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RESEARCH ARTICLE

EVALUATION OF SERUM LEVELS OF IL-17, IL-20 AND IL-22 IN PSORIATIC PATIENTS FROM NORTH INDIA AND THEIR CORRELATION WITH DISEASE SEVERITY

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Key Messages: Studies on role of IL-17, IL-20 and IL-22 in psoriatic inflammatory conditions from North Indian patients are not available at all. The present study provides data on total surface area affected in severe cases and explore the role of IL-17, IL-20 and IL-22 in the severity of the psoriasis.

ABSTRACT

Background: Convincing evidence suggests that Psoriasis is an inflammatory disease. Inflammatory response in psoriasis is mediated by over expression of proinflammatory cytokines produced by Th1 cells and relative under expression of Th2 cytokines. These cytokines induce chemokines and other effecter cells via production of IL-17, IL-20 and IL-22, thus play role in pathogenesis of Psoriasis.
Objective: To correlate the serum level of IL-17, IL-20 and IL-22 with Psoriatic lesions and area affected with Psoriasis in North India.
Patients and Methods: In this study we calculated serum levels of IL-17, IL-20 and IL-22 in 150 Psoriatic patients as well as 200 healthy controls. Further the level of cytokines was assessed by ELISA and correlated to disease severity measured by psoriasis area severity index (PASI) score.
Results: The present study includes 150 Psoriatic patients (101 males and 49 females) of age group 18-75 years with mean and SD of age 39.55±14.65. The mean and SD of PASI was 15.10±11.96, ranged from 0.3-49.2. Observations revealed that serum level of IL-17 in psoriatic patients was found 143.78±33.99 pg/ml. Serum level of IL-22 among studied psoriatic patient was found 74.42±24.08 pg/ml and serum level of IL-20 was found to be 96.73±26.52 pg/ml.
Limitations: Follow-up of psoriatic patients was not done. A larger sample size would have validated the results further.
Conclusion: Results show significant difference in serum level of IL-17, IL-20 and IL-22 in Psoriatic patients as compared to healthy controls. As it was observed that serum cytokines were significantly elevated in psoriatic patients, thus present study correlated the elevated level of serum cytokines with disease severity.

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INTRODUCTION

Psoriasis is an ancient, non contagious, universal immune mediated inflammatory, polygenic and chronic skin disease, affecting 2-3% population worldwide (Baliwag *et al*.,2015). It is characterised by plaques of red (erythematous), scaly and well-demarcated skin lesions formed by the abnormal differentiation and hyperproliferation of epidermal keratinocytes (Christophers *et al*., 2001). Recent study on North Indian Punjabi population shows that about 0.3636 percent population with 5:1 male female ratio are suffering with Psoriasis (Kaur *et al*., 2011). The pathogenesis of psoriasis has not been clearly understood so far. Some studies report that it is an immunological disorder having abnormal keratinocyte proliferation mediated by T lymphocytes (Bos *et al*., 1999 and Griffiths *et al*., 2003), infiltration of T cells, macrophages, and dendritic cells (DC) into the psoriatic skin (Griffiths *et al*., 2007). Human IL-17 belongs to a recently discovered family of cytokines that contribute to the crosstalk between adaptive and innate immunity (Stumhofer *et al*., 2006). IL-17 and its relative IL-17F have strong proinflammatory properties on a broad range of cellular targets, including epithelial and endothelial cells, fibroblasts, keratinocytes, osteoblasts, and monocytes/macrophages (Weaver *et al*., 2007). So far it has confirmed that IL-17A plays key role in physiopathogenesis of psoriasis (Lee *et al*., 2004; Langrish *et al*.,2005 and Martin *et al*., 2005). Its mechanism of action involves the increased expression of S100 proteins, chemokines as CCL20, CXCL1, CXCL3, CXCL5, CXCL6, and CXCL8, and VEGF in keratinocytes leading to aberrant cell differentiation, proliferation, and immune activation (Batycka-Baran *et al*., 2014; Johnston *et al*., 2013 and Girolomoni *et al*., 2012). IL-17 have also been identified to be act through cholesterol in pathogenesis of psoriasis

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(Varshney *et al*., 2016). Keratinocytes produce IL-20 in the presence of IL- 22, TNF-α, and IL-17 but not IFN-γ or IL-20 itself. IL-20 is also produced by stimulated monocytes and DCs. IL-20 has an important role in the psoriasis pathogenesis, in which it inhibits the differentiation of cells, increases antimicrobial competence, and production of chemokines for neutrophils in keratinocytes (Sabat *et al*., 2011 and Wolk *et al*., 2009). IL-22 is produced by Th17, Th22, and mucosal NK cells belonging to IL-10 cytokines family (Aujla *et al*., 2007; Cella *et al*., 2009 and Wolk *et al*., 2006). It is hypothesized that together all these cytokines play key role in pathogenesis and progression of the Psoriasis. There are some studies which have identified the role of gene polymorphism in pathogenesis of psoriasis in Indian population (Indhumathi *et al*., 2015). Present study designed to correlate the serum level of IL-17, IL-20 and IL-22 with Psoriatic lesions and area affected with Psoriasis in North India. To the best of our knowledge, no studies have been done to evaluate the serum level of different cytokines in psoriasis in the North India. So the present study is an endeavor to look into the role of IL-17, IL-20 and IL-22 in severity of Psoriasis.

MATERIALS AND METHODS

Patients and their selection

Patients included in the study were either freshly diagnosed (prior to treatment) or those who undergone off treatment for topical (for two weeks) and systemic and phototherapy (for four weeks). Any patient takes treatment (allopathic, ayurvedic, homeopathic) for psoriasis and have any other coexistent autoimmune disorders, acute or chronic infections, and malignancies was not included in the study. A total of 150 Patients including 101 males (67.33 %) and 49 females (32.67%), and 200 healthy controls age ranged from 18-75 years were included in the study after taking written consent from patients visiting skin outdoor patients (OPD) of Dermatology Department of Government Hospitals and Medical Colleges of North India.

Almost three millilitres (3 ml) of peripheral blood was collected from each subject in sterile BD Vacutainer plane vials with the help of medically trained laboratory technician. Serum was separated by centrifugation at 3000 rpm for 10minutes and stored at -80^{0}C for further analysis.

Assessment of Psoriasis Severity

To assess the severity of disease, surface area under disease was calculated using PASI calculator developed by Fredrikkson and Petterson in 1978 (Van *et al*., 1997). The total body surface area is divided into four sections viz. Head(H) (10%), Arm(A) (20%), Trunk(T) (30%) and Legs(L) (40%), the percentage of area of skin involved is estimated by using the patients palm and transformed into a grade from 0-6(as prescribed in the PASI calculator).

Assessment of Quality of Life

Quality of life of psoriatic patient was assessed by using Psoriasis Disability Index (PDI) (Finlay *et al*., 1995).

Measurement of cytokines

Cytokines were measured from serum samples of psoriatic patients and controls. Serum levels of IL-17, IL-20 and IL-22 were measured by using enzyme-linked immunosorbent assay (ELISA) kits (KrishGen Biosystems, USA) according to the protocol.

Statistical Analyses

Statistical analyses were performed by Graph Pad PRISM 5.0 software. Spearman rank correlation test was done for assessment of correlation by using VassarStats: a website for Statistical Computation (http://vassarstats.net/corr_rank.html). Continuous variables were presented as mean ± standard deviation. The Psoriasis Disability Index (PDI) measures the impact of psoriasis on specific aspects of daily living consisting of 15 disease-specific items (Finlay *et al*., 1995). The significance level was set at $P<0.05$.

RESULTS

Clinical and demographic characteristics of patients

The patients comprised 101 (67.33%) males and 49 (32.67%) females with male: female ration of 2.1:1. The demographic picture of the studied groups showed that mean age of onset of psoriasis was 39.55±14.65 (SD) years. Further it was found that PASI value of psoriatic patients calculated 15.10±11.96 (MEAN±SD), which ranged from 0.3-49.2. Body Mass Index (BMI) of psoriatic patients with mean and SD was found to be 24.89±05.17 Kg/m^2 (Table 1).

Serum Levels of IL-17, IL-20 and IL-22 in Psoriatic Patients and Healthy Controls

Serum levels of studied cytokines in psoriatic patients were found to be significantly high as compared to control group. Level of IL-17 was found to be 143.78±33.99 pg/ml in Psoriatic patients which was significantly high as compared to healthy controls having serum values for IL-17 32.68±18.71 pg/ml. Level of IL-20 was found to be 96.73±26.52 pg/ml ($p <0.0001$) where as in control group it was found to be 49.23±09.14 pg/ml. Similarly significant differences were observed in serum levels of IL-22 between the two groups. Level of IL-22 was observed to be 74.42±24.08 pg/ml in Psoriatic patients whereas in controls level of IL-22 was found to be 28.01±07.86 pg/ml (Table 2).

Serum Levels of IL-17, IL-20 and IL-22 in Psoriatic Patients (gender specific patients)

When compared the serum level of IL-17, IL-20and IL-22 in male and female psoriatic patients separately we did not observe any significant difference among the two gender specific groups (Table 3).

Correlations between IL-17, IL-20 and IL-22 Serum Levels of Psoriatic Patients and PASI Score

Correlations among disease severity and serum level of cytokines are shown in Table 4.

Table 1. Characteristics of Psoriatic Patients and Control Groups

Characteristics	Patients (n=150)	Controls (n=200)
	Mean (range or SD)	**Mean (range or SD)**
Age	39.55±14.6	37.38±7.2
Male	101 (67.33%)	146 (73%)
Female	49 (32.67%)	54 (27%)
Disease Duration(Years)	8.68±8.2	-----
BMI(Kg/m^2)	24.89±5.1	21.80±3.48
PDI	19.22±6.5	-----
PASI	15.10±11.9	-----

Clinical features of psoriasis patients and healthy controls

Table 2. Serum levels of IL-17, IL-20 and IL-22 in psoriatic patients and controls

Cytokine	Patients (n = 150)	Controls (n = 200)	*P* values
IL-17(pg/ml)	143.78±33.99	32.68±18.71	<0.0001
IL-20(pg/ml)	96.73±26.52	49.23±09.14	<0.0001
IL-22(pg/ml)	74.42±24.08	28.01±07.86	<0.0001

Values are represented by mean±SD

Table 3. Serum levels of IL-17, IL-20 and IL-22 in Psoriatic patients (Gender wise)

Cytokine	Psoriatic Female patients (n=49)	Psoriatic Male patients (n=101)	*p* values
IL-17(pg/ml)	**140.33± 33.43**	**145.45±34.31**	**>0.05**
IL-20(pg/ml)	**97.32± 31.83**	**96.45±23.71**	**>0.05**
IL-22(pg/ml)	**72.97± 23.39**	**75.12 ±24.50**	**>0.05**

Values are represented mean±SD

Table 4. Correlation between serum levels of IL-17, IL-20 and IL-22 with PASI Score, PDI and Disease Indurations in psoriatic patients

PASI, PDI and cytokines	Statistical Values	IL-17	IL-20	IL-22
PDI	r	0.17	0.13	-0.23
	p	0.04	0.01	0.00
PASI	r	0.26	-0.02	-0.25
	p	0.00	0.77	0.00
Disease Induration	r	0.04	-0.02	0.03
	p	0.03	0.05	0.02
IL-17	r		-0.05	-0.20
	p		0.55	0.02
IL-20	r			0.05
	p			0.56

We have presented Speareman rank correlation among elevated serum levels of cytokines, PASI, PDI and disease Induration. In our study we observed that elevated serum levels of IL-17 were significantly ($p < 0.05$) correlated with the severity of disease. On the other hand there were no statistical significance ($p > 0.05$) observed between serum level of IL-20 and PASI score. Correlation between serum levels of cytokines i.e. IL-17 was found to be non-significant with IL-20 and IL-22 whereas IL-17 and IL-20 were significantly ($p < 0.05$) correlated to PDI. Disease indurations was also found to be significantly ($p<0.05$) correlated with serum levels of cytokines IL-17 and IL-22 as observed spearman rank correlation (Table 4).

DISCUSSION

It is reported that expression of IL-17, IL-20 and IL-22 is found to be increased at the site of inflammation in psoriasis (Res *et al*., 2012 and Sabat *et al*., 2007). IL-17 plays a key role in defense against pathogens by stimulating the release of antimicrobial peptides, proinflammatory cytokines and chemokines. IL-17 family consists of six ligands (IL-17A –IL-17F) and five receptors (IL-17RA-IL-17RE), with most homologous IL-17A and IL-17F (Baliwag *et al*., 2015). It is mainly expressed by keratinocytes in lesional skin and arises from innate immune cells like NK cells, gamma-delta T cells, mast cells, neutrophils, NKp44+ CD3-negative innate lymphoid cells (ILC's) as well as the Th17 (CD4+ IL-17+) and Tc17 (CD8+ IL-17+) cells of the acquired immune system (Baliwag *et al*., 2015). The increased expression of interleukin-17 at the sites of inflammation in psoriasis (Kryczek *et al*., 2008 and Lowes *et al*., 2008) strongly suggests a role in promoting autoimmune pathology (Maddur *et al*., 2012 and Zhu *et al*., 2012). We reported here that serum level of IL-17 was found to be highly increased in the Psoriatic patients as compared to healthy control group. Some other studies also support the current finding which also shows overexpression of IL-17 in Psoriatic lesions (ALmakhzangy *et al*., 2009 and Caproni *et al*., 2009). Interleukin-20 and interleukin-22 belongs to the IL-10 family and members of subfamily IL-20.

IL-20 signals through 'type I' (IL-20R1) and 'type II' (IL-20R2) receptors heterodimers. Both of these receptor complexes are primarily expressed on epithelial cells and activate the transcription factor STAT3 by promoting wound healing, tissue remodeling and antimicrobial peptide expression. IL-20 is mainly secreted by myeloid and epithelial cell, whereas IL-22 by lymphocytes (Commins *et al*., 2008). IL-22 is elevated in serum of psoriatic skin (Wolk *et al*., 2006; Kryczek *et al*., 2008 and Ward *et al*., 1997). IL-22 induces epidermal hyperplasia but not keratinocyte proliferation. One of its genetic variant induces childhood psoriasis by increasing activity of pro-inflammatory gene expression (Boniface *et al*., 2005). Thus IL-22 is another critical cytokine in the pathogenesis of psoriasis and is a target for drug development (Gudjonsson *et al*., 2012). We observed that serum level of IL-20 and IL-22 was found to be increased in psoriatic patients. Some previous studies supported the present findings which also reported the increase in serum level of IL-20 and IL-22 in the psoriatic patients (Gudjonsson *et al*., 2010; Suárez-Fariñas *et al*., 2012 and Sabat *et al*., 2014). We found a significant correlation in the levels of both IL-17 and IL-20 with PDI score and IL-17 with PASI, which clearly indicates that these cytokines might have pathogenic role in psoriasis (ALmakhzangy *et al*., 2009). In agreement with these findings we also observed that a significant correlation was observed between disease induration with elevated serum levels of IL-17 and IL-22 whereas we did not found any significant correlation between level of IL-20 and disease induration in psoriatic patients. So in nut shell we can say that interleukins plays an important role in inflammatory and immunoregulatory skin disease.

Conclusion

Present study identified the increased level of IL-17, Il-20 and IL-22 in psoriasis. IL-17, IL-20 and IL-22 stands as the therapeutic target in psoriasis and several new drugs should be explored which inhibit IL-17, IL-20 and IL-22 signal transduction pathways and Th 17 gene expression. So, serum level of IL-17, IL-20 and IL-22 can be useful for diagnostic purpose and helpful in the pharmacogenomics for the development of antipsoriatic drugs. Our data indicated that human cytokines IL-17, IL-20 and IL-22 were found to be correlated in one or other way with disease severity in psoriatic patients thus reveals that cytokine producing skin cells may play a role in the pathogenesis of disease.

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