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Serum calgizzarin (s100a11) level in psoriatic patients and its association with disease activity: A case-control study

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Abstract
Objectives: A wide variety of extrinsic and intrinsic risk factors may play a role in the development of psoriasis, a long-lasting systemic inflammatory disease. In multiple tissues, the proteins known as (S100) perform a few different activities. Basal epidermal keratinocytes' cytoplasm and the cell periphery of spinous layer cells both contain S100A11. It occurs in regular human keratinocytes in culture. The present investigation was to contrast the blood calgizzarin levels of individuals with psoriasis against those in normal people and to determine whether there was an association between the levels and the degree of severity of the condition.
Methods and materials: Forty individuals with psoriasis enrolled in this case-control clinical trial, while a control group of forty individuals in good health who had been assigned for age and sex provided a standard for comparison. The patients underwent PASI score assessment and serum calgizzarin levels were assessed through ELISA technique.
Results: Calgizzarin serum levels were considerably higher in psoriasis patients compared to the control group (p=0.037). In comparison to male individuals who had psoriasis, substantially increased blood levels of calgizzarin were found in female patients. (p=0.044). According to the degree of severity of the disorder determined by the PASI score, the mean of the calgizzarin levels gradually increased but not substantially. Serum levels of calgizzarin in psoriasis patients did not show any statistically significance relation to the presence of positive family history of the psoriasis, presence of arthropathy, nail affection, psoriasis type, or disease severity.
Conclusion: The current study points out the possibility of involvement of calgizzarin in the etiology of the psoriasis condition. Significantly higher values of serum calgizzarin in females with psoriasis might indicate higher inflammatory state and risks in this patient group.
Limitations: The small sample size is the major limitation of this study.

Keywords: Calgizzarin, Psoriasis, S100A11

Introduction

Psoriasis is a determined, multisystem inflammatory disorder that mostly affects the skin and joints [1, 2].

The onset and maintenance of psoriatic inflammation are caused by changes in the natural and adaptive cutaneous immune responses. On an auto inflammatory backdrop, psoriasis exhibits characteristics of an autoimmune illness, with both routes interfering with and possibly amplifying another on [3].

A lesser-known participant of the large calcium-binding S100, also known protein family, S100A11 (also known as S100C or calgizzarin) has been recommended to play particular biologic functions related to the mechanisms of endocytosis and exocytosis, enzyme activity control, cell growth, apoptosis, and low-grade inflammation [4].

Growth is stimulated by calgizzarin's action on healthy human keratinocytes, which increases the generation of proteins from the EGF family. Calgizzarin-triggered signal transduction is controlled by the receptor for advanced end products of glycation (RAGE), nuclear factor-kappa B (NF-kB), Akt, and cAMP response element-binding protein [5]. Oncogenesis, inflammation, and myocardial injury are all correlated with it [6].

This study's objective was to compare the serum calgizzarin levels of individuals suffering from psoriasis to those of normal controls and look for any possible associations to the

status of prisoners, unsafe sex practices and needle-sharing habits all add up to why tuberculosis (TB) is very commonly seen in Indian prisons. High rates of TB have been reported by Human Rights Watch in India and a study in 2008 had found that 9% of prison deaths was attributed by TB.

Degree of severity of the condition

Methods

This case-control clinical investigation included 40 psoriasis individuals as well as an equal number of healthy control participants who were allocated for age and sex for comparison.

They were all collected from the outpatient clinics of Dermatology and Venereology Department, Tanta University. Hospital, during the period from April 2021 to October 2021.

The research ethics committee of the Quality Assurance Unit's institutional review board gave permission to the study protocol, Faculty of Medicine Tanta University (approval code: 34574/3/21). An informed written consent was obtained from every individuals in the study after full explanation of the nature, aim and possible risks of the study.

Exclusion criteria were psoriasis patients receiving systemic treatment for psoriasis during the preceding three months, those receiving topical treatment during the preceding two weeks prior to incorporation in the study, psoriatic patients who have any other dermatological or systemic diseases that may alter serum calgizzarin levels such as rheumatoid arthritis, diabetes mellitus, osteoarthritis, and chronic kidney disease in addition to pregnant or lactating women.

Individuals with psoriasis had a complete general and dermatologic investigation, a full history collecting procedure, and PASI score evaluation. 7 In accordance with the manufacturer's instructions, a commercially available ELISA kit (BioVendor, Brno, Czech Republic) was used to assess the serum levels of calgizzarin in both individuals and controls. The assay's detection limit is 0.01 ng/ml.

Statistical analysis and sample size

The sample size is determined by the main goal. Initially, the sample size needed was forty cases and forty normal individual using a 95% confidence interval that the positive probability ratio is more than two, considering a proportion of 1:1 cases to controls, and an estimated sensitivity of 0.8 and specificity of 0.7.

Data management and analysis

Data was tabulated and introduced into a PC using SPSS version 26.0. Non-numerical information is presented as frequency and percentage and compared through the Chi-square test. The Shapiro-Wilk test was used to determine whether numerical results were regular, after which they were expressed as mean and standard deviation or median and range, and finally, and contrasted through the Student-t test. The Spearman correlational test was utilized to determine the connection among serum calcizzarin quantities and other numerical parameters. Two tailed P value< 0.05 was regarded as a statistically significant difference.

Results

The subjects' clinical information and the blood calgizzarin concentration of ng/ml are shown in Table 1. Concerning age or sex, there was no substantial variation found among psoriasis patients & normal individual.

Patients with psoriasis had substantially higher levels in their serum of calgizzarin than the control group.

(P=0.037), (Table 1).

Serum levels of S100A11 didn't substantially correlate with individuals' age, age at the beginning of the disease, disease duration, or PASI level (Table 2).

A statistically significant higher serum levels of calgizzarin was detected in female psoriasis patients than male patients (P=0.044). There was a statistically insignificant sequential elevation in the mean calgizzarin levels in relation with psoriasis disease severity evaluated by PASI score. Serum levels of calgizzarin in psoriasis patients did not show any statistically significance relation to the presence of positive family history of the psoriasis, presence of arthropathy, nail affection, psoriasis type, or disease severity (Table 3).

Discussion

A multigene family of protein molecules of low molecular weight having several activities in a variety of tissues and cell types makes up the S100 proteins. The epidermal differentiation complex is connected to several members of this gene family. Given that it contains several genes that are produced by epidermal keratinocytes, this area is of great importance. S100A11 (calgizarrin) is located in the cytoplasm of basal keratinocytes in the epidermis and at the cell periphery in brickle cell layer cells. It is also expressed in cultured normal human keratinocytes [5].

The human epidermis generates eight S100 proteins (S100A2, S100A7, S100A8, S100A9, S100A10, S100A11, S100A12, and S100), but it is generally unclear what these proteins do [8]. According to Broome *et al*.'s [9] hypothesis, S100 proteins are essential for the differentiation of keratin cells and the development of psoriasis. In the current research, individuals with psoriasis had considerably greater blood levels of calgizzarin than the unaffected group. Calgizzarin dysregulation has been associated with a number of human conditions, including neoplastic, neurological, and metabolic diseases [10, 11, 13]. Closer to the context of our study, it was found that calgizzarin levels are elevated in several inflammatory disorders. Navrátilová *et al*. [14] reported that the pro-inflammatory cytokines IL-6 and TNF can be produced when calgizzarin levels are high, indicating a connection among calgizzarin and an aggravated inflammatory reaction. This could be a plausible explanation to the elevated calgizzarin levels in psoriatic patients in the present study which was further emphasized by the sequential elevation (though non-significant) in the mean serum levels of calgizzarin in relation to disease severity presented as PASI score, with the highest values found in patients with severe disease.

Another possible explanation could be reached. As a form of defense against the host, neutrophils may generate neutrophil extracellular traps (NETs), and this procedure is known as NETosis. Many autoimmune conditions, including psoriasis, have been associated to the imbalance of NETosis, in which NETs are the main source of mediators like IL-17, which can further enhance neutrophil deposition by enhancing CXCL1, CXCL2, and IL-8 production. It has also been demonstrated that the neutrophil production of IL-17 is essential for the formation of neutrophils. [16] Calgizzarin constitutes one of the proteins related with neutrophils in inflammatory tissues, according to Gravius *et al* [17]. NETosis is associated with neutrophil calgizzarin production. Last but not least, we could

hypothesize that calgizzarin's inflammatory mediators action on neutrophils may be an essential connection among this substance and psoriasis. Another possible link between calgizzarin and psoriasis could emerge from its extracellular localisation, so Calgizzarin has the ability to connect to the RAGE receptor as a signaling molecule. Calgizzarin attaching to RAGE can cause the chemokine monocyte chemotactic protein 1 (MCP-1/CCL2) to be produced [18].

After CCL2 attaches to the chemokine receptor CCR2, which is largely found on the surface of monocytes and causes the monocytes to develop into macrophages and move from the blood stream to areas of inflammation, the keratinocytes in individuals with psoriasis are the major source of CCL2. The development of lesions may result from this procedure. As a result, it has been proposed that CCL2 may serve as a possible indicator to track the development of psoriasis. In turn, this supports considering calgizzarin as a potential role player in psoriasis [19].

This study explored a statistically significant difference in the calgizzarin levels according to gender with significantly higher values noted in females. Investigations on the epidemiology of diseases have repeatedly shown that women have more ferocious immune responses than males, and that they also have a greater frequency of autoimmune and inflammatory disorders [20].

The existence of psoriatic arthropathy did not correlate substantially with calgizzarin levels in the current investigation. This is not coinciding with the data suggesting its association with joint inflammation, such as in cases of osteoarthritis [21]. It should be noted that individuals with rheumatoid arthritis demonstrated higher amounts of calgizzarin in their synovial tissues and synovial fluid, respectively, but not in their blood, according to a previous investigation [4]. In the present study the levels of calgizzarin have been assessed only in serum, not in joints of patients with psoriasis arthropathy. Therefore, further studies investigating calgizzarin levels in the joint tissue in such patients would be more tangible.

To the best of our understanding, this study is the first clinical investigation that evaluates calgizzarin concentrations in individuals with psoriasis. This led to lack of data available for comparison. Our study highlighted the role of calgizzarin as a potential factor in psoriasis disease pathogenesis. Additionally, it seemed to suggest an effect for calgizzarin in the progression of severity of psoriasis as measured by the PASI result, although the results lacked statistical importance, perhaps as a result of the present research's small sample size. More extensive research with a bigger sample size is necessary.

Table 1: Participants' clinical and laboratory data

	Psoriasis patients (n = 40)	Controls (n = 40)	Test of Significance	p-value
Gender, n (%)				
Male	22(55)	26(65)	χ^2=0.38	0.54
Female	18(56)	14(35)		
Age (years)				
Min-Max	17 - 61	66– 20	U=633	0.11
Mean ± SD	14.5 ≠41.8	14.1≠36.5		
Family history of psoriasis, n (%)				
Positive	3(7.5)			
Negative	37(92.6)			
Associated arthropathy, n (%)	10 (25%)	-		
Associated nail affection, n (%)	8 (20%)	-		
Psoriasis type, n (%)		-		
Generalized plaque psoriasis	29 (72.5%)			
Localized plaque psoriasis	6 (15%)			
Palmoplantar psoriasis	3 (7.5%)			
Scalp psoriasis	1 (2.5%)			
Erythrodermic psoriasis	1 (2.5%)			
Disease severity, n (%)				
Mild (PASI <5)	19 (47.5%)			
Moderate (PASI=5-10)	13 (32.5%)			
Severe (PASI > 10)	8 (20%)			
Age of disease onset in years, mean(SD)	29.7(13.3)	-		
Serum S100A11 (calgizzarin) level				
(ng/ml) Min –Max	225.9- 697.5	167.5- 650	t-test=2.13	0.037
Mean± SD	358.1±89.1	313.3±99.5		

Table2: Correlation between the serum calgizzarin level and the patients' clinical data

Calgizzarin levels (ng/ml)	
Age (years)	
r	0.083
p-value	0.613
Age of onset (years)	
r	0.149
p-value	0.358
PASI score	
r	0.021
p-value	0.897

R: Spearman's correlation coefficient, PASI: psoriasis area severity index

Table 3: Serum calgizzarin levels in relation to patients' clinical data

Calgizzarin levels (ng/ml)	
Sex	
Male	332.6±70.4
Female	389.2±101.3
p-value	0.044*
Family history	361.7±14.8
p-value	0.94
Associated arthropathy	351.1±91.9
p-value	0.4
Associated nail affection	336.4±71.5
p-value	0.45
Disease severity	
Mild	348.3±72.9
Moderate	359.2±72.8
Severe	379.6±144.1
p-value	0.72
Psoriasis type	
Generalized plaque psoriasis	355.1± 94.2
Localized plaque psoriasis	354±85.3
Palmoplantar psoriasis	390.5±68.6
Scalp psoriasis	442.1[#]
Erythrodermic psoriasis	287.1[#]
p-value	0.79

#: one case only in the group and was not included in the comparison,
***:** statistically significant, Data are represented as Mean ± SD, or Frequency (%)

Conclusion

The outcomes of the current investigation promote the potential involvement of calgizzarin in the pathophysiology of the psoriasis diseases and abnormal epidermal cell division. Significantly higher values of serum calgizzarin in females with psoriasis might indicate higher inflammatory state and risks in this patient group.

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Nil

Conflict of Interest

Nil

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