Original Article

Serum IL-23, IL-17 and TNF-α level as Psoriasis severity markers: A hospital based cross sectional study.

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ABSTRACT:

Background: *Psoriasis is an autoimmune chronic inflammatory disease where serum cytokines are marked as prime drivers of disease progression and severity.*

Objectives: To investigate serum TNF-α, IL-17 and IL-23 level according to disease severity of psoriasis.

Methods: *A total of 35 psoriasis patients and 35 healthy controls were enrolled. Disease severity of psoriatic patients was assessed by Psoriasis Area and Severity Index (PASI) scoring. Serum TNF-α, IL-17 and IL-23 of study subjects were measured by ELISA.*

Results: *Serum level of is significantly increased in psoriasis patients than healthy controls. Among 35 patient 56.7% were suffering from moderate to severe psoriasis. Serum TNF-α level was more in mild group (P =0.70) and serum IL-23 level increased in moderate to severe psoriasis (P=0.42). Whereas serum IL-17 level significantly increased along with disease severity (P=0.03).*

Conclusion: *Our study underscores the role of TNF-α, IL-17 and IL-23 in disease severity of psoriasis.*

Key Words:
Psoriasis; Interleukin;
Psoriasis Area and Severity Index.

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Introduction

Psoriasis is an autoimmune mediated inflammatory skin disease with worldwide review prevalence ranged from 0.5-11.4% in adults. Few studies have been carried out about psoriasis in Bangladesh. It's been reported that prevalence of psoriasis is 11.47% in indoor patient at a tertiary care hospital in Dhaka. [1]

Psoriasis is characterized by epidermal hyper proliferation, impaired differentiation of keratinocytes, excessive angiogenesis and immunological dysfunction.[2,3] (The etiology is complex. Following presentation of specific psoriasis auto-antigens on certain environmental stimuli (e.g. trauma or infection), TNF-α released by plasmacytoid dendritic cells (pDCs) in pre-psoriatic skin. Which in-turn increase production of IL-23 from myeloid dendritic cells (mDCs). Following that pathogenic Th-17 cells activated. Th17 producing cells in the skin produce substantial amounts of IL-17, as well as TNF-α, IL-22 and IL-29 (IFN-λ1). Together, these cytokine signals create a feed forward inflammatory response in keratinocytes. Th17 cells also promotes Th1 cell differentiation and inhibit T-reg activity. That enable infiltrated T effector cells escape from the suppression.[4-6] IL-17 also acts synergistically with TNF-α to potentiate IL-17 induced transcription of several pro-inflammatory genes (e.g. TNF-α, IL-1β, IL-6 and IL-8), which activate myeloid dendritic cells (mDCs) and promote the differentiation of Th17 cells in the skin and draining lymph nodes.[7]

Advances in our understanding of disease pathogenesis, has led to targeted immuno-modulatory or biologic therapies that act on the up regulated cytokine pathways in psoriasis. The clinical efficacy of multiple TNF antagonists (e.g. adalimumab, etanercept and infliximab) underscore the importance of this cytokine in pathogenesis of psoriatic skin lesions, though the percentage of patients experiencing dramatic improvement in their skin lesions is significantly lower than those seen with novel IL-17 and IL-23 antagonists. Treatment with new biologics (IL-17 inhibitor, IL-23 inhibitor) leads to complete reversal of regenerative. To date, three IL-17 pathway antagonists have been approved for the treatment of psoriatic disease: secukinumab, ixekizumab and brodalumab. As a ''master regulator'' of Th17 cell development, IL-23 inhibition targeting p19 subunit (eg: tildrakizumab, guselkumab, risankizumab) are now the new therapeutic solutions.[8]

In this study we evaluated Th17 cell associated cytokines (TNF-α, IL-17 and IL-23) to see the detrimental effect in psoriasis disease severity.

Methodology:

This cross-sectional study was carried out in the department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2019 to February 2020. This study was approved by institutional review board (IRB) of BSMMU (BSMMU/2019/6913) and all study subjects provided informed consent. A total 35 psoriatic patients and 35 healthy controls were enrolled according to the Declaration of Helsinki. Psoriasis patients were diagnosed by an expert dermatologist. Psoriasis patient with diabetes, infection, pre-existing thyroid disease, hypertension, malignancies and undergoing systemic therapy in the last three months and topical treatment for 1 month were excluded. Individuals, without any skin and infectious diseases and without a family history of autoimmune diseases, were recruited as healthy controls. The clinical characteristics including disease severity (assessed by psoriasis area and severity index, PASI scoring).10 Three milliliter of peripheral venous blood was collected from each study subject and taken in tube without anticoagulant, then centrifuged at 4000 rpm for 5 minutes. Separated serum was stored at -20°C till analysis of cytokines. Frozen serum was thawed and the level of TNF-α, IL-17 and IL-23 were measured by ELISA kit (Ray-Biotech, USA; Catalog #: ELH-TNFa, Catalog #: ELH-IL17 and Catalog #: ELH-IL23) as per standard protocol following manufacturer's instruction. The values were recorded at a wavelength of 450 nm. Standard curve was generated for each cytokine by plotting the average absorbance of each standard on vertical axis versus the corresponding cytokine standard concentration on the horizontal axis. Cytokines in each sample were determined by extrapolating OD values against cytokine standard concentration using the standard curve. Data expressed as mean ± SD/SE and comparison of serum cytokines between groups were done by Mann-Whitney U test. For all test a P value <0.05 was considered as statistically significant. Statistical analyses were performed using SPSS software package version-22 (Strata Corporation, College station, Texas).

Results:

A significant difference was observed between psoriatic and healthy controls, for serum level of IL-17 (150 ± 21.67 Vs 84.10 ± 15.35, P=0.002), IL-23 (231.70 ± 128.22 Vs

13.97 ± 6.17, P<0.0001) and TNF-α (534.68 ±151.65 Vs 84.26 ± 30.67, P=0.002).

PASI score of almost two-third (23) patient were >10 (Moderate to severe). Mean PASI score was 13.68 ± 6.60 with a range of 3.70 – 27.2 (Table I).

IL-17 showing significant difference among the groups according to disease severity (P=0.03). Level of IL-23 level showed difference among group, though it was not statistically significant (P=0.42). TNF-α level was more in mild group, but the TNF-α level didn´t show variation according to severity in psoriasis patients (P =0.70) (Table II).

Table I: Distribution of psoriatic patients according to PASI score (n=35).

PASI Score	Frequency (%)	Mean ± SD	Range
Mild disease (≤10)	12 (34.3%)	6.80±1.83	3.70-9.60
Moderate to Severe (>10)	23 (56.7%)	12.27±5.15	10.20-27.20
Total	-	13.68±6.60	3.70-27.20

Table II: Association of serum cytokine level of psoriasis patients with severity of disease according to PASI (n=35).

Cytokine	Severity of Disease		P value
	Mild disease (≤10) Mean ± SE	Moderate to Severe (>10) Mean ± SE	
IL-17	147.47 ± 56.52	151.59 ± 16.46	**0.03**
IL-23	33.78 ± 14.51	334 ± 280.79	0.42
TNF-α	639.47 ± 285.11	480.00 ±180.24	0.70

P value calculated by Mann-Whitney U-test.

Discussion

Being a systemic disease, psoriasis is associated with multiple comorbidities. Approximately one third of the patients develop chronic inflammatory arthritis (psoriatic arthritis) and two third patients develop nail changes that leading joint deformity. Disfiguration, disability, marked loss of productivity, social exclusion, discrimination and stigma are common challenges for people with psoriasis are psychologically devastating for individuals suffering from psoriasis and their families.11

The diagnosis of psoriasis is primarily clinical and a skin biopsy is seldom required. Depending on the severity of disease, different topical and systemic therapy may require. Whether mild or severe, the need for treatment is usually lifelong and is aimed at remission.[11] Biologics have emerged as highly potent treatment options in psoriatic patients as its modification in clinical outcome with limited side effects. That's why current therapeutic options are focused on the newly developed IL-23/Th17 axis.[8] But data focusing on this aspect in psoriatic patient of Bangladesh is yet not available. This cross-sectional study was designed to see the relationship of serum level of cytokines (IL-17, IL-23 and TNF- α) with disease severity in psoriatic patients.

The psoriasis area and severity index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. As diagnosis of psoriasis mainly done clinically, reliable and appropriate documentation of the severity is important in clinical practice and essential for clinical trial research. PASI score was used in this study to correlate different parameters that has been observed. In this study, the mean PASI score was 13.68 ± 6.60, ranging from 3.70 – 27.2. Among 35 psoriasis patients 23 (56.7%) psoriatics had moderate to severe psoriasis, while 12 (34.3%) had mild psoriasis. PASI ≤10 considered as mild disease and PASI>10 as moderate to severe disease. A study done at UK, showed mean PASI score was 12 ± 6 12(Benham et al., 2013). Similar findings (mean PASI score15±5.2) was also found in a study done in India. 9 In another study carried out by Oliveira et al. (2015) found mean PASI score was 16.4 ranging from 7- 41. So, most of the study showed that mean PASI corresponds to moderate to severe group (PASI>10). This result indicates most of the psoriatic patients of our country, who need medical attention are suffering from moderate to severe disease. Lack of knowledge or awareness about psoriasis may be responsible for that.

For decades Th1 cytokines are thought to be major initiator of inflammatory cascade. The discovery IL-23/Th17 immune axis have drastically changed the paradigm of the pathogenesis of T cell mediated inflammatory diseases like psoriasis. 13 In present study, we evaluated serum level of cytokines (TNF- α, IL-17 and IL-23) that might reflect the activity of the cells usually present in the psoriatic lesions, in the active stage of the disease, during and after the treatment. In response to different stimulatory event in genetically susceptible person, TNF-α is released by epidermal plasmacytoid dendritic cells (pDCs), which in

turn activates myeloid dendritic cells (mDCs) and IL-23 released. Researchers termed IL-23 as master regulator of psoriatic pathogenesis. TNF-α further potentiate inflammatory event by acting synergistically with IL-17.

In this study serum level of TNF-α was significantly elevated in psoriatics compared with healthy controls (534.68 Vs 84.26, P=0.002). The estimated level was more in mild psoriatics. In a study conducted in Greece, showed serum levels of TNF-α were significantly higher in psoriatic patients compared to those of controls (P< 0.0001) without any significant difference between the 2 groups.[14] Several studies observe association of increased level of TNF-α in psoriatics by applying anti TNF-α monoclonal antibody therapy like infliximab and found decreased level of TNF-α after therapy. [15] It indicates pathogenic role of TNF-α in psoriatics.

The present study showed concordance and discordance with the findings of aforementioned studies regarding association of TNF-α with disease severity. TNF-α can be synthesized from different sources like adipose tissue. So, elevated levels of TNF-α in mild psoriatic group may be from the contribution of other infections which contribute in synthesis of this cytokine.

IL-17 is a potent inflammatory cytokine, down regulate the T-reg cell activity and promotes Th1 cell differentiation.[9] Several studies reported increased mRNA levels of the IL-23/Th17 axis in psoriatic lesions. In present study serum IL-17 and IL-23 level was elevated. Both IL-17 and IL-23 level showed difference among patients with different degree of disease severity.

The findings of several studies are in agreement with the present study. The studies in China and Japan found significant serum level of IL-17 along with strong correlation with disease severity.[16,17] A study in Brazil showed increased IL-17 level in psoriasis patients in comparison with healthy controls. They also observed differences among patients with different degree of severity, but no statistical correlation with severity was found.[18] Another study done in Libya showed, increased IL-17 in psoriatics, but no correlation with PASI was detected.[19] A study in India showed, the mean plasma levels of IL-23 was significantly increased in psoriasis patients, compared with that of controls (37.65 ± 19.4 vs. 34.55 ± 21 pg/mL, p = 0.02).[20] IL-23 has been demonstrated to be a key cytokine in the inflammation in peripheral tissues. 21 Chhabra et al. (2016) didn't find any significant difference and correlation in serum IL-17 and IL-23 level between patients and healthy controls. [22]

IL-17 is produced by Type 17 cells including CD4+ T cells (Th17), CD8+ T cells (Tc17), type-3 innate lymphoid cells (ILCs) and γδ T cells.8 But activated Th17 cells are the major source of IL-17 during inflammation.[23] Production of IL-17 by these cells is influenced by mDCs derived IL-23.8 So, it can be concluded that both serum IL-17 and IL-23 level are significantly elevated in psoriatics that corresponds with severity. Different clinical trial showed efficacy of mAbs against IL-17 and IL-23 that underscore the central role of these cytokine as predominant drivers of psoriatic disease. Phase III clinical trials evaluating that IL-23p19 antagonists have showed long time treatment response with just single dose.[8]

Although the small sample size and a relatively narrow PASI range were insufficient to provide a gross information but data provided here is strongly evident of activation of IL-23/Th17 axis in psoriasis, which is a current topic of interest. As PASI score can varied within physician, by evaluating serum TNF-α, IL-17 and IL-23 levels in psoriasis patients, a potent anti-cytokine therapy can be planned and monitoring of the patient for disease progression and other systemic diseases can be done accordingly.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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