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A Study of The Association Between Cysteinyl Aspartate Protease -5 (CASP5) Gene Expression & Plasma Level and The Risk of Rheumatoid Arthritis (RA)

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Abstract
Background: Rheumatoid The prevalence of arthritis (RA), a systemic inflammatory illness that worsens over time, ranges from 0.2% to 1.1% worldwide. An essential component of the caspase family, the caspase-5 (CASP5) gene is involved in the regulation of immune response and cell death. The correlation between CASP5 plasma levels and CASP5 expression gene levels in B cells and T cells PBMCs implies that CASP5 may represent a new risk biomarker for RA. In a case-control study with 80 participants, researchers discovered that mild activity accounted for 15.0% of RA cases, moderate activity for 30.0%, and high activity for 55.0%. In comparison to the control group, RA patients were found to have a considerably higher ESR and a lower Hb. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were all improved when CASP5 gene expression levels and CASP5 plasma levels were matched. Levels of CASP5 gene expression and plasma CASP5 levels were both shown to be strongly associated with RA susceptibility when logistic regression analysis was used to forecast RA vulnerability.one, two, three (1)

Keywords: The prevalence of arthritis (RA), (CASP5) ,PBMCs

Introduction

A systemic auto-inflammatory condition known as rheumatoid arthritis (RA) affects not just the joints of the hands, feet, and wrists, but also the skin, kidneys, lungs, and liver. It mostly affects women and affects 0.5-1% of the world's population. Environmental variables such as smoking, microbiome, infectious agents, nutrition, and socioeconomic status join genetic, hormonal, and neuroendocrine risk factors in RA, which is a complex illness with several causes. One of the hallmarks of RA is inflammation, and cysteine cathepsins play a role in this process. Proinflammatory cytokines, such as IL-1β and IL-18, are activated by inflammasomes, which are complexes of several proteins found inside cells. Active rheumatoid arthritis patients have elevated expression levels of the NLRP3 inflammasome, which plays a pivotal role in the disease.(4)(5) The purpose of this case-control research was to investigate if there was a correlation between the expression of the cysteinyl aspartate Protease -5 (CASP5) gene and the likelihood of rheumatoid arthritis (RA) in a population of Egyptians. It will look at the gene expression and protein levels of CASP5 in the blood of RA sufferers and those who seem to be in good health.the sixthRheumatoid arthritis (RA) is a long-term autoimmune disorder that affects more than just the joints; it causes inflammation and may spread to other parts of the body. Joints further away from the source usually experience it first, before moving closer to the source. Untreated rheumatoid arthritis (RA) may lead to permanent impairment and exhibits a wide range of symptoms, outcomes, and reactions to treatment.(8)(9) Rheumatoid arthritis affected 17.6 million persons globally in 2020, up 14.1% from 1990. The frequency was greater among females. There was a 23.8% drop in the mortality rate between 1990 and 2020. Rheumatoid arthritis will affect 31.7 million individuals by 2050, with the prevalence expected to rise with age.(10) Research with monozygotic twins and family clustering has shown that RA susceptibility is hereditary, accounting for half of the risk. Additional risk factors for RA include certain gene variants, polymorphisms, and the HLA-DRB1 allele. A number of epigenetic alterations, including changes to DNA methylation and histone modifications as well as non-coding RNA-mediated control, have been linked to changes in gene expression and, by extension, the pathophysiology of autoimmune disorders such as RA.(11) Environmental variables, such as smoking, occupational exposures, food, and hormonal factors, increase the risk of rheumatoid arthritis (RA), a prevalent inflammatory disease. The most potent environmental risk factor is cigarette smoking, which triggers the expression of peptidyl arginine deaminase by alveolar macrophages, which in turn leads the production of

antibodies against citrullinated proteins and pro-inflammatory cytokines. Construction workers are exposed to silica, asbestos, mineral oils, pesticides, dust from roadside sources, textiles, and electrical and electronic work. Environmental factors like as food and nutrition might also play a role; consuming a high-calorie, fatty diet can raise the likelihood of having RA. Additional risk factors include obesity and vitamin D insufficiency. A well-known risk factor is gender; women are 2.5 times more likely to be affected than men. A history of pregnancy or other hormonal variables may provide some protection against RA. The likelihood of developing RA is higher in women who have early menopause.(12)(13) Mycoplasma, mycobacterium, parvovirus, Epstein-Barr virus, and retroviruses are among the infectious pathogens linked with rheumatoid arthritis (RA). In those with a predisposition to the illness, it may start with a direct synovial infection, molecular mimicry, or innate immune system activation. Porphyromonas gingivalis, a RA-associated periodontal disease-causing bacterium, expresses peptidylarginine deiminases (PAD). The risk of RA may be increased, according to research, by mucosal damage caused by environmental contaminants and occupational exposures. Dysbiosis and other alterations to the gut microbiota may also have a role in RA. Crucial to RA are immunologic components, including as cytokines, antigen-presenting cells, T and B lymphocytes, and others.(14)(15)

During the pre-symptomatic or pre-clinical phase of rheumatoid arthritis (RA), autoimmunity starts to manifest. Serum and synovial fluid autoantibodies are indicators of systemic autoimmunity in RA. It may take up to ten years before RF and ACPA antibodies manifest as arthritic symptoms in RA. Autoantibodies also attack enzymes, proteins in the nucleus, components of cartilage, and stress proteins. B cells in germinal center-like structures and lymphoid follicles create rheumatoid factor, an IgM class antibody that targets immunoglobulin G. There is a correlation between RF positive at diagnosis and increased disease activity and joint structural deterioration at baseline.(16) In certain cases, rheumatoid factors may be present even before rheumatoid arthritis (RA) begins to manifest, suggesting that the illness may have begun much earlier. Joint injury and disease activity are linked with preclinical RA, a developmental stage characterized by increased disease-related biomarkers. The highly sensitive and specific anti-citrullinated peptide antibody (ACPA) test may be used to diagnose RA. Its excellent specificity and sensitivity have earned it the title of "gold standard" RA diagnosis in the medical community. Understanding the natural history of RA and creating predictive and preventative methods may be aided by ACPA testing, which can identify asymptomatic persons at elevated risk of developing clinically evident RA in the future. In addition to citrulline, RA patients may also have antibodies against carbamylated proteins (anti-CarP), which have a similar but unique chemical structure. In individuals who test positive for ACPA as well as those who test negative, these antibodies have been linked to RA.(17)(number one)

Individuals diagnosed with rheumatoid arthritis (RA) often have antibodies against carbamlylated protein (anti-CarP) and anti-acetylated protein (anti-ACEPO). Both ACPA-positive and ACPA-negative individuals with RA have anti-CarP antibodies, which are separate antibodies. Forty percent of RA patients, especially seropositive individuals, have antibodies that target acetylated proteins. Some of the pathophysiological processes involved in RA include synovial hyperplasia, recruitment of inflammatory cells, neoangiogenesis, loss of cartilage, and erosions of bone tissue around joints. To find predictive markers and create successful therapies, it is essential to measure the elevated levels of several cytokines in RA patients. In order to find prognostic markers and create successful therapies, it is crucial to understand these pathophysiological processes.(19) Osteoclast production and bone erosions result from invasive alterations in the rheumatoid synovium's FSC. In lymph nodes, antigen-presenting cells engage with B and T cells, which promotes the generation of cytokines and the creation of autoantibodies. We get synovitis, which means inflamed joints. Joint deformity and persistent discomfort are possible outcomes of untreated synovitis. Modern RA treatments aim to restore immunological homeostasis by targeting certain inflammatory cytokines and cells.(20)

Rheumatoid arthritis (RA) begins and advances in large part due to the innate immune system's involvement, which includes monocytes, macrophages, and dendritic cells. Inflammasomes and these cells work together to control inflammation and the innate immune response once translation has taken place. An important pathogenic mechanism in RA that causes inflammation is the activation of Toll-like receptor agonists or Fc receptor interaction in the synovium.(21)

Infiltrating T cells primarily generate effector cytokines such as TNF-α, IL-17A, interferon

(IFN)-γ, and RANK-L. IL-6 promotes the activation of local leukocytes and the formation of autoantibodies, while TNF-α initiates the expression of cytokines and chemokines. Macrophages secrete IL-8, which attracts inflammatory cells and accelerates the breakdown of bone and cartilage. In rheumatoid arthritis, cytokines from the IL-1 family are highly produced, which in turn activate leukocytes, endothelial cells, chondrocytes, and osteoclasts. The degradation of bone and cartilage is facilitated by IL-1β, a significant pathogenic component of RA. When RANKL attaches to precursor cells of osteoclasts, it triggers their differentiation and activation, ultimately resulting in bone degradation. IL-1β has a role in the breakdown of cartilage by inducing the secretion of matrix metalloproteinase by fibroblasts and chondrocytes, worsens inflammation in the synovial joints, and leads to the degradation of bone. Dendritic cells connect the innate and adaptive immune systems, which is vital in rheumatoid arthritis. Autoimmunity is triggered by changed proteins such as citrullinated proteins, while adaptive immunity consists of B cells and T cells that react to antigenic stimuli. In autoimmune diseases, B cells have a role via malfunctions in tolerance checkpoints, cells that display antigens, and cells that produce antibodies.(22)

Synovitis, the outward manifestation of inflammation of the synovial membrane, is a hallmark of rheumatoid arthritis (RA), a disease of the joints. When innate and adaptive immune cells interact with fibroblast-like synoviocytes (FLSs), it triggers inflammation. Damage to cartilage is severed in RA because to hyperplastic synovium, which results from FLS failure. Localized, periarticular, and systemic bone loss are pathological hallmarks of RA. Rheumatoid nodules are fibrous lesions that are white in color and include yellowish patches; they are an example of extra-articular pathology. In cases of necrotizing pan arteritis, the most common damaged blood vessel is the vasculature. Systemic or articular symptoms might manifest; in fact, some individuals have constitutional symptoms first. Patients' quality of life is greatly affected by the general manifestations, which include symptoms such as fever, stiffness, exhaustion, weakening of the muscles, poor mood, and sadness. Forty to eighty percent of RA patients indicate that fatigue is the most debilitating symptom.(22)

Cytokines IL-1 and IL-18 are produced by the NLRP3 inflammasome, an important intermediate step between innate and adaptive immunity. IL-1 is primarily expressed in monocytes, macrophages, and dendritic cells; it is a powerful cytokine that promotes inflammation. It promotes the polarization and development of T cells, especially Th17 cells. IFN-γ production in Th1 cells and activation of natural killer cells are driven by IL-18, while IL-1β promotes B cell proliferation and antibody production. Rheumatoid arthritis and other autoimmune illnesses may be caused by the NLRP3 inflammasome.(23)

Many inflammatory illnesses, including psoriasis vulgaris, sepsis, and inflammatory bowel disease (IBD), include cysteinyl aspartate protease -5 (CASP5). Intestinal epithelial barrier failure is closely related to its principal role, which is to start or enhance the cellular response to LPS. In cases of bacterial sepsis, malaria, and sickle cell disease, CASP5 levels are increased 20-fold in the affected skin, suggesting that it may play a role in inflammation. Cancers have been shown to have CASP5 mutations, and the rs3181320*C allele may be a risk factor for a number of different types of cancer. RA, a chronic multi-system inflammatory illness linked to proinflammatory cytokines such as interleukin-18, interleukin-1, and TNF-α, is mostly caused by CASP5. Additional information on the pathophysiology of RA may be uncovered by investigating CASP5. One of the main factors in osteoclast development and activation is RANKL, and IL-1 indirectly upregulates this protein while directly inducing osteoclast differentiation.(24)

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