk for major adverse cardiovascular events, including stroke, MI, and cardiovascular death [45, 46]. Adverse event profiles were comparable between ustekinumab and placebo groups in a multicenter, randomized, double-blind, placebo-controlled study of 121 patients with moderate-to-severe psoriasis [47]. Rates of adverse events seen in patients treated with ustekinumab are consistent with rates seen in the general and psoriasis populations [48]. However, one of two recent meta-analyses reported a significant increase in MACEs (major adverse cardiovascular events) in patients receiving IL-23/12 inhibitors, and these agents

should be used with caution in patients with a predisposition for cardiovascular events [49].

IL-17 is another targeted cytokine produced by a variety of cells but mostly T_h17 and γδ T cells [50]. Although not in the market or used in practice, IL-17 inhibitors, including ixekizumab and brodalumab, are under development and study. Ixekizumab is a humanized monoclonal antibody targeting IL-17 whereas brodalumab is a human antibody to IL-receptor antibodies, the receptor that binds IL-17 [34, 51]. Two phase II clinical trials have shown the clinical efficacy of these two agents in the treatment of psoriasis; few adverse events were noted [52, 53]. Another similar agent in phase III development as a potential psoriasis treatment is secukinumab, a fully human monoclonal antibody neutralizing IL-17 [51]. Future trials with larger sample sizes and longer follow-up times are needed to fully elucidate the safety profiles of these drugs and clarify their effects on the cardiovascular system.

4 Discussion

The majority of studies examining the association between psoriasis and cardiovascular disease indicated an increased risk for future cardiovascular complications within psoriasis patients. However, there were a few studies that presented an insignificant difference between psoriasis and non-psoriasis patients in the presence of particular cardiovascular co-morbidities such as obesity [8]. There were also a few other articles that indicated a lack of evidence to suggest a relationship between increased cardiovascular risk and increased duration of psoriasis [7].

The effect of psoriasis on increased cardiovascular risk suggests the need for the treatment and reduction of psoriasis and its repercussions. Recent NPF guidelines have provided recommendations for psoriasis patient care. Smoking cessation, decreased alcohol consumption, screenings for potential diseases, histories of co-morbidities, and increased exercise should be applied. Though data suggest an increased risk for cardiovascular diseases within psoriasis patients, there are presently no data indicating that increasing cardiovascular screening rates in patients yields a significant difference.

Dermatologists should consider cardiovascular screenings in addition to clinical symptoms of psoriasis, bearing in mind that a substantial number of dermatology patients do not receive regular primary care [54]. When possible, dermatologists can encourage their patients to see a primary care physician to manage their cardiovascular co-morbidities effectively.

Dermatologists should also bear in mind the most influential aspect for the reduction in psoriasis symptoms – the patient. The foremost reason for treatment failure is poor adherence, so a good understanding of the patient's psychology is essential [55]. Dermatologists may find and present their patient with the perfect remedy, but without good adherence, all efforts are in vain. Physicians can do a great deal to increase motivation and adherence, such as calming the patient's fear of a medication, scheduling early return visits, and prescribing the patient's preferred vehicle [56, 57]. They should communicate to all psoriasis patients that successful treatment of psoriasis is one of the best things they can do to reduce their risk of cardiovascular disease.

Limitations of these findings include the large number of possible confounding factors involved in the association of psoriasis with cardiovascular disease. The precise reasons that psoriasis patients have higher cardiovascular risk are not well understood, and studies cannot control for every factor that might differ between psoriasis patients and the general population. Limited safety data are available on newer treatments, especially IL-17 and IL-12/23 inhibitors.

5 Conclusion

Future research should include larger and longer trials on the new treatments, as well as more detailed consideration of the ways that psoriasis can contribute to poor general health through a sedentary lifestyle, mental health impact, and impairment of social life. Altogether, a commendable form of psoriasis treatment must take into account the symptoms themselves, their potential co-morbidities, and especially the lack of motivation and poor adherence frequently found in the patients.

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