Serum Thymus and Activation-Regulated Chemokine (TARC/CCL17) in Atopic Dermatitis

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Abstract: Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease which occurs most frequently in children but can occur in adults following a relapsing course, characterized by intense pruritus with marked exacerbation and remission. Chemokines have been proposed to play a role in pathogenesis of AD. Thymus and activation- regulated chemokine (TARC⁄CCL17) has been suggested to be a pivotal mediator in the inflammatory reaction as AD. Aim of work: The aim of this study is to determine serum level of TARC in AD patients in order to evaluate its role in the pathogenesis of the disease. Subjects and methods: This study included 20 patients with AD in addition to 10 healthy subjects of matched age and sex who served as a control. Serum samples were taken from all patients and controls for detection of serum TARC level by Enzyme- linked immunosorbent assay (ELISA). Results: A highly significant increase was found in the mean serum TARC level in AD patients compared to controls. Serum TARC level was statistically correlated with severity of the disease as determined by six- area, six- sign atopic dermatitis (SASSAD) severity score. Also, a significant correlation was demonstrated between serum TARC level and age of AD patients as well as duration of the disease. Conclusion: TARC has been implicated as an important chemokine in the pathogenesis of AD. TARC can be used as a useful marker for assessing AD severity and open the way for a further therapeutic approach.
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1. Introduction

Atopic dermatitis (AD) is a common chronic inflammatory relapsing eczematous dermatitis characterized by intense pruritus that involves peripheral blood eosinophilia and a high level of serum immunoglobulin (Ig) E [(1)]. The prevalence of AD is increasing world wide approaching five to twenty percent, ninety percent of children with AD are affected by the age of five years while, sixty percent of AD patients present the disease within the first year of life [(2).] The exact pathogenesis of AD is unclear. However, several constitutional abnormalities such as, genetic, immunologic, cellular, and environmental factors, as well as defects in skin barrier function may contribute to the disease [(3)]. Acute lesional skin of patients with AD is characterized by eosinophil-derived granule deposits as well as macrophage and T-cell infiltration, which predominantly T-helper (Th) 2-type cells expressing such cytokines as interleukin (IL)-4, IL-5 and IL-13 [(4)] . The lymphocytes and eosinophils are attracted to the skin by many different chemoattractants and among these are the chemokines [(5)] . Chemokines have been identified as attractants of different types of leukocytes to the sites of infection and inflammation. They are divided into four subfamilies, CX, CC, CX3C and C chemokines, depending on the position of the first two N-terminal cysteine residues[(6)]. They are produced locally in the tissues and act on leukocytes through specific receptors. They also function as regulatory molecules in leukocyte maturation, trafficking and homing in the development of lymphoid tissues [(7)]. A systematic nomenclature has been devised for chemokines and their corresponding seven-trans-membrane G-protein- coupled receptors [(8)], among them is TARC⁄CCL17 [(9)]. TARC⁄CCL17 is a ligand for CC chemokine receptor-4 (CCR4) and is produced mainly by epidermal keratinocytes (KCs), monocyte-derived dendritic cells (DCs), endothelial cells, bronchial epithelial cells [(10)]. It is considered to be a pivotal mediator in the inflammatory reaction specially AD disease. It has been reported that the blood level of TARC⁄CCL17 is significantly elevated in AD [(11)], which suggest that it might be possible to utilize TARC⁄CCL17 as a clinical marker of AD disease activity and response to treatment[(12)].

Aim of the Work:

The aim of this study is to determine serum level of TARC in AD patients in order to evaluate its role in the pathogenesis of the disease.

2. Subjects and Methods

This study was carried out on twenty patients with AD collected from the Outpatient Clinic of Dermatology, Tanta University Hospital. The patients were 14 males and 6 females, their ages ranged from

1.5 year and 20 years with a mean age of 6.37 ± 3.73 years. The diagnosis was made in each case according to the criteria of *Hanifin and Rajka* [13] for diagnosis of AD. Patients with history of other allergic diseases, such as asthma, allergic rhinitis or allergic conjunctivitis were excluded from the study. None of the patients received any systemic or topical treatment for at least 6 weeks before testing. In addition, 10 age and sex matched healthy persons their ages ranged from 1.5 year and 19 years with a mean age of 5.70 ± 4.21 years with no history of allergic symptoms served as control. They included 3 females & 7 males. All patients and controls were subjected to a detailed medical history and general physical examination. The severity of the disease was evaluated using SASSAD score [14]. The SASSAD severity score has provided a simple and effective system for recording and monitoring the disease severity of AD. The score is obtained by grading six signs [erythema, exudation, excoriation, dryness, cracking and lichenification], each on a scale of 0 (absent), 1 (mild), 2 (moderate), 3 (severe), at each of six sites [arms, hands, legs, feet, trunk and (head, and neck)]. Accordingly, the patients were divided into 3 groups: mild AD (score < 21 points), moderate AD (score 21-40 points) and severe AD (score > 40 points).

Laboratory assessment

Venous blood samples (5ml) from AD patients and control subjects were collected in sterile tubes and allowed to clot, then centrifuged at 2000g for 10min. The obtained serum samples were stored at (-70ºC) to be used for assessment of serum TARC level using ELISA. The frozen serum samples of patients and controls were thawed once and used for TARC determination. The serum level of TARC was measured for each sample by a quantitative ELISA technique using a commercially available kit provided by R and D systems, USA.

3. Results

Negative family history of atopy was found in 4 (20٪) of AD patients, while positive family history was observed in 16 (80٪) patients. The duration of AD ranged from 0.04 to 8.0 years with a mean of 2.35 ± 3.97 years. The activity of AD using SASSAD score ranged from 10 to 60 with a mean of 33.10 ±17.25 (Table 1). Accordingly, the severity of the disease was divided into mild (SASSAD <20) 6 (30٪) patients, moderate (SASSAD 20-40) 8 (40٪) patients and severe (SASSAD >40) 6 (30٪) patients. In this study, serum TARC level of AD patients ranged from 120.00 to 590.00 pg/ml, with mean of 324.00 ± 139.41 pg/ml. while, its level in the control group ranged from 20.0 to 100.0 pg/ml, with mean of 79.50 ± 23.68 pg/ml. A highly significant increase ($p<0.001$) was found in the mean serum TARC level in AD patients compared to control (Table 2). Table (3) shows serum TARC level in AD patients with different grades of severity. Serum TARC level in mild group ranged from 120.0 to 260.0 pg/ml with mean of 170.00 ±37.41 pg/ml, serum TARC level in moderate group ranged from 180.0 to 450.0 pg/ml with mean of 327.50 ± 69.02 pg/ml while in severe group ranged from 320.0 to 590.0 pg/ml with mean of 473.33 ± 102.69 pg/ml. The difference in mean serum TARC level between the three groups were statistically highly significant ($p<0.001$) .Table (4) shows correlation between serum TARC level, SASSAD score, duration of the disease and age of patients. Serum TARC level was directly correlated with SASSAD score [$r = 0.980$, $p<0.001$] .Also, there was a positive correlation between serum TARC level and duration of the disease [$r = 0.730$, $p <0.001$],as well as with the age of patients [$r =0.782$, $p <0.001$] .

Table (1): Clinical evaluation of AD patients

		Severity							
		Mild Group I		Moderate Group II		Severe Group III		Chi-square	
		N	%	N	%	N	%	X^2	P-value
Sex	*Female*	2	33.3	2	33.3	2	33.3	0.952	0.621
	Male	4	28.6	6	42.8	4	28.6		
Age (years)	Range	1.5-5.5		2.5-5.0		6.0-20.0		9.516	0.002*
	Mean±SD	3.50±1.52		3.94±1.24		10.25±5.23			
Duration (years)	Range	0.04-0.5		0.3-3.0		0.08-8.0		8.363	0.003*
	Mean ±SD	0.15±0.18		1.20±0.93		4.430±3.33			
SASSAD (points)	Range	10.0-20.0		22.0-40.0		49.0-60.0		86.563	<0.001*
	Mean ±SD	14.00±3.41		30.88±6.98		55.17±4.62			

Table (2): Serum TARC level in AD patients and control group

Group	TARC (pg/ml)						T-test	
	Range			Mean	±	SD	t	P-value
Control n=10	20.00	-	100.00	79.50	±	23.68	5.027	<0.001*
Patients n=20	120.00		590.00	324.00	±	139.41		

-p-value<(0.001) highly significant.

Table (3): Correlation between serum TARC level and severity of the disease

	TARC (pg/ml)						ANOVA	
	Range			Mean	±	SD	f	P-value
Mild	120.00	-	260.00	170.00	±	37.41	21.97	<0.001*
Moderate	180.00	-	450.00	327.50	±	69.02		
Severe	320.00	-	590.00	473.33	±	102.69		
Tukey's test								
Mild & Moderate			Mild & Severe			Moderate & Severe		
0.014*			<0.001*			0.003*		

-p-value<(0.001) highly significant.

Table (4): Correlation between serum TARC level, SASSAD score, duration of the disease and age of patients

		SASSAD	TARC	Duration
TARC	r	0.980		
	P-value	<0.001*		
Duration	r	0.736	0.730	
	P-value	<0.001*	<0.001*	
Age	r	0.703	0.782	0.681
	P-value	<0.001*	<0.001*	<0.001*

4. Discussion

The results of this study showed that serum TARC level in AD patients was higher than that of the control group with statistically highly significant difference. This result coincided with the reports of many authors [12,15,16-19] who demonstrated elevated serum TARC level in AD patients when compared to controls. Also, this result agreed with Hijnen *et al.*[20] who reported elevated serum levels of TARC and cutaneous T cell attracting chemokine(CTACK) in AD patients and they are disease- specific markers for AD**.** Fujisawa *et al.*[21] and Horikawa *et al.*[22] found significant increase in plasma TARC level in AD patients. Similar finding were observed in the study of Hussein *et al.* [23] who found significant increase in plasma TARC level in Egyptian AD patients. To further characterize the clinical utility of TARC/ CCL17 Fujisawa *et al.*[24] detected that serum level of TARC/ CCL17 is 10-50 fold higher than its plasma level and that the serum/plasma ratio of TARC /CCL17 was significantly higher in AD patients than their normal counterparts. Also, they have demonstrated that platelets contained and released TARC and that TARC content in platelets from AD patients was significantly higher than in those from normal individual, suggesting that serum level of TARC represents the circulating plasma level of TARC plus additional protein released, partly from activated platelets in AD. These observations indicate that the TARC level in serum may better reflect the disease severity of AD than its plasma level. In addition, as serum samples are easier to handle than plasma samples in ordinary laboratories, serum TARC/CCL17 would be a better clinical marker for AD [24]. Kakinuma *et al.*[12] revealed that, CCR4 is a specific ligand for TARC/CCL17 and monocyte derived chemokine (MDC/CCL22). They examined CCR4 and CXCR3 expression on peripheral blood memory T cells and found that the percentage of CCR4 expression on memory T cells was significantly higher in AD patients compared with normal controls and psoriasis patients**.** Also, CCR4 expression in the severe AD group was significantly higher than that seen in the mild group ($P < 0.05$). An immunohistochemical study of CCR4 and CXCR3 expression was also performed. In acute and chronic lesions, CCR4 was expressed on more than 70% of CD4+ T cells which

had a higher ratio compared with that of psoriasis and healthy control. Taken together, these data indicate that CCL17 and CCR4 play an important role in the pathogenesis of AD and may reflect the disease severity of AD[12]. In this study, a significant direct correlation was demonstrated between serum TARC level and age of the patients. There was an increase in serum TARC in infants and young children with AD versus controls, but the elevation was more in childhood patients than in infants. Lin *et al.* [25] and Leung *et al.*[26] reported that TARC and MDC were elevated in the sera of infants and young children with AD. Also, Furusyo *et al.* [27] found significant elevation of TARC levels in European children with AD. Also, Mostafa *et al.* [28] demonstrated a significant increase in serum levels of TARC and MDC in Egyptian children with AD compared to controls. Furusyo *et al.* [27] found a significant elevation of serum TARC levels in Japanese children with AD compared to healthy children and concluding that monitoring serum TARC level of AD children may be a useful marker for biological evaluation of AD. Nakazto *et al.* [29] reported that serum levels of Th2 chemokines, CCL17, CCL27 and CCL22 were the important markers of severity in infantile AD. Fujisawa *et al.* [24] demonstrated that, serum level of TARC was elevated in normal infants. Also, they revealed that CCL17 / CXCL10 ratio seemed to be elevated in group of infants < 2 years compared with group of children from 2-5 years. Their explanation attributed to a reduced microbial burden during early childhood [30] [the so-called hygiene hypothesis][31]. The immunological basis for the hygiene hypothesis is that reduced microbial stimuli in early childhood inhibits immune deviation from Th2 to Th1 immune responses. In addition, overproduction of TARC in infancy might represent the default Th2- polarized state, and lack of subsequent Th1- polarizing stimuli might cause further production of the chemokine, leading to the development of AD and other atopic diseases. It was reported that neonatal BCG vaccination, which polarizes to Th1, significantly reduced the asthma risk [32]and various attempts are currently being made to modify immune responses in order to prevent allergy. So, they considered TARC as a useful clinical marker for monitoring the effects of immunoregulatory agents during treatment [24]. Moreover, this study proved that adults with severe AD had significantly higher serum level of TARC ($p<0.001$). This result was going with what previously reported in AD adult studies [15, 22] , where serum TARC level increases in severely affected group than in moderate or mild groups. The patients with old age who suffered from AD for a long period showed severe eruptions and the serum TARC levels of these aged group showed relatively higher CCL17 levels compared with those of young patients. In the present study, a significant positive correlation was found between serum TARC level in AD patients and severity of the disease. It was significantly elevated in severely affected group than in mild or moderate groups. This result agreed with that of Kakinuma *et al.*[12] and *Fujisawa et al.*[24] who demonstrated that serum TARC level reflects the severity and therapeutic response in AD. Also, Galli *et al* .[17] and, Shimada *et al.* [19] proved that serum level of TARC is closely related with disease activity. Jahnz-Rozyk *et al.*[33] reported that TARC, eotaxin and MDC have a significant positive increase with severity of AD Hussein *et al.* [23] proved that TARC is one of the chemokines that are closely related to the disease activity and response to treatment in AD. Furthermore, they demonstrated significant increase of TARC level in AD patients with clinical evidence of secondary bacterial infection in contrast to those without such evidence. This revealed that secondary bacterial infection probably plays an important role in causing further elevation of TARC level. They depend in their explanation on the fact that patients with AD have been found to have increased tendency to develop bacterial infection. *S. aureus* is found in high number in over 90% of AD skin lesions either acute or chronic. In case of AD, it has been proposed that *staphylococcal* super antigens secreted at the skin surface could penetrate inflamed skin and stimulate epidermal macrophage or LCs to produce IL-1, TNF-α and IL-12. Local production of IL-1 and TNF-α induces the expression of E-selectin on vascular endothelium, allowing an initial influx of cutaneous lymphocyte antigen (CLA) memory and effector cells [34,35]. Secretion of IL-12 increases CLA expression on those T cells activated by allergen or super antigen and increases the efficiency of T cell recirculation to the skin. IL-12 secreted by toxin-stimulated LCs that migrate to skin and serve as antigen-presenting cells could up regulate the expression of CLA and influence the functional profile of virgin T-cells activated by toxins, thereby creating additional skin-homing memory-effector T cell. Together, these mechanisms would amplify the initial cutaneous inflammation in AD, creating conditions favoring *staphylococcal* colonization. Hence, it can be concluded that infection leads to upregulation of CCR4 expressing T cells resulting in increased production levels of Th2 cytokines. These include IL-4 and IL-13, which are known to induce isotype switching to IgE synthesis. IL-4 also was found to upregulate TARC production [23]. IL-5 plays an important role in eosinophil development and survival. Elevated IL-5 expression in skin also leads to enhanced survival of monocyte-macrophages and

also LCs which will in turn increase TARC production of skin. TARC will enhance more infiltration of skin by T cell expressing CCR4 thereby maintaining the inflammatory process. Therefore, this could be considered a preliminary report highlighting that TARC level in patients with secondary *bacterial* infection is significantly higher than in those without infection [23]. In the present study, a significant positive correlation was found between serum TARC level in AD patients and severity of the disease based on SASSAD score, when the activity score increases the serum levels of TARC increase. This indicates a possible role of TARC in the extent and activity of AD. This result agreed with Kakinuma *et al.* [12] Fujisawa *et al.* [16] Fujisawa *et al.* [21] Hussein *et al.* [23] Mokhtar *et al.* [36]. Furthermore, Hijnen et al. [20] found that serum TARC level but not CTACK showed significant decline during treatment with Cyclosporin A and they found significant positive correlation between serum TARC, CTACK and severity. They concluded that serum TARC level is specifically elevated in patients with AD irrespective of allergic respiratory co-morbidity [20]. This study revealed a significant direct correlation between serum TARC level of AD patients and duration of the disease. This is going with Furusyo *et al.* [27] who demonstrated strong association between TARC level and natural course (newly developed, regressed, and maintained AD) of childhood AD through analysis of data from KIDS, a population -based cohort study with a large number of children) [27]. In a study of Miyahara *et al.* [37] they suggested that the umbilical cord blood CCL17 may be involved in the pathogenesis of infantile AD and in fetomaternal inheritance. Serum levels of CCL17 from umbilical cord blood may be a predictive marker for AD in infancy [37]. In a study of a murine model of bacteria-induced hepatic failure, TARC mediated infiltration of CCR4 cells in hepatic lesions was inhibited by administration of a monoclonal antibody to TARC [38]. The use of monoclonal antibody to TARC suppresses allergic inflammation and attenuates the accumulation of eosinophils in a murine model of allergen-induced asthma. In addition, basic studies demonstrated the intracellular signaling pathways linked to TARC and CCR4-mediated chemotaxis [39]**.** Furthermore, in a clinical study, the production of TARC by peripheral blood mononuclear cells in adult patients was dramatically inhibited by administration of an antagonistic drug against the histamine H1 receptor, Olopatadine[40] and Roxithromycin [41]. Taken together, chemokine-target treatment may be an effective strategy for the treatment of allergic disease including AD [27].

Conclusion

TARC has been implicated as an important chemokine in the pathogenesis of allergic inflammation including AD. TARC can be used as a useful marker for assessing AD severity. Taken together, chemokine-target treatment may be an effective strategy for the treatment of allergic disease including AD. Further studies evaluating tissue TARC level as well as peripheral blood chemokines in AD patients may help to explain the role played by this chemokine in the pathogenesis of the disease and open the way for a further therapeutic approach.

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