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Original article

Evaluation of plasma gelsolin level in chronic atopic dermatitis children patients versus adult patients: A case control study



Évaluation du taux plasmatique de gelsoline chez les enfants atteints de dermatite atopique chronique par rapport aux adultes : une étude cas-témoins

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ABSTRACT

Background. – Atopic dermatitis (AD) is a chronic inflammatory disease with exacerbations and remissions affecting patient quality of life. Gelsolin is an actin-binding protein with multiple functions as an anti-inflammatory and anti-apoptotic effect. Few studies evaluating level of plasma gelsolin (pGSN) in AD patients.

Objectives. – Estimate pGSN in chronic AD patients and evaluate its relation to age and disease severity.

Methods. – A case control study included 40 patients with chronic AD and 40 age and sex matched healthy controls. Both patient and control groups were sub-divided into 2 groups: Children group (2–18 years) and adult group (above 18 years). pGSN level was measured for all participants with ELISA method.

Results. – pGSN level showed a statistically significant decrease in AD children patients compared to their healthy controls [23 (20.2–37.65) versus 44.10 (25.25–70.5) ng/ml, $P=0.016$]. Also, pGSN showed a statistically significant decrease in AD adult patients compared to their healthy controls [22.75 (19.5–27) versus 43.65 (23.0–80.0) ng/ml, $P=0.017$]. No statistically significant difference in pGSN level between chronic AD children patients and adult patients ($P=0.665$). A highly significant negative correlation between pGSN and SCORAD score in both children and adult chronic AD patients ($P=0.001$, $P=0.001$) respectively.

Conclusions. – Decreased pGSN levels in both children and adult chronic AD patients with correlation to disease severity pointing to its role in AD disease process.

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R É S U M É

Situation du problème. – La dermatite atopique (DA) est une pathologie inflammatoire chronique marquée d'épisodes d'exacerbations et de rémissions affectant la qualité de vie des patients. La gelsoline est une protéine liant l'actine à multiples fonctions dont des propriétés anti-inflammatoires et anti-apoptose. Peu d'études se sont consacrées à étudier le taux de gelsoline plasmatique (pGSN) chez les patients atteints de DA.

But de l'étude. – Mesurer le taux de pGSN chez des patients atteints de DA chronique et évaluer sa relation avec l'âge et la sévérité de la maladie.

Méthodes. – Étude cas-témoins incluant 40 patients atteints de DA chronique et de 40 témoins sains appariés sur l'âge et le sexe. Les patients et les cas contrôles ont été divisés en 2 groupes : enfants (2–18 ans) et adultes (plus de 18 ans). Le taux de pGSN a été mesuré chez tous les participants par méthode ELISA.

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Résultats. – Le taux de pGSN est significativement plus bas chez les enfants atteints de DA par rapport aux témoins sains [23(20.2–37.65) versus 44.10 (25.25–70.5) ng/ml, $P=0,016$]. De même le taux de pGSN montre une diminution statistiquement significative chez les adultes atteints de DA chronique par rapport aux témoins sains [22.75 (19.5–27) versus 43.65 (23.0–80.0) ng/ml, $P=0,017$]. Aucune différence significative n'a été observée dans les taux de pGSN entre enfants et adultes atteints de DA chronique ($P=0.665$). Une corrélation négative hautement significative a été observée entre le taux de pGSN et le score SCORAD à la fois chez les enfants et les adultes atteints de DA ($P=0,001$: 0,001 respectivement).

Conclusions. – Il existe une diminution des taux de pGSN à la fois chez les enfants et les adultes atteints de DA en corrélation avec la sévérité de la maladie alertant sur le rôle de la gelsoline dans la physiopathologie de l'affection.

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1. Introduction

Atopic dermatitis (AD) is a multifaceted, chronic inflammatory skin disease with relapsing nature. AD is commonly associated with other atopic manifestations such as allergic rhinitis, food allergy, and asthma. AD affects nearly 15% to 20% of children and 1% to 3% of adults. Symptoms of AD commonly resolve by time; however, AD can persist throughout adulthood in about 10% to 30% of patients [1]. Genetic, immunologic, inflammatory and environmental factors all can play a role in pathogenesis of AD leading to a dysfunctional skin barrier and immune system dysregulation. The actin cytoskeleton contributes in the regulation of apoptosis through interplay with mitochondria. Several actin-binding proteins including gelsolin regulate assembly, disassembly and also organization of actin filaments [2]. Gelsolin is an intracellular actin-binding protein with multiple cellular functions including anti-apoptosis and an anti-inflammatory effect. Apoptosis of keratinocytes mediated by Fas/Fas Ligand molecular interaction and subsequent caspase activation has been considered as a key mechanism of atopic dermatitis (AD) [3]. Gelsolin exists in the human body as 2 isoforms, a cytoplasmic and a secreted isoform, both isoforms originate from the same 70 kb gene on chromosome 9 [4].

pGSN circulates in the blood of healthy subjects at a concentration of 200 ± 50 mg/L. Gelsolin has been considered as a key component of an extracellular actin-scavenging system during tissue injury. Studies reported decreased levels of pGSN during acute injury and inflammation, and improved outcomes after sepsis and burn injuries with recombinant plasma gelsolin administration in animals models [5].

Few studies evaluated role of gelsolin in patients with chronic inflammatory and allergic disorders [5,6]. So, the aim of the present study was to estimate pGSN level in chronic AD patients and evaluate its relation to age and disease severity.

2. Materials and methods

The present study is a case control study included 40 patients with chronic AD and 40 age and sex matched healthy controls. Patients and healthy controls were randomly selected from the Dermatology Outpatient's Clinic at Al-Zahraa University Hospital, Cairo, Egypt. Both patients and controls were sub-divided into 2 groups: group I (children group, 2–18 years) and group II (adults, above 18 years). Informed written consent was signed by all participants in the study or their caregivers before inclusion in the study.

The study was approved by the Research Ethics Committee of Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt.

The patients were diagnosed as AD according to criteria of Hanifin and Rajka [7]. Chronic AD Patients with different severity (mild, moderate and severe), were assessed by objective SCORAD index [8]. Pregnant or breastfeeding females, patients who have other

chronic skin disease, or autoimmune diseases that could affect the outcome of the study as rheumatoid arthritis and systemic lupus erythematosus, and patients with concurrent significant medical conditions such as malignancy, diabetes mellitus, hepatic, renal, or cardiovascular diseases were excluded. Also, patients with concurrent topical corticosteroid or systemic treatment one month prior to the study were also excluded.

2.1. Measurement of plasma gelsolin level:

5 ml venous blood was collected from each participant by the use of disposable sterilized plastic syringes. Blood was added into tubes with anticoagulant (EDTA), tubes centrifugated for 15 minutes at 2000 rpm. Then the plasma collected and stored at -80°C for subsequent measuring of gelsolin level by enzyme linked immunosorbent assay (ELISA) Kit from Bioneovan Co., Lt with Catalog#: 14177 (China).

2.2. Statistical analysis

The Statistical Package for Social Science (version 23 of IBM SPSS Statistics for Windows, Armonk, NY, IBM Corp.) was used to perform the data. The qualitative variables were performed as number and percentages. Mean, standard deviations and ranges used to present the quantitative variables with parametric distribution and median with inter-quartile range (IQR) when non-parametric. The relationship between qualitative data was performed by using Chi² test. The relationship between two independent groups with quantitative variables and parametric distribution was performed through independent t-test, while Mann-Whitney test was created for handling non-parametric data.

The relation between more than two independent groups with quantitative variables and non-parametric was performed by Kruskal-Wallis test. The correlation between two quantitative parameters in the same group was assessed by Spearman correlation coefficients. We considered P values <0.05 as significant.

3. Results

In the present study, group I enrolled 20 chronic AD children patients (18 females and 2 males) with a mean age of 7.10 ± 2.95 years and 20 age and sex matched healthy controls. pGSN levels of the AD children patients ranged from (12.4–68.5) ng/ml with median (23) ng/ml, while pGSN levels of their healthy controls ranged from (15.5–99.5) ng/ml with median (44.10) ng/ml showing a statistically significant decrease in pGSN levels in children AD patients compared to their controls ($P=0.016$) (Fig. 1A).

Group II involved 20 chronic AD adult patients (19 females and 1 male) with a mean age of 26.05 ± 7.28 years and 20 age and sex matched healthy controls. In adult AD patients, pGSN levels ranged from (15–78) ng/ml with median (22.75) ng/ml, while pGSN lev-

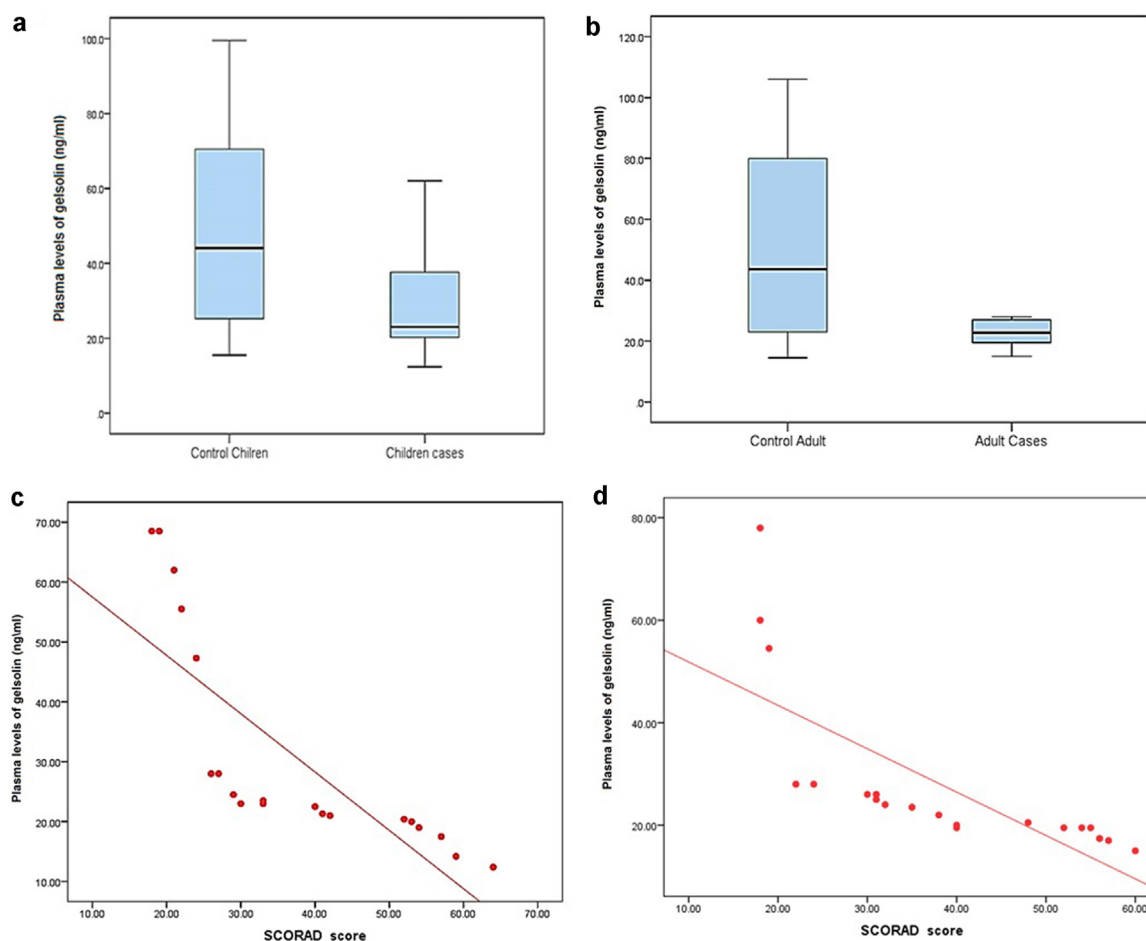


Fig. 1. Decreased pGSN levels in AD patients with negative correlation to SCORAD score. A. Plasma levels of gelsolin in children cases and the healthy controls ($P=0.016$). B. Plasma levels of gelsolin in adult cases and the healthy controls ($P=0.017$). C. Correlation between pGSN and SCORAD score of the chronic AD children patients ($P=0.001$). D. Correlation between pGSN level and SCORAD score of the chronic AD adult patients ($P=0.001$).

Table 1

Correlation between pGSN levels of the children patients and age, age of onset, duration and SCORAD score.

	Plasma levels of gelsolin	
	Children patients	
	<i>r</i>	<i>P</i> -value
Age	0.391	0.088
Age of onset/year	0.349	0.132
Duration of the disease/year	0.352	0.128
SCORAD score	−0.996**	0.001

els of their healthy controls ranged from (14.5–106) ng/ml with median (43.65) ng/ml revealing a statistically significant decrease in pGSN levels in the adult patients compared to their controls ($P=0.017$) (Fig. 1, B).

pGSN levels showed no statistically significant difference between chronic AD children patients and adult patients ($P=0.665$).

Correlation between pGSN levels and age, age of onset of AD, duration of disease and SCORAD score in the children patients showed a highly significant negative correlation between pGSN levels and SCORAD score ($P=0.001$) (Table 1, Fig. 1C).

Correlation between pGSN levels and age, age of onset of AD, duration of disease and SCORAD score in the adult patients showed a highly significant negative correlation between pGSN levels and SCORAD score ($P=0.001$) (Table 2, Fig. 1D).

In group I, median value of pGSN level in patients with positive asthma history was (23.00) ng/ml while in patients with

Table 2

Correlation between pGSN levels of the adult cases and age, age of onset, duration and SCORAD score.

	Plasma levels of gelsolin	
	Adult cases	
	<i>r</i>	<i>P</i> -value
Age	−0.163	0.493
Age of onset/year	0.220	0.351
Duration of the disease/year	−0.441	0.052
SCORAD score	−0.986**	0.001

negative asthma history was (24.50) ng/ml showing no statistically significant relation between history of asthma and pGSN level (P -value >0.05). Also, no statistically significant relation was found between sex of the children cases, family history of allergy and pGSN level (p -value >0.05) (Table 3).

In group II, median value of pGSN level in patients with positive asthma history was (19.50) ng/ml while in patients with negative asthma history was (26.00) ng/ml showing a highly statistically significant differences between history of asthma and pGSN level with decrease level among the positive asthma patients (P -value <0.001) (Table 4, Fig. 2).

4. Discussion

Plasma gelsolin and its residues bind lipopolysaccharide (LPS), lipoteichoic acid (LTA), in addition to other mediators, as

Table 3

Relation between sex, history of asthma, family history of allergy and pGSN level in the Children cases.

Children cases	Plasma level of gelsolin		Test value	P-value	Sig.
	Median (IQR)	Range			
Sex					
Female	23.00 (20.40–28.00)	12.40–68.50	–0.441 ^a	0.659	NS
Male	44.25 (20.00–68.50)	20.00–68.50			
History of asthma					
Yes	23.00 (19.00–28.00)	12.40–62.00	–1.468 ^a	0.142	NS
No	24.50 (21.30–68.50)	21.00–68.50			
Family history of allergy					
Yes	23.00 (20.00–28.00)	12.40–68.50	–0.206 ^a	0.836	NS
No	22.40 (21.00–55.50)	14.20–68.50			

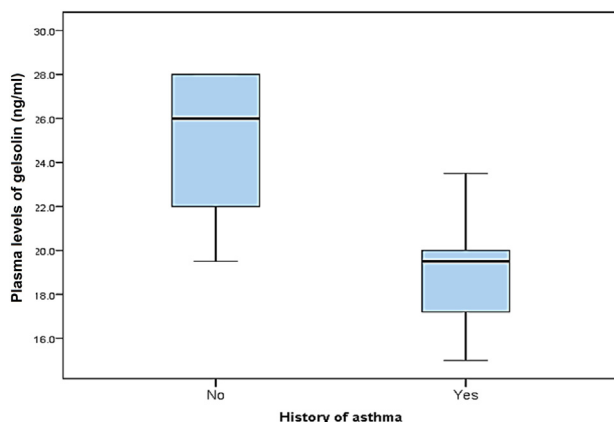
P-Value > 0.05 is considered not significant.

^a Mann–Whitney test.**Table 4**

Relation between sex, history of asthma, family history of allergy and pGSN level in the adult cases.

Adult cases	Plasma level of gelsolin		Test value	P-value	Sig.
	Median (IQR)	Range			
Sex					
Female	22.00 (19.50–28.00)	15.00–78.00	–0.261 ^a	0.794	NS
Male	24.00 (24.00–24.00)	24.00–24.00			
History of asthma					
Yes	19.50 (17.00–20.50)	15.00–23.50	–2.906 ^a	0.004	HS
No	26.00 (22.00–28.00)	19.50–78.00			
Family history of allergy					
Yes	20.00 (19.50–25.00)	15.00–78.00	–0.992 ^a	0.321	NS
No	24.00 (19.50–28.00)	17.00–60.00			

P-Value > 0.05 is considered not significant.

^a Mann–Whitney test.**Fig. 2.** Relation between pGSN levels and personal history of asthma in adult cases (P= 0.004).

lysophosphatidic acid (LPA), platelet-activating factor (PAF), and β -amyloid peptide [9,10]. It is hypothesized that pGSN acts as its anti-inflammatory by binding to these molecules and inactivating them. pGSN scavenges and severs actin filaments released from cells during injury and inflammation and thus preventing the possible toxicity of insoluble F-actin filaments [9,10]. Previous studies showed decreased pGSN levels in acute inflammatory conditions. In addition to decreased levels in acute inflammatory conditions, it was shown that pGSN levels were also decreased in chronic inflammatory conditions as well [3,5,11]. Local pGSN consumption by a shift of binding toward actin during actin exposure after injury allows mediators to stimulate proper defense and repair functions. This set of events is theoretically also applicable to chronic inflammatory disorders where cellular damage and mediator release occur [4], but few studies have examined pGSN levels in AD.

Reported efficacy of administered pGSN in animals exposed to systemic inflammation suggests that it has a protective role in inflammation, and that gelsolin can be a broad-spectrum anti-inflammatory buffer [12–14].

The present study which was designed to measure pGSN in chronic AD patients, demonstrated significant decrease in plasma GSN levels of chronic AD patients compared to their healthy controls, with non-significant differences between children and adult patients. This findings goes with the study of Eke Gungor et al. [3] who investigated level of plasma GSN in children with AD and revealed a significant decrease in plasma GSN level in children patients.

Our results showed non-significant relation between family history of allergy, personal history of asthma and pGSN level in AD children patients. This is comparable to the findings of Eke Gungor et al. [3], who divided studied patients into 2 groups depending on the presence (AD+/Atopy+) or absence of Skin prick testing (SPT) positivity (AD+/Atopy-) and reported no significant differences in the pGSN levels between patients with AD (+ve atopy) and patients with AD (-ve atopy). They attributed the role of pGSN on AD disease itself regardless of the presence of atopy that plasma gelsolin affects AD disease process with different mechanism other than the IgE-mediated type 1 hypersensitivity reactions.

However, these findings should be emphasized by evaluating tissue expression of GSN in AD skin lesions, which is considered a limitation in the current study.

The present results showed significant relation between pGSN level and history of asthma in AD adult patients, but can be attributed to the small sample size which is considered a limitation in the current study. No other studies evaluated pGSN level in adult AD patients.

Our findings were close to Osborn et al. [5], who reported reduced pGSN levels in plasma of patients with RA as the first example of such depletion during chronic inflammation. The decrease

was inversely related to the intensity of systemic inflammation. In addition, they reported that, pGSN levels are even lower intra-articularly in affected joints. However, the cause of this depletion remains unclear as enzymatic degradation or decreased production cannot be excluded.

But they thought that the ability of pGSN to bind several factors found in the inflamed joint and the lack of detection of proteolytic fragments points to a local consumption.

The present study revealed, a highly negative significant correlation between PGSN levels and SCORAD Score of AD disease in all patients suggesting that pGSN may reflect over all disease severity in these patients. This finding disagreed with Eke Gungor et al. [4], who demonstrated no significant correlation between PGSN and disease severity.

Present findings showed decreased levels of pGSN in patients of AD, which is a chronic inflammatory disease with remissions and acute exacerbations. So our findings can be comparable to the mentioned studies [3,5]. Few studies on gelsolin levels in patients with allergic diseases were found. Kawamoto et al. [15], was the first to prove that the gelsolin family molecule Der f 16 as a new class of house dust mite allergen. Gelsolin superfamily is highly conserved in multicellular organisms, so it could be expected that this protein family may act as a pan-allergen with IgE cross-reactivity [15]. In addition, it was found that gelsolin is the most abundant protein that breaks down actin filaments in human bronchial epithelial cell cultures [16].

Janciauskiene et al. [6], reported that allergic rhinitis patients without immunotherapy had decreased levels of anti-apoptotic protein (gelsolin), indicating a direct relation between pGSN and soluble forms of Fas and Fas-L, as markers of apoptosis and systemic inflammation. T cell-mediated, Fas-induced keratinocyte apoptosis plays a main role in AD pathogenesis [17]. With the decreased pGSN levels in both children and adult AD patients in the present study, it can be suggested that anti-apoptotic effects of pGSN are more important than the apoptotic effects in patients with AD. This finding calls for larger studies evaluating tissue expression of gelsolin in AD skin lesions might help in better understanding the pathogenesis and possibly aid in future treatments.

5. Conclusion

Decrease level of pGSN in AD patients (children and adult) in comparison to their healthy controls, with significant correlation to disease severity pointing to its role in the disease progress in AD patients. further researches to evaluate tissue expression of gelsolin in cutaneous lesions are required to validate the present results.

Disclosure of interest

The authors declare that they have no competing interest.

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