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Review Article

Systematic review of proposed inflammatory mechanisms by which patients with psoriasis are considered at greater risk of cardiovascular disease

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Abstract Systemic literature review on proposed inflammatory mechanisms by which patients with psoriasis are considered at greater risk of cardiovascular disease. A thorough search of the scientific literature on quality of life impairment in psoriasis patients from January 1, 1998, to Dec 30, 2018, was done using the electronic databases PubMed, EMBASE, NIH and Web of Science. Studies were included in accordance with the selection criteria. The survey did not include any editorials, letters to the editor, or commentaries. To repeat, these experimentations have provided evidence of association of cardiovascular comorbidity risk in the patients of psoriasis with the concept of numerous inflammatory pathways linked to one another. To summarize, the leading processes proposed to be correlating these two diseases, includes vascular inflammation, oxidative stress and dyslipidemia, inflammatory cytokines, overexpression of inflammatory genes, inflamed adipocytes, and a hypothesis of psoriatic march, role of numerous biomarkers etc. Future studies should be carried in consideration of treatment regimens to decrease the disease burden of comorbidities, as well as improve the quality of life of patients of psoriasis.

Key words
Psoriasis; Cardiovascular disease; Inflammatory.

Introduction

"Psoriasis is a common chronic inflammatory disease of the skin, that is increasingly being recognized as a systemic inflammatory disorder".[1] Until now, psoriasis is reviewed as an unregulated immune mediated response manifested by the constituents of both innate and adaptive immunology resulting in occurrence of characteristic erythematous scaly plaques, corresponding to key pathogenesis such as inflammation, hyperproliferation and angiogenesis.[2] Psoriasis has a complex pathological process; but the actual mechanisms are unknown.[3] However, multiple factors affect the severity and confers susceptibility of the disease such as genetic, epigenetic parameters and extrinsic triggers.[4]

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As shown in an illustrative video on immunology of skin by a nature research Journal,[5] an elusive antigenic stimulator causes the plasmacytoid dendritic cells activation which in turn produces increasingly high levels of Type 1IFN, with a simultaneous release of proinflammatory mediator IL1α by affected keratinocytes, causing hyperactivation of dendritic cells in dermis which contributes to further differentiation of T-cells. Epidermal infiltration with CD8 T cells, neutrophils and dendritic Langerhans cells, lead to the occurrence of an apparent psoriatic lesion, whereas epidermal thickening is promoted by the release of IFN γ, IL12, TNF-α, IL17, and

IL22 from the specific subgroups of T cells i.e. Th22, Th17, and Th1. Particularly, Th17 is considered as the main role player in psoriasis, not only because of its contributory promoting effects on inflammation, but also its involvement in feedback inflammatory circuit resulting in excessive production of antimicrobial peptides, cytokines and chemokines.[3]

Certainly, findings from the current studies have shown that psoriasis is a systemically affecting inflammatory disease, associated with various comorbidities along a significant risk of causing severe vascular events such as myocardial infarction and stroke, however it was previously considered to involve skin and joints only.[1,6-8] Above all, several studies[9,10,11] reported that the mechanical links between psoriasis and cardiovascular consequences are dyslipidemia, altered high-density lipoprotein and decreased cholesterol efflux capacity leading to increased formation of atherosclerosis. The Sorokin study "demonstrated that oxidative stress, commonly seen in this skin disease, actually changed cholesterol and lipoproteins in a way that accelerated atherosclerosis and coronary plaque".[12] The study suggested aortic vascular inflammation as a surrogate endpoint in psoriatic patients for cardiovascular disease due to its association with high-risk plaques, luminal stenosis and non-calcified coronary plaque burden.[13]

Method

The area of discussion of this review, will be the analysis and exploration of the various proposed inflammatory processes involved in psoriasis leading to cardiovascular comorbidity. Key sources for the literature search used were Scopus, Pubmed, Medscape (Medline), and Google Scholar. In all databases keywords used are 'inflammatory mechanisms', 'psoriasis', or 'cardiovascular disease', individually and then in combination by the application of Boolean operators. Additional citations were taken and searched from the references in articles. The parameters of search include human studies, English language and studies from 2013 till 2018. Also, the data retrieved is from abstracts and full text.

Results

Epidemiology and Prevalence Psoriasis is a global problem.[14] Around 1-3% of the population is affected worldwide.[15] This is almost equivalent to 125 million people.[16] According to three different studies 2-4% of western world inhabitants are estimated to be diseased with psoriasis.[17-19] The estimated data of prevalence in the USA and Norway for adults is 0.91% and 8.5%, respectively.[15] As stated in the global report on psoriasis by WHO,[14] that prevalence figures differ among countries from 0.09% to 11.4%, whereas in the cosmopolitan countries it is found to be in the range of 1.5 and 5%. The disease is found to be more prevalent among northern European nations.[4,20] According to a study held in United States in 2009-2010, in Caucasians to be 3.6% prevalent, as compared to those with black ethnicity with a rate of 1.4%.[21]

The age of incidence of psoriasis is not confirmed as it can occur in any age, the mean age of onset is indicated to be 33 years. Bimodal onset of psoriasis has been demonstrated as the appearance of disease with two peaks, initially between 16 and 22 and the next between 57 and 60 years of age.[14]

Psoriasis is considered to affect both male and female genders equally in all countries regardless of ethnicity and age as shown in an article by Institute of health metrics and Evaluation.[14,22] **Table 1** illustrates the estimated data according to the disease distribution in men

Table 1 Prevalence gender based.

	Norway 2007-2008	*Spain 2013*	*United Kingdom 2009*	*United States of America 2009-2010*
Male	12.10%	2.70%	1.80%	3.60%
Female	10.80%	1.90%	1.90%	3.10%

and women in different western countries, collected from various studies.[14]

The geographical prevalence data in psoriasis global workshop report, states that in African and Asian countries the prevalence is lower in contrast to those at higher latitudes with cold and dry climates.[23] At present the available statistics on the epidemiology of psoriasis are short roughly estimated facts of knowledge from all around the globe due to variations in the data assembling methodologies, therefore it is a difficult task for the researchers to put accurate conclusions in terms of burden of disease and its trends.[14]

Proposed Pathogenic Mechanisms In various studies it has been proposed that atherosclerosis, thrombosis, systemic as well as vascular inflammation are the consequences of chronic inflammation.[24,25] However, the correspondence among psoriasis and cardiovascular disease could be demonstrated to some extent through common inflammatory mechanisms.[22] For instance, Th1 and Th17 are the similar cytokines reported to be found in the mechanistic pathways of both psoriasis and atherosclerotic vascular lesions.[26] Angiogenesis is characteristically observed in both skin lesions of psoriasis and as well as atherosclerotic plaques.[27] From numerous studies, commonly shared oxidative stress pathways, suggest inflammatory mechanical connection between atherosclerosis and psoriasis.[28,29]

Furthermore, in a research, which was a ACCEPT trial a phase 3, multicenter, randomized, active controlled, parallel, 3-arm study of patients with moderate to severe psoriasis to investigate and identify any evidence of dysregulation of inflammatory and lipid genes in selected diseased patients related to atherosclerotic cardiovascular disease. This study reported overexpression of inflammatory genes MCP-1 (monocyte chemoattractant prot 1) and MDC (macrophage derived chemokine) ($p<0.001$ each), in the samples of serum and skin lesions of patients with psoriasis.

Moreover, the dysregulation of these inflammatory components indicates the common pathogenetic pathway between psoriasis and atherosclerosis leading to increased risk of cardiovascular disorders. The approach of this experimentation is very well understood but the method of interpretation is not reliable due to unequal sample size distribution among healthy vs. diseased i.e. 89 patients for skin specimen compared to nondiseased, n=149 patients for serum sampling in contrast to n=162 healthy controls. This concept of shared mechanism is not discussed in recent studies.[30,31]

According to another research, inflammation is the ultimate association between atherosclerosis and psoriasis, in which chronic inflammation leads to increased aortic vascular inflammation and other cardiovascular disease comorbidity. For further analysis of the process of atherogenesis and to quantify this mechanical link, a cross-sectional cohort study of imaging on 215 psoriasis patients was performed by them.

For this purpose, fludeoxyglucose F 18 (^{18}FFDG) positron emission tomography/ computed tomography for aortic vascular inflammation and computed tomography

angiography for coronary artery disease were used as the tools of assessments. The broad cardiovascular disease indices such as total plaque burden (TB), noncalcified plaque burden (NCB), luminal stenosis and high-risk plaque were evaluated. The statistical data shows that patients with increased aortic vascular inflammation had a raised total plaque burden ($p<0.001$), enhanced luminal stenosis ($p=0.001$) and widespread high-risk plaque ($p=0.004$). Hence, their study suggests that aortic vascular inflammation is an important factor leading to increased risk of initial cardiovascular events due to its association with cardiovascular indices. The amount of analysis shared is conceptually clear and has upgraded the previous studies about the associations between the two diseases. It has also provided a tool to investigate and monitor surrogate markers at an early stage to further quantify the incidence and inflammatory concordance of psoriasis and atherosclerosis.[13]

In relevance to the above mentioned study, exploration of the interconnection between oxidation modified lipids might guide to understanding the concepts of enhanced cardiovascular risk in psoriasis patients. In accordance with this, an observational cohort study was carried out by Sorokin, to examine (through computed tomographic angiography) the correlation of oxidation modified lipids with traditional lipids parameters, cardiometabolic disease biomarkers, and total coronary plaque, with non-calcified burden as a center of interest in psoriasis. Moreover, analysis in n=252 including both psoriasis patients and healthy controls was performed by assaying oxidation modified; HDL, lipoprotein [a], LDL, cholesterol efflux capacity, PON-1 (paraoxonase-1 an enzyme that prevents the formation of oxidized LDL) activity and the measure of lipoprotein particle by Nuclear magnetic resonance spectroscopy. High levels of oxidised LDL ($P=0.020$) and HDL ($p=0.007$) signify their relationship with NCB, slightly high activity of PON-1 in the psoriasis patients suggests a compensatory effect.[12]

This profiling as determined with NCB, indicates that customary lipids do not enhance any risk of atheromatous plaque, however, it displayed the strong link with oxidised LDL and oxidised HDL. This literature has given more established evidence of cardiovascular comorbidity and its mechanical relativity with this inflammatory driven disease.

Correspondingly, another novel biomarker GlycA (glycoprotein acetyl) has been hypothsised and studied as an inflammatory component in subclinical cardiovascular disease in psoriasis. A two-stage cross sectional cohort research (PENN & NIH),[25] carried out on total n=412 psoriasis patients and healthy controls, demonstrated various important detections from investigations such as; (1) significant high levels of GlycA (PENN cohort: $p<0.0001$; NIH cohort: $p<0.0001$) in psoriasis patients, (2) notable association of GlycA with high- sensitivity C reactive protein (hsCRP), cytokines (TNFα,IL-6,MCP-1,VCAM-1 & ICAM-1), and cardiometabolic risk factors (hypertension, obesity, diabetes mellitus type2, smoking etc.), (3) correlation of GlycA, with vascular inflammation and cardiovascular disease determined by 18-FDG PET/CT and CCTA respectively, apart from cardiovascular biomarkers in psoriasis.

Broadly, they suggested that GlycA is one of the crucial inflammatory pathogenic factors and indicator of subclinical cardiovascular risk in psoriasis patients. According to the study the results are valid and provide an evidence that is helpful to rule out the comordity inclusive of its risk factors to decrease mortality chances in later stages. Although, the interventional tools for

screening GlycA are useful clinically, the cost outweighs its benefits as concern for the patient's affordability is one of the main aspects of good clinical practice.

In addition to this, various studies have suggested, that proinflammatory adipokines (leptin, adiponectin and resistin) which are the consequence of systemic inflammation, contribute to increased risk of cardiometabolic comorbidity.[3] Moreover, studies from the past revealed significantly raised levels of microparticles containing inflammatory mediators in the serum samples of psoriasis patients, proposed to be involved in initiating atherogenesis.[32] On the other hand, hypercoagulability which is a consequence of elevated plasminogen activator inhibitor-1 in psoriasis patient blood (as well as from platelet aggregation) is also suggested as a contributing factor in of increasing risk of cardiovascular events such as thromboembolism.[33,34]

Furthermore, the presence of modified levels of cardiovascular biomarkers (for instance, CRP, soluble CD40 ligand, human matrix Gla protein and fetuin-A) linked to systemic inflammation have also been observed in the serum of psoriasis patients.[35-37] Similarly, other inflammatory biomarkers and enhanced risk of cardiovascular in psoriasis are proposed in several more research studies[38,39] (such as YKL40 and complement C3).

As stated, proposed concept of interconnection among systemic inflammation in psoriasis with cardiovascular disease is poorly understood and controversial. It has not been established whether risk factors of cardiovascular disease lead to dysfunction of immune system resulting in psoriasis or systemic inflammation itself is the pivotal player that increases risk of cardiovascular disease in psoriasis patients. However, the latter concept is supported by proposed theory of "psoriatic march", indicating systemic inflammation in psoriasis causes insulin resistance and endothelial dysfunction that induces atherogenesis resulting in atherosclerosis under the influence of various cytokines, enhancing a risk of cardiovascular comorbidity.[6,40]

Conclusion

The data analysed from several studies discussed above is the most recent and reliable with aspects to its originality, methods and the results achieved. These experimentations have provided evidence of association of cardiovascular comorbidity risk in the patients of psoriasis with the explanation of numerous inflammatory pathways linked to one another. Accordingly, atherosclerosis is the fundamental originator of cardiovascular adverse events, in which various mechanisms of inflammation are playing a crucial role.

The leading processes proposed to be correlating these two diseases, includes vascular inflammation, oxidative stress and dyslipidemia, inflammatory cytokines, overexpression of inflammatory genes, inflamed adipocytes, and a hypothesis of psoriatic march, role of numerous biomarkers etc. However, for being to validate these components further research needs to be done, especially in terms of incidence to get the novel findings.

In the past clinical experience, where evidence-based practice concept is not fully understood or followed by all healthcare professionals, the management of psoriasis has been limited to a cutaneous topical treatment. Patient awareness about the disease and its adverse effects is very low. No screening is carried out to evaluate any associations or any risk factors leading to increased morbidity and mortality. The disease has always been a challenge for the physicians to comprehend from its core knowledge related

to causative factors and comorbidities and apply it to routine clinical practice. Although, most of the time it's the patient itself who does not cooperate, does not take medication on a regular basis, no follow up checkups are made, but the practitioners are also not managing the disease as a multisystem disorder, in fact, only as a dermatological problem. Likewise, due to lack of follow up visits the analysis on the complications and the disease outcome as well as the monitoring of the on-going treatment has been difficult.

Certainly, a complete contemporary management plan should be introduced and recommended to all the dermatologists as well as cardiologists in relevance to the comorbidity risk. Patient should be made aware of the disease course, with lifestyle modification advice and follow up visits. Additionally, screening interventions, and profiling should be performed, keeping the traditional cardiovascular risk factors in mind. Future studies should be carried in consideration of treatment regimens to decrease the disease burden of comorbidities, as well as improving the quality of life of patients of psoriasis.

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