Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (9) Issue (8) (2024), (9- 12) **online: ISSN 2356–976x**
http://bjas.bu.edu.eg

Evaluation of Serum Cathepsin-S Level in Psoriatic Patients

Dalia. M. Moursi[1], Asmaa. M. Alrefaie[1], Aliaa. E. Mohammed [1] and Maha. T .Rachwan[2]
1 Dermatology, Venerology and Andrology Department, Faculty of Medicine, Benha University, Benha, Egypt
2 Clinical Pathology Department, Faculty of Medicine, Benha University, Benha, Egypt
E-Mail: Daliamossad2@gmail.com

Abstract
Background: Psoriasis is a skin condition characterized by the development of raised, red, and scaly plaques over time. Multiple comorbidities, including Crohn's disease, cancer, obesity, and cardiovascular disease, are more common in those with psoriasis. It is well-known that proteases, of which cathepsin S is a part, degrade damaged and undesired proteins. More and more evidence points to its role in a wide range of pathological states and inflammatory disorders. Purpose: The cathepsin-S serum level in psoriasis patients and how it relates to the severity of the illness will be reviewed in this study. Final thoughts: It is possible that serum cathepsin-S is involved in psoriasis. The possible use of cathepsin-S as a biomarker for psoriasis severity is supported by the link between the two.

Keywords: Herpes simplex virus; cathepsins.

1. Introduction

Psoriasis epidermal hyperproliferation, aberrant keratinocyte differentiation, T-lymphocyte infiltration, and elevated production of cytokines are hallmarks of this chronic inflammatory skin illness. Roughly 2% to 3% of the global population experiences psoriasis[1].

Psoriasis etiology involves genetic, immunological, and environmental components. Nevertheless, the exact cause has not been completely determined. Intrinsic and adaptive immune cells set off an inflammatory cascade in the dermis, which is the pathogenic mechanism in psoriasis [2].

Subcutaneous white adipose tissue may release cytokines like interleukin-36 (IL-36) and adipokines like leptin, which may exacerbate the cutaneous inflammation. They may have a role in the formation of psoriatic lesions by influencing the activation, proliferation, and differentiation of keratinocytes and immune cells via their aberrant cutaneous and systemic expression [3].

The main activator of interleukin-36 is thought to be cathepsin-S. Aspartic proteases (cathepsins D and E) and serine proteases (cathepsins A and G) are the other two families of cathepsins, with cathepsin-S being the biggest of the three [4].

2. Materials and methods

Data Sources:

The PubMed and Medscape searches were used to gather literature on psoriasis's etiology, pathophysiology, clinical images, and the function of cathepsin-S serum levels in psoriasis patients and their link with the severity of the disease's decline up to 2024.

Choose Your Course of Study: The inclusion of all research was determined by separate evaluations. Inclusion was contingent upon them meeting the following requirements: 1. The text was written and published in English. 2. Publicated in publications that undergo a rigorous peer review process. 3. Go over the background of psoriasis, including its etiology, pathophysiology, and clinical images. Then, talk about how the amount of cathepsin-S in a patient's blood affects the severity of their condition.

Data Extraction: Research was deemed ineligible if it failed to meet the specified requirements. Considerations for judging the study's quality included whether or not it had received ethical clearance, the clarity of its eligibility requirements, the effectiveness of its controls, the quantity and quality of its data, and the clarity of its assessment tools. For our concerned research outcomes, data were independently extracted from all qualifying studies utilizing a data collecting form.

Bibliographical survey:

Psoriasis

Psoriasis is a chronic inflammatory skin disease characterized by sharply demarcated erythematous plaques with whitish scale. Psoriasis is one of the most frequent chronic inflammatory skin diseases. Psoriasis is an immune-mediated inflammatory disease with autoimmune pathogenic traits that affects the skin and joints. The prevalence of psoriasis varies with the country, and psoriasis can appear at any age, suggesting that ethnicity, genetic background, and environmental factors affect the onset of psoriasis [5]

Psoriasis is associated with many other medical conditions, and affects over 60 million adults and children worldwide. Psoriasis occurs equally in men and women, with a mean age of onset of 33 years. It can present

earlier in women, associated with two different subtypes based on genetic and immunological features: early onset, before the age of 40 years, and late onset, after the age of 40 years age[6].

Psoriasis pathogenesis

According to popular belief, keratinocytes interact with a wide variety of skin cells, leading to inflammation in the epidermal layers and the eventual creation of psoriatic plaques [7].

Hereditary factors

The primary factor that determines the likelihood of having psoriasis is heredity. Monozygotic twins have a risk that is two to three times greater than dizygotic twins. One of the key genetic risk factors for early-onset psoriasis is the HLA-C*06:02 allele, which is also known as psoriasis. HLA-C*06:02 is not linked to late-onset psoriasis, psoriatic arthritis, or pustular psoriasis[8].

Environmental factors, such as stress, infections (especially streptococcal), alcohol, smoking, drug exposure (especially lithium, antimalarials, and non-steroidal inflammatory agents), and, in rare instances, sunlight, can cause psoriasis to flare up. Living with psoriasis can also lead to weight gain and obesity, which are risk factors and triggers for the disease [9].

The immune system's innate and adaptive components, as well as feed-forward alterations

The pathophysiology of illness involves several immune cells, both classic (such dendritic cells and neutrophils) and non-classic (like keratinocytes). Cytokines such tumor necrosis factor (TNF-α), interferon (IFN-γ), IL-17, and IL-22 are the primary means of communication between these cells. Activation of keratinocytes also plays a role, leading to epidermal hyperproliferation and the production of antimicrobial proteins, growth factors, and chemokines. The angiogenesis, neutrophil infiltration, and increased numbers of T helper cells type 1 (Th1) and Th17 cells that are typical of psoriasis are promoted by these components, which create a self-sustaining cycle of inflammation [10].

Cytokine circuits in psoriasis

IL-23 and Th17 and beyond

IL-23 and Th17 responses are considered important drivers of psoriasis. IL-23, composed of p40 and p19 subunits, plays a major role in IL-17 biology through maintenance and expansion of IL-17-producing immune cells. IL-23 is closely related to IL-12; with which it shares the p40 subunit (the therapeutic target of ustekinumab). IL-12 promotes Th1 responses, characterized by the production of IFN-γ, but direct therapeutic targeting of this cytokine is ineffective[11].

Tumor necrosis factor alpha (TNF)-α

Tumor necrosis factor alpha (TNF)-α is a pro-inflammatory cytokine produced by immune cells including dendritic cells, macrophages, and T cells. It has a broad range of biological effects through the induction of expression of other pro-inflammatory cytokines (by dendritic cells and T cells) and of neutrophil chemoattractants, inducing vascular adhesion molecules facilitating the influx of inflammatory cells, and amplification of the effects of other cytokines, including IL-17[12]. Interferon gamma (IFN)-γ

IFN-γ induces expression of pro-inflammatory mediators including the chemoattractants CXCL9 and CXCL10 that attract additional Th1 and cytotoxic T cells type 1 (Tc1) to the site of inflammation, thereby setting up a positive feedback loop involving interferon responses[13].

Clinical presentation

Chronic plaque psoriasis

The classic morphology is that of well demarcated, salmon-pink plaques covered in silvery scales in white skin (figure 1A) and of grey plaques in black skin (figure 1B). Removal of the adherent scales can result in small bleeding points (known as the Auspitz sign). Plaques can have highly variable sizes and thicknesses, which can in turn signify active disease (small plaques) or responsiveness to some therapies (e.g., thin plaques are more likely to respond to phototherapy) [14].

guttate psoriasis

presents as numerous, small, and scaly papules distributed in a centripetal pattern. Approximately two thirds of patients have a preceding episode of pharyngitis or tonsillitis, and about half have elevated antistreptolysin O, anti-DNase B, or streptozyme titres. Whereas most children and young adults with guttate psoriasis have spontaneous resolution after several weeks or months, approximately 40% of cases progress to chronic plaque disease[15].

The persistent acrodermatitis of Hallopeau

Pustules appear on the tips of fingers and sometimes toes, causing the nail plate to fall off; around 40% of people with this condition also have chronic plaque psoriasis[15].

Cathepsin S

Among cysteine cathepsins, cathepsin S stands out. It is linked to immune cells including macrophages and antigen presentation cells in the lymphatic and splenic systems [16]. The role of cathepsin S in

various conditions is being more thoroughly studied, revealing its potential as a therapeutic target. This is due to the development of tools like genetic ablation models, chemical biology probes and substrates, which are facilitating this investigation [17].

Autoimmune disease

Given that it is an inflammatory condition caused by immune cells, and that cathepsin S can cleave myelin basic protein (MBP), it is speculated that the protease might play a crucial role in the development of the disorder. Clinical investigations have joined this early mechanistic work, and they have shown that MS patients have elevated levels of cathepsin S expression, which is shown at both the transcriptional and translational levels [17].

Asthma, allergic reactions, and inflammation

Based on its function in the antigen presentation pathway, cathepsin S has the ability to exacerbate asthma pathophysiology, as shown in many pre-clinical studies [18].

Diabetes and obesity

Exploration research on cathepsin S and other pro-inflammatory proteins in diabetic mice that were not overweight led to the discovery of their potential function in the onset of type 2 diabetes. An upregulation of cathepsin S was seen in the research, both in terms of messenger RNA levels and protein levels as assessed by immunofluorescence and activity. An other investigation found that preventing diabetes by removing cathepsin S considerably reduced its development [19].

One possible target for bringing patients' blood glucose levels back to normal and so slowing the course of diabetes is cathepsin S. Increased levels of cathepsin S and adipocyte markers in the tissues of obese people suggest a possible association between the protease and obesity.All things considered, the fact that recombinant cathepsin S increased adipogenesis when administered to preadipocytes suggests that the protease may play a causal role in obesity [18].

Cardiovascular illness

Atheroma and its surrounding tissues have higher levels of cathepsin S expression than normal, healthy tissues. This is likely because protease-rich immune cells are drawn to these areas.One possible mechanistic explanation for the over-expression of cathepsin S via the AT1 receptor in atherosclerotic lesions is that Olmesartan blocks macrophage migration to the disease site [19].

Cancer

Angiogenesis is a process in which cathepsin S plays a crucial role. Research has shown that cathepsin S may release other peptides that regulate

angiogenesis, including pro-angiogenic γ2 from the anti-angiogenic peptide laminin-5 and endostatin from the NC-1 domain of type XVII collagen. This suggests that it may play a role in regulating the formation of micro vessels [20].

Cauliflower disease

Although there is no correlation between the activity of cathepsin S and the presence of Pseudomonas aeruginosa, it is known to play a role in the breakdown of surfactant protein A, a protein with an inherent protective function, and defensins, which are protective proteins that have an antimicrobial effect against pseudomonas in cystic fibrosis patients. The physiological symptoms experienced by CF patients may be worsened by cathepsin S's proteolytic processing of the amiloride-sensitive epithelial sodium channel [21].Dry skin

The activity of cathepsin S was significantly increased in psoriasis patient samples compared to healthy control samples. Psoriasiform alterations were generated in human skin-equivalent models by IL-36γ-Ser18, which is the primary end product of cathepsin S-dependent IL-36γ cleavage [22].

The most well-documented job of cathepsin S is in the processing and presentation of antigens. The degradation of the MHC class II-associated invariant chain is one of the proteolytic processes carried out by cathepsin S inside the early endosomes of the majority of professional antigen presentation cells [23]. In light of this role, the capacity of keratinocytes to produce MHC class I and II antibodies, and the observed increase in MHC class II immunoreactivity in psoriatic epidermis, II[24].

References

[1] AS .Nash, H .McAteer, J. Schofield, R .Penzer, AK. Gilbert.: Psoriasis today: experiences of healthcare and impact on quality of life in a major UK cohort. Prim Health Care Res Dev.;VOL .16(4):PP .415-423.2015.

[2] A. Rendon, K. Schäkel.: Psoriasis Pathogenesis and Treatment. Int J Mol Sci.;VOL. 20(6):PP.1475.2019.

[3] F. Bai, W .Zheng, Y. Dong, J. Wang, MA. Garstka, R .Li, J .An, H .Ma.: Serum levels of adipokines and cytokines in psoriasis patients: a systematic review and meta-analysis. Oncotarget.; VOL 9(1):PP.1266-1278. 2017.

[4] J. Reiser, B. Adair, T. Reinheckel.: Specialized roles for cysteine cathepsins

in health and disease. J Clin Invest.; VOL .120(10):PP. 3421-3431. 2010.

[5] K. Kamiya, M .Kishimoto, J .Sugai, M .Komine, M .Ohtsuki.: Risk Factors for the Development of Psoriasis. Int J Mol Sci.; VOL . 20(18):PP.4347. 2019.

[6] CEM. Griffiths, AW .Armstrong, JE. Gudjonsson and JNWN . Barker: Psoriasis. Lancet.; 397(10281): 1301-1315. 2021.

[7] M .Tokuyama and T. Mabuchi.: New Treatment Addressing the Pathogenesis of Psoriasis. Int J Mol Sci.; VOL .21(20): PP. 7488.2020.

[8] N. Dand, M. Duckworth, D. Baudry, A .Russell, CJ. Curtis, SH. Lee, I .Evans, KJ. Mason, A .Alsharqi, G. Becher, AD .Burden, RG. Goodwin, K. McKenna, R .Murphy, GK. Perera, R. Rotarescu, S. Wahie, A .Wright, NJ. Reynolds, RB. Warren, CEM. Griffiths, CH .Smith, MA. Simpson, JN .Barker; BADBIR Study Group; BSTOP Study Group; PSORT Consortium. : HLA-C*06:02 genotype is a predictive biomarker of biologic treatment response in psoriasis. J Allergy Clin Immunol.; VOL .143:PP. 2120–2130. 2019**.**

[9] G .Girolomoni, R. Strohal, L .Puig, H .Bachelez, J. Barker, WH. Boehncke, JC .Prinz. : The role of IL-23 and the IL-23/TH 17 immune axis in the pathogenesis and treatment of psoriasis. J Eur Acad Dermatol Venereol.; VOL. 31(10):PP.1616-1626. 2017.

[10] JE .Hawkes, TC. Chan and JG. Krueger.: Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol; VOL .140: PP. 645–653.2017.

[11] AW .Armstrong and C. Read.: Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA.; VOL .323(19):PP. 1945-1960. 2020.

[12] G .Dupire, C. Droitcourt, C .Hughes and L. Le Cleach. Antistreptococcal interventions for guttate and chronic plaque psoriasis. Cochrane Database Syst Rev; 3: CD011571. 2019.

[13] S. Dogra and H. Mehta: Biological treatment for erythrodermic psoriasis. Expert Opin Biol Ther.; VOL . 22(12): PP.1531-1543. 2022.

[14] KM. Hoegler, AM. John, MZ . Handler and RA. Schwartz: Generalized pustular psoriasis: a review and update on treatment. J Eur Acad Dermatol Venereol; VOL .32: PP.1645–1651. 2018.

[15] S. Twelves, A .Mostafa, N. Dand, E. Burri, K. Farkas, R. Wilson, HL. Cooper, AD .Irvine, HH .Oon, K S.Kingo, U. Köks, L. Mrowietz, N. Puig, ES. Reynolds, A. Tan, K. Tanew, H. Torz,. Trattner, M Valentine, S .Wahie, RB .Warren, A .Wright, Z. Bata-Csörgő, M. Szell, CEM. Griffiths, AD. Burden, SE. Choon, CH. Smith, JN. Barker, AA. Navarini, F .Capon.: Clinical and genetic differences between pustular psoriasis subtypes. J Allergy Clin Immunol; VOL . 143: PP.1021–1026. 2019**.**

[16] BF. Sena, JL .Figueiredo and E .Aikawa.: Cathepsin S As an Inhibitor of Cardiovascular Inflammation and Calcification in Chronic Kidney Disease. Front Cardiovasc Med.; VOL . 4: PP.88. 2018.

[17] RD .Wilkinson, R .Williams, CJ. Scott and RE. Burden.: Cathepsin S: therapeutic, diagnostic, and prognostic potential. Biol Chem.; VOL .396(8):PP. 867-882. 2015.

[18] T .Yadati, T .Houben, A .Bitorina and R. Shiri-Sverdlov: The ins and outs of cathepsins: physiological function and role in disease management. Cells.; VOL .9(7): PP.1679. 2020.

[19] Y .Jing, J .Shi, B .Lu, W .Zhang, Y. Yang, J. Wen, R. Hu, Z. Yang, X .Wang. : Association of Circulating Cathepsin S and Cardiovascular Disease Among Patients With Type 2 Diabetes: A Cross-Sectional Community-Based Study. Front Endocrinol (Lausanne).; VOL . 12:PP. 615913.2021.

[20] N. Fuchs, M. Meta, D .Schuppan, L. Nuhn, T .Schirmeister.: Novel Opportunities for Cathepsin S Inhibitors in Cancer Immunotherapy by Nanocarrier-Mediated Delivery. Cells.; VOL .9(9): PP.2021.2020.

[21] Y .Yoo, E. Choi, Y. Kim, Y. Cha, E .Um, Y. Kim, Y. Kim, YS .Lee.: Therapeutic potential of targeting cathepsin S in pulmonary fibrosis. Biomed Pharmacother.; VOL 0145:PP. 112245. 2022.

[22] JS. Ainscough, T. Macleod, D .McGonagle, R .Brakefield, JM .Baron, A. Alase, M .Wittmann, M. Stacey.: Cathepsin S is the major activator of the psoriasis-associated proinflammatory cytokine IL-36γ. Proc. Natl. Acad. Sci. U.S.A; VOL .114(13):PP.E2748- E275757.2017.

[23] K. Brix, A. Dunkhorst, K. Mayer, S .Jordans.: Cysteine cathepsins: cellular roadmap to different functions. Biochimie : VOL . 90: PP.194–207.2008.

[24] C .Albanesi, O. De P, G. Girolomoni: Resident skin cells in psoriasis: a special look at the pathogenetic functions of keratinocytes. Clin Dermatol.: VOL .25: PP0581–588. 2007.