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Angiotensin Converting Enzyme in Psoriasis A comprehensive review

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Abstract
Objectives: To assess the function of the enzyme angiotensin converting in psoriasis.
Background: The powerful vasoconstrictor angiotensin-converting enzyme (ACE) is essential for maintaining healthy cutaneous homeostasis. Serum ACE levels have been reported to be higher in psoriasis patients in studies, indicating that this enzyme may be involved in the aetiology of psoriasis as well as preclinical atherosclerosis and hypertension.**Data Sources:** by looking through and scanning medical databases (Pub Med and Medscape) for information on patients with psoriasis and their blood levels of angiotensin converting enzyme.**Study Selection:** For inclusion, each study underwent an independent evaluation. If they met the requirements listed below, they were considered: Serum Levels of Angiotensin Converting Enzyme in Patients with Psoriasis were explored in English-language publications in peer-reviewed journals.**Data Extraction:** Studies were disqualified if they didn't meet the criteria for inclusion. A study's ethical permission, eligibility requirements, proper controls, adequate information, and stated assessment methods were all considered in the evaluation of the study's quality. A data collecting form was used to independently extract data from each qualifying research in order to record details about the study results we were interested in.**Conclusion:** With respect to nail psoriasis, plaque psoriasis, psoriatic arthritis, and scalp psoriasis, no significant changes were found. However, there is a higher level of serum ACE among psoriasis patients, and these individuals have a much lower proportion of ACE.

Key words: Angiotensin converting enzyme , Psoriasis.

Introduction

The quality of life of psoriatic patients is negatively impacted by the chronic immune mediated inflammatory condition known as psoriasis vulgaris, which is polygenic and multifactorial. Approximately 2 to 5 percent of people have the condition (1)

Several comorbidities, such as metabolic syndrome, type 2 diabetes, depression, and non-alcoholic fatty liver disease, are linked to psoriasis. As a result of an increased risk of cardiovascular disease, myocardial infarction, and stroke, it is also linked to a greater incidence of death (2).

It affects both men and women equally, usually starting to show up between the ages of 20 and 30, peaking between the ages of 15 and 20 and again between the ages of 55 and 60.

Around 75% of all instances of psoriasis are Type I, which often begins before the age of 40, has a more severe course of disease, and has a strong relationship with the human leukocyte antigen (HLA). Contrarily, type II psoriasis has a late start, a moderate course, is intermittent, and is independent to the HLA type (3).

enzyme that converts angiotensin

A hormonal mechanism called the renin-angiotensin-aldosterone system (RAAS) controls the balance of electrolytes, water, and blood pressure. The renal juxtaglomerular cells produce renin into circulation when there is hypovolemia or hypotension (4).

Angiotensinogen produced by the liver is converted to angiotensin I by plasma renin. The lungs' angiotensin converting enzyme then transforms angiotensin I into angiotensin II. A strong vasoconstrictor peptide that raises blood pressure is angiotensin II. The hormone aldosterone is stimulated by angiotensin II to be released from the adrenal cortex. The renal tubules are stimulated by aldosterone to enhance the blood's reabsorption of salt and water. As a result, the body's fluid volume will rise, raising blood pressure (5).

The peptidyl dipeptidyl choline and zinc dependent angiotensin converting enzyme (dipeptidyl carboxy peptidase) is membrane associated and catalyses the cleavage of carboxy terminal dipeptidyl residue. The gene encoding ACE is situated on the long arm of chromosome 17, and the enzyme is mostly found in plasma and released by pulmonary and renal endothelial cells (17q23). There are 26 exons and 25 introns in the 21 kilobase (kb) long gene. The somatic (sACE) and testicular (tACE) isoforms of ACE are encoded by the gene. Additionally identified in humans, the gene encoding ACE2 has 18 exons and maps to Xp22 (6).

The insertion (I) or deletion (D) of a 287 bp non-coding Alu repeat sequence provides the

basis for the polymorphism of the ACE gene. Higher blood ACE concentrations were discovered among DD homozygotes, which accounted for almost 47% of the variation in ACE concentrations. Despite the significant correlation between ACE levels and activity, enzyme activity may be a more important measure in the presence of ACE modulators (7).

Relationship between several illnesses and the **ACE I/D gene polymorphism:**

(A)Hypertension

The D allele was strongly associated with essential hypertension susceptibility in the Chinese and Indian population, suggesting a linkage between the ACE gene I/D polymorphism and essential hypertension (8).

B) Ischemia and coronary artery disease:

A condition of oxidative stress, which is prevalent in many cardiovascular illnesses and is one of the variables that predisposes to atherogenesis, is suggested by higher ACE levels. As a result, it was discovered that the ACE gene DD genotype was linked to a higher risk of left ventricular hypertrophy and coronary artery disease (9).

C) Type 2 diabetes

Patients from Saudi Arabia and Egypt have a substantial correlation between the ACE I/D gene polymorphism and type 2 diabetes mellitus (10).

D) Renal conditions:

The advancement of renal illness and the emergence of hypertension are both significantly influenced by the ACE enzyme. The renal hemodynamics are adversely affected by the elevated angiotensin II level, which also causes the protein production of certain growth factors. IgA nephropathy, focal segmental glomerulosclerosis, and the idiopathic nephrotic syndrome (INS) have all been linked to variations in the ACE I/D gene. Albuminuria is a marker for the severity of nephropathy, and it has been shown that decreasing the frequency of the ACE II genotype is associated with increasing the severity of albuminuria (11).

E)Psoriasis

The ACE insertion/deletion (I/D) polymorphism seems to be one of the several genetic risk factors for the multifactorial illness psoriasis. Angiotensin II is a potent activator of the enzyme NADPH oxidase and augments production of reactive oxygen species (ROS), creating an oxidative stress state. It has been demonstrated that ACE activity is higher in psoriatic patients and suggests an oxidative stress state, as seen in many cardiovascular disorders (12).

Numerous transcription factors, including NF-B, PPAR, p53, HIF-1, and Nrf2, may be activated by oxidative stress. It has been reported that the release of inflammatory factors is one of the earliest events to occur in psoriasis. Activation of these transcription factors causes expression of more than 500 different genes, including those for inflammatory cytokines, growth factors, chemokines, and cell cycle regulatory molecules (13).

Th1, Th17, and Th22 cell subset growth and activation are part of the pathogenesis of psoriasis. Atherosclerosis is often associated with these Th1 and Th17 cascades. In reality, atherosclerotic plaques and psoriatic lesions may both have comparable inflammatory cell infiltrates (14).

Furthermore, it was shown that psoriatic individuals had increased blood levels of triglycerides, total cholesterol (TC), and LDL cholesterol. The fact that this has been recorded even before the commencement of the illness raises the likelihood that dyslipidemia may come before the development of psoriasis. However, it is not apparent if these alterations in lipid profiles are merely a result of the increasing prevalence of obesity in psoriatic populations and how that has an impact on lipid metabolism (15).

It has not yet been completely determined how the ACE I/D polymorphism and psoriasis susceptibility are related at the molecular level. Additionally, it has been researched whether using ACE inhibitors in clinical settings can worsen or cause psoriasis. Some studies suggest that ACE and its related products may have widespread effects on immune responses and skin inflammation, but they neglected to consider genotypes/allele distribution, rate the quality of the included studies, or look at patient subgroups based on various factors and psoriasis variants (16).

Psoriasis pathogenesis:

1. The genetics of psoriasis

The tendency to develop psoriasis seems to be significantly influenced by genetic predisposition. This opinion is supported by several findings:

First, some HLA-types are linked to psoriasis (HLA- Cw6, HLAB13, HLA-B17, HLA-Bw57 and HLA-DR4). In Caucasian populations, HLA-Cw6 has continuously shown the greatest relative risk for psoriasis. It has also been linked to psoriatic arthritis and a predisposition for early development of skin lesions, with a

10-fold increased chance of acquiring the condition (17).

Second, having first-degree relatives with the condition increases the risk of acquiring psoriasis. If one parent has psoriasis, the risk is around 20%; if both parents have it, the risk is almost 75%. The likelihood that the second monozygotic twin will also have psoriasis is more than 55% if one twin has the condition (18).

The most important locus, PSORS1, has been linked to nearly 50% of the heritability of the disease. PSORS1 is located on chromosome 6p21 within the major histocompatibility complex (MHC), specifically in the class I telomeric region of HLA-B, and spans an approximately 220 kb-long segment that corresponds to HLA-Cw. Genome-wide linkage studies of diseased families had discovered at least 60 chromosomal loci linked (19).

2) Environmental elements

A)Trauma

Psoriatic lesions have been reported to be caused by a variety of stimuli, including physical, chemical, surgical, electrical, infective, and inflammatory assaults. Vaccinations, scrapes, and sunburns may also cause a Koebner's reaction. Trauma has also been linked to psoriatic arthritis (PsA), especially when it affects the bones and joints. This finding has given rise to the theory that PsA may be affected by a "deep Koebner" phenomena that is similar to the Koebner's phenomenon in psoriasis of the skin (20).

B)Infection

The presence of bacteria:

The most frequent culprit is pharyngitis caused by streptococcal infection. Strong correlations exist between acute guttate psoriasis and concurrent or prior streptococcal infection. Between 55% and 95% of cases of this kind of psoriasis are caused by or worsened by streptococcal infections (21)

Additionally, psoriasis patients seem to have an increase in staphylococcal aureus infection. Since it can activate Th1 and Th17 cells, promoting the production of tumour necrosis factor (TNF-) and interferon (IFN-), which sustains keratinocyte damage, it has also been linked to disease exacerbations. Additionally, staphylococcal enterotoxins can activate T cells, inducing a more systemic immune response, and staphylococcal peptidoglycan can favour keratinocyte proliferation (22).

Yeast infections

A frequent symptom of scalp psoriasis is an overgrowth of malassezia species. It is also believed that psoriasis may arise from seborrheic dermatitis as a result of a Koebner's reaction to malassezia yeast colonisation. Candida may create superantigenic substances that drive T cell activation similarly to streptococcal and staphylococcal toxins, which can also function as a trigger for intertriginous psoriasis (23).

infection with a virus

Psoriatic arthritis is substantially more common in HIV positive patients than in those who do not have the virus. Additionally, one research found that zidovudine improved psoriasis associated with HIV not just by reducing HIV infection but also by having a direct impact on keratinocyte growth (24).

drinking and smoking

Abuse of alcohol raises the possibility of psoriasis developing or becoming worse. Studies have also shown a connection between smoking and pustular types of psoriasis, notably palmoplantar pustulosis. It may also limit treatment compliance, worsen skin lesions, and represent a manifestation of stress induced by severe psoriasis (25).

Biological hormones and electrolytes:

A role for hormonal variables in the aetiology and evolution of the illness is strongly suggested by the early beginning of psoriasis in women, the disease's peak around puberty, alterations during pregnancy, and the worsening of psoriasis by high-dose oestrogen treatment (26).

Obesity

Psoriasis is more common and severe in obese people, and both conditions have been linked to increased risk for metabolic and cardiovascular disease owing to elevated ACE levels. According to many research, psoriasis and its prognosis in obese persons may be improved by weight reduction. It has been shown that psoriasis risk increases somewhat with a modest rise in Body Mass Index (BMI) of 26-29%, and increases double with morbid obesity (BMI > 29). This link is further supported by the finding that people with severe psoriasis are more likely to be obese than those with milder cases (27).

Drugs

There are various medications that may either start or exacerbate psoriasis. Lithium salts, beta blockers, antimalarials, ACE inhibitors, non-steroidal anti-inflammatory medicines (NSAIDs), and stopping corticosteroids are the major therapies (28).

Stress

Numerous studies have shown that stress and anxiety have a part in the development and worsening of psoriasis. Several stress-related neuro-trophins and neuropeptides, including as corticotropin-releasing hormone (CRH), substance P, calcitonin gene-related peptide

(CGRP), and nerve growth factor, work as mast cell secretagogues to cause this (29).

3. Immunological elements

Studies have demonstrated that several cells of the innate immune system may release IL-17 and IL 23, and can interact with adaptive immune system cells like Th17 and CD8+ T lymphocytes. These interactions were the major focus of the psoriasis pathogenesis (30).

(A)Dendritic cells

In psoriasis, dendritic cells play a key role in the production of inflammatory cytokines and chemokines by acting as antigen-presenting cells that activate T cells. DCs can stimulate T-cells in an allogeneic mixed lymphocyte reaction and induce allogeneic T-cells to produce IFN- and IL-17. There is a 30-fold increase in CD11c mDCs in the dermis of psoriatic patients. Myeloid DCs (mDCs) express specific cell surface marker, CD11c, which is essential in the development of the disease (31).

Keratinocytes:

Keratinocytes organise innate and adaptive immune responses in response to a variety of potentially harmful signals. These responses include the release of antimicrobial peptides (AMPs), including LL37, -defensins, calcium-dependent lectins (C-type lectins), S 100 proteins, and iron-metabolizing proteins. These compounds enhance the upregulation of pro-inflammatory cytokines and chemokines, which modulates immune cells in addition to having direct antibacterial effect (32).

Macrophages:

Although macrophages' exact function in psoriasis is unclear, they do contribute to the disease's pathogenic inflammation by generating important inflammatory cytokines including TNF. Following effective treatment, macrophage numbers in psoriatic skin lesions increase by threefold and show symptoms of normalcy (33).

Neutrophils:

Due to their role in the proliferation, activation, and differentiation of T cells and keratinocytes, neutrophils are crucial in the early stages of psoriasis. Munro's micro abscesses, which were first discovered in 1898, are recognised as one of the main histo-pathological characteristic findings of psoriasis (34).

Natural killer (NK) cells:

Since there are more NK T-cells in psoriatic lesions than in healthy skin, it has been hypothesised that these cells may contribute to the development of the disease by secreting inflammatory cytokines such IFN-, TNF-, and IL-22 (35).

ILCs, or innate lymphoid cells:

Based on cytokine production and transcription factor expression, Innate Lymphoid Cells are classified as ILC1, ILC2, and ILC3 respectively. ILCs1 generate IL-12/IFN-, ILCs2 produce IL-4/IL-5, and ILCs3 produce IL-17/IL-22. ILCs3 are differentiated into natural cytotoxicity receptor-positive (NCR+) ILC3, NCR- ILC3, and lymphoid tissue inducer (LTi) cells, and their development is dependent on the transcription factor RORt (36).

Some ILC3s have the potential to create IL-17, and because of this, it is known that ILC3s have a role in the pathogenesis of psoriasis. While NCR- ILCs3 are often seen in normal skin, NCR+ ILCs3 are more prevalent in psoriatic lesions. In response to stimulation with IL-2, IL-23, and IL-1, NCR- ILCs3 isolated from healthy skin change into NCR+ ILCs3 in vitro (37).

cells in T helper 1:

Due to the high levels of Th1 pathway cytokines seen in patient psoriatic plaques and peripheral blood, psoriasis has been categorised as a Th1 illness. IFN- and TNF are generated when the Th1 differentiation pathway is active. In addition to TNF and IL-1, the production of IFN- and IL-18 on activated Th1 cells helps to identify them. IFN- is thought to play a more important role in the early stages of the disease, speeding up immune cell migration into the skin and activating antigen-presenting cells. It also enhances chemokine (CXCL10 and CXCL11) and adhesion molecule secretion from keratinocytes, epidermal cell proliferation, and inhibits keratinocyte apoptosis, resulting in the hyperproliferation of keratinocytes seen in (38).

T-cell regulatory cells

It has been discovered that T regulatory (Treg) cells—or, more precisely, the disruption in the Th17/Treg balance—play crucial roles in the pathogenesis of psoriasis. Inflammation in psoriasis has been connected to Treg cell abnormalities. Treg cells thereby suppress the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules and lessen inflammation by releasing IL-10 (39).

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