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RESEARCH ARTICLE

INTERLEUKIN-22 SERUM LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS IN SANA'A CITY, YEMEN

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ABSTRACT
Interleukin (IL) -22 is a novel mediator of a member of IL-10 family cytokines that is produced by many different types of lymphocytes including both those of innate and adaptive immune system. This cytokine has potent proliferative and inflammatory effects on different cell lines. Recently, accumulated data has indicated that IL-22 plays an important role in the pathogenesis of rheumatoid arthritis (RA). We aimed to investigate the levels of IL-22 and its association with demographic, clinical data as well as serological markers in RA. IL-22 serum levels were measured in 45 newly diagnosed RA patients without any treatment and 45 healthy individuals as control by a manual Enzyme linked immunosorbent assay (ELISA). Correlations of IL-22 serum levels were sought with demographic, clinical data and serological parameters. IL-22 levels were significantly elevated in serum of RA patients (median= 86.89ng/ml and range = 896) compared to serum of healthy control (median=75.36ng/ml and range=459), p=.022. The IL-22 levels were correlated positively with C-reactive protein (CRP), anti-cyclic citrullinated peptide (ACCP) antibodies in RA patients. Significant higher levels of serum IL-22 in RA patients compare with those in healthy control. Highly significant association between serum levels of IL-22 and the serological markers (CRP and ACCP antibodies) in the diagnosis of RA suggest the potential levels of IL-22 as a valuable biomarker for the evaluation of disease severity in RA patients.
Keywords: Anti-cyclic citrullinated peptide antibody, C-reactive protein, Interleukin-22, rheumatoid arthritis, rheumatoid factor.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that represents one of the most common autoimmune-related disease. Histologically, it is characterized by prominent infiltration of inflammatory mononuclear cells, such as T cells and macrophages, and the proliferation of synovial fibroblasts[1]. In RA, it is clear that inflammatory cytokines play a key role in driving T cell activation and migration that lead to joint destruction[2].

Interleukin (IL)-22 is a novel α-helical protein, the human IL-22 encoding gene is located in the longer arm (q15) of chromosome 12[3]. It belongs to a group of cytokines called the IL-10 family which is a class of potent mediators of cellular inflammatory responses[4,5]. IL-22 differs from other cytokines of IL-10 family by being a potent proliferative and inflammatory agent for different cell lines[3,6]. Many types of cells from lymphoid lineage can secrete IL-22, including both those of the innate and adaptive immune system. In humans, these cells include activated $CD4^+$ T cells, $CD8^+$ T cells[7-9] and γδ T cells[10] as well as various innate lymphoid cells such as Natural killer (NK) cells, NKT cells[11-13] lymphoid tissue inducer (LTi) and LTi-like cells[14]. Several studies have shown that IL-22 has a major role in both defense against certain microbes and the development and maintenance of chronic inflammatory diseases[15,16]. In addition, it plays an important role in mucosal tissue protection and wound healing[16,17]. Moreover, it induces proliferative and anti-apoptotic pathways in responsive cells allowing for tissue preservation[18].

The IL-22 receptor complex is composed of IL-22R1 and IL-10R2[19-21] IL-22R1 subunit is restricted to cell lineages of a non-haematopoitic origin, in particular, pancreas, kidney and liver as well as barrier surfaces such as the skin, intestine and lung[22, 23]. It is important to note that the bone marrow, peripheral blood

mononuclear cell, spleen, thymus do not express IL-22R[5, 24] and therefore immune cells are not targets of IL-22[23]. In humans, Th22, a subset of CD^{4+} T cells that specifically express IL-22 is mainly found in tissues[25]. Animal models as well as human studies have identified both inflammatory [23, 26] and protective roles for IL-22 in autoimmune diseases[18]. In RA, IL-22 is assumed to play a pathogenetic role. However, the mechanism by which IL-22 contributes to RA pathogenesis is not completely clear. The assumption was mainly based on the observed minimally reduced susceptibility of the $IL\text{-}22^{-/-}$ mice to collagen-induced arthritis (CIA) and decreased incidence of pannus information. In this model of inflammatory arthritis, IL-22 was found to promote osteoclastogenesis and this effect may be associated with the reduced severe arthritis in IL-22-deficient mice[27]. Previous studies suggest that IL-22, through the STAT3, ERKV2, and p38 MAKP pathways stimulate synovial fibroblasts proliferation and monocyte chemoattractants protein (MCP)-1production, leading to inflammation[6,28]. Recently, Sakar *et al.* reported that IL-22 reduces the severity of CIA, when administered prior to the onset of the disease and showed that the mechanism of which is associated with increased with levels of IL-10[29]. Other recent study, has been shown that IL-22 significantly enhanced fibroblast-like synoviocytes proliferation in RA and suggests that its contribution to the synovium hyperplasia and joint destruction. This study showed that potential stimulus present in the rheumatoid joint, such as TNF-α and lipo-polysaccharides are able to induce IL-22 expression[30]. A more recent study, reported that IL-22 promoted osteoclastogenesis in RA by induction of receptor activator of nuclear factor kappa-B ligand (RANKL) in human synovial fibroblast[31].

This study was conducted to investigate the presence of IL-22 in the sera of patients with RA and healthy controls and to determine the association between the level of IL-22 and the blood parameters including C-Reactive Protein (CRP), rheumatoid factor (RF), and anti-citrullinated-peptide (ACCP) antibodies, as well as its association to demographic and clinical data in RA cases.

SUBJECTS AND METHODS

This case-control study was conducted at Al-Thawra Modern General Hospital and University of Science and Technology Hospital, Sana'a city, Yemen during a period of one year starting in April 2015 and ending in April 2016. The study group; 45 patients with new onset RA were recruited and diagnosed, according to the revised criteria for classification of RA by the American College of Rheumatology (ACR) criteria[32]. These patients had never been treated with immunosuppressive drugs. The control group is 45 healthy subjects without RA were used as healthy controls. The personal and clinical information of patients and control are shown in Table 1. We conducted the study in accordance with ethical standards, and verbal informed consents were obtained from all participants before their enrollment. Patients were excluded if they had any other autoimmune diseases or infection or he/she had received immunosuppressive or glucocorticoid therapies within the past 6 months.

Five ml of venous blood was collected from each subject. The specimens were allowed to clot at room temperature and centrifuged at 3500 rpm for five minutes. Serum was separated from each sample into three ependroff tubes; one tube for IL-22 test, second for RF test and CRP test and the third for ACCP test. They stored at -20°C till tested. The sera of the selected subjects were tested to determine the IL-22 by a commercially available manual enzyme linked immunosorbent assay (ELISA), Glory Science Co., Ltd, USA]. ACCP antibodies were determined by a manual ELISA kit manufactured by (INOVA Diagnostics Kits, San Diego, CA-USA). The levels of serum CRP, and RF were analyzed by latex tests (Vitro Science Co, Egypt).

DATA ANALYSIS

According to data distribution, the quantitative data were expressed as median and range[33]. The demographic and clinical data were expressed as number and percentage. Independent sample T test was used for comparison between the patients and control groups. The potential correlation between variables was analyzed by the spearman rank correlation test. All statistical tests were performed by using the SPSS version 20 for windows (SPSS, Inc., Chicago, IL, USA) with 95% confidence interval. A two sided p-value of≤ 0.05 was considered statistically significant.

RESULTS

The demographic data of healthy control and patients showed in Table 1. At presentation, most of patients (97.8%) had joint pain and morning stiffness (93.3%), while 86.7% had swollen joints and 80% had fatigue. Twenty seven patients (60%) had symmetric arthritis, 19 (42.2%) had fever and only 8 patients (17.8%) had family history (Table 2).

IL-22 levels in serum of RA patients were significantly higher compared to that in the healthy control (p= .022). As we expected, there were significant differences between patients and healthy control in the levels of CRP, RF, and ACCP (p=0.000) Table 3.

Correlational analysis between the serum levels of IL-22 in the patient and personal and clinical data show no significant difference. As regard serologic parameters, a significant positive correlation was found between the levels of serum IL-22 and CRP and ACCP (rho=.416 p=.004, rho=.559 p=.000, respectively), however, there was no significant correlation between levels of IL-22 and RF in RA patients (Table 4 and Fig. 1 and 2, respectively).

DISCUSSION

IL-22 has been recently suggested to be involved in the pathogenesis of autoimmune arthritis. In our study, we observed significantly elevated levels of IL-22 in serum of RA patients compared to healthy controls (p=.022). Our data are in accordance with previous reports that found elevation of IL-22 in serum and plasma of patients with RA[34-37]. In consistent with our

study, IL-22 mRNA was detected in synovial tissue directly as well as in synovial fluid mononuclear cells in patients with RA[6, 37, 38]. As regard to the sources of IL-22 in humans, many studies reported that the higher frequency of peripheral IL-22^{+}CD^{4+}T cells in RA patients than those in the controls[36, 39]. Moreover, Zhoa *et al.* showed that IL-22^{+}CD4^{+}T cells were correlated positively with the disease activity in RA patients and the percentage of these cells were correlated positively with the levels of plasma IL-22 in these patients[36]. Another recent study has been shown that the synovium in RA patients is infiltrated by T lymphocytes especially Th17 which is also a source of IL-22[40].

Correlation analysis revealed that a significant positive correlations between levels of serum IL-22 and CRP and ACCP antibodies (rho=.0416, p=.004 and rho=.559, p=.000, respectively). In line with our result, kim *et al.* found a significant association between serum IL-22 and ACCP antibodies[37]. Of potential implication, the strong association of elevated serum IL-22 with the more specific serologic marker, ACCP antibodies. In addition, many recent studies reported that IL-22 has been involved in joint destruction in RA[27, 34, 35] thus, determination of ACCP antibodies and IL-22 levels may provide a novel means for predicting aggressive disease in these patients. Regarding to the correlation between IL-22 levels and RF in RA patients, our study showed no significant association between them; however, some previous studies demonstrated a positive correlation between them[36, 37]. While we did not find any previous study about the correlation between IL-22 and CRP.

To our knowledge, there is no report available on the correlation between IL-22 and the neither individual nor clinical data in RA. In our study, there are no correlations between serum IL-22 and neither demographic nor clinical data of our patients. In line with our observation, disease activity in IL-22 knockout mice of CIA did not differ from that of their wild-type littermates[27]. In addition, recent study between high and normal levels of serum IL-22 in early untreated RA patients showed no differences in the clinical inflammatory parameters of the two groups of patients, although these studies showed an association between serum IL-22 levels and bone erosin[34, 27]. On the other hand, previous studies on patients with RA have been a correlation between levels of Il-22 and disease activity or severity[35]. However, recent an experimental study has been shown that synovial inflammation was not affected in IL-22-/- mice and this study concludes that the local IL-22 produced by adaptive or innate immune cell have no direct contribution to the induction of T cell-mediated synovial inflammation[29]. Many studies suggest that the possible explanation for these differences is depending on different phases of the disease development[29, 30, 41].

CONCLUSION

In conclusion, our data indicated high levels of IL-22 in RA patients and that the strong association with ACCP antibodies suggests the potential of IL-22 and ACCP antibodies levels as predictive markers in this disease. It is also of interest that as immune cells do not express IL-22, targeting IL-22 and related signaling may be an effective therapeutic approach for treating autoimmune RA.

CONFLICT OF INTEREST

"No conflict of interest associated with this work".

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Table 1: Demographic data of control and cases of RA.

Demographic data		Healthy controls (N=45)	Patients with RA (N=45)	*P*
Age (years)	Median	40	40	.734
	Range	80	50	
	Min-Max	(10-90)	(10-60)	
Gender	Female	36	39	.402
	Male	9	6	
Residence	R	10	19	.043
	U	35	26	
Smoking habit	No	41	38	.340
	Yes	4	7	
Qat chewing	No	30	32	.653
	Yes	15	13	

R/U: Rural/ Urban; Probability value (*p)* ≤0.05 (*: significant)

Table 2: The distribution of clinical data among cases of RA.

Clinical data		
Duration (years)	Median Min-Max Range	2.0 (0.16-10) 9.840
Family history N (%)		8 (17.8)
Fever N (%)		19 (42.2)
Joint pain N (%)		44 (97.8)
Morning stiffness N (%)		42 (93.3)
Swollen joints N (%)		39 (86.7)
Fatigue N (%)		36 (80)
Symmetric arthritis N (%)		27 (60)

Table 3: The levels of Il-22 and serologic markers of RA in control and cases.

Parameters		**Healthy controls (N=45)**	**Patients with RA (N=45)**	***P***
IL-22 (ng/mL)	Median Range Min-Max	75.36 459 (55-514)	86.89 825 (56-881)	0.022**
CRP (mg/mL)	Median Range Min-Max	.00 24 (0-24)	24.0 48 (0-48)	0.000**
RF (IU/mL)	Median Range Min-Max	.00 32 (0-320)	32.0 64 (0-64)	0.000**
ACCP (U/mL)	Median Range Min-Max	.00 320 (0-320)	221.0 517 (0-517)	0.000**

CRP: C-reactive protein; RF: rheumatoid factor; ACCP: anti-cyclic citrullinated peptide. The normal ranges of CRP, RF and CCP, and are 0–25 U/mL, 0–15 mg/L and 0–15 IU/Ml respectively. Probability value (p) ≤0.05 (*: significant)

Table 4: Correlation between the levels of IL-22 and different variables in patients with RA

	IL-22 (ng/ml) (N=45)
Demographic data	
Age (years)	rho=.272, p= .071
Gender (Female/Male)	rho=.015, p= .922
Residence (R/U)	rho=.121, p= .428
Smoking habit (%)	rho=.012, p= .939
Qat chewing (%)	rho=.098, p= .521
Clinical data	
Family History (%)	rho=.219-, p= .148
Joints pain (%)	rho=.128-, p= .403
Morning stiffness (%)	rho=.144-, p= .0345
Swelling joints (%)	rho=.078-, p= .610
Fever (%)	rho=.097, p= .526
Fatigue (%)	rho=.017, p= .911
Symmetric arthritis (%)	rho=.070-, p= .648
Duration (years)	rho=.280, p= .062
Serologic parameters	
CRP (mg/mL)	rho=.416**, p= .004
RF (IU/mL)	rho=.291, p= .053
ACCP (U/mL)	rho=.559**, p= .000

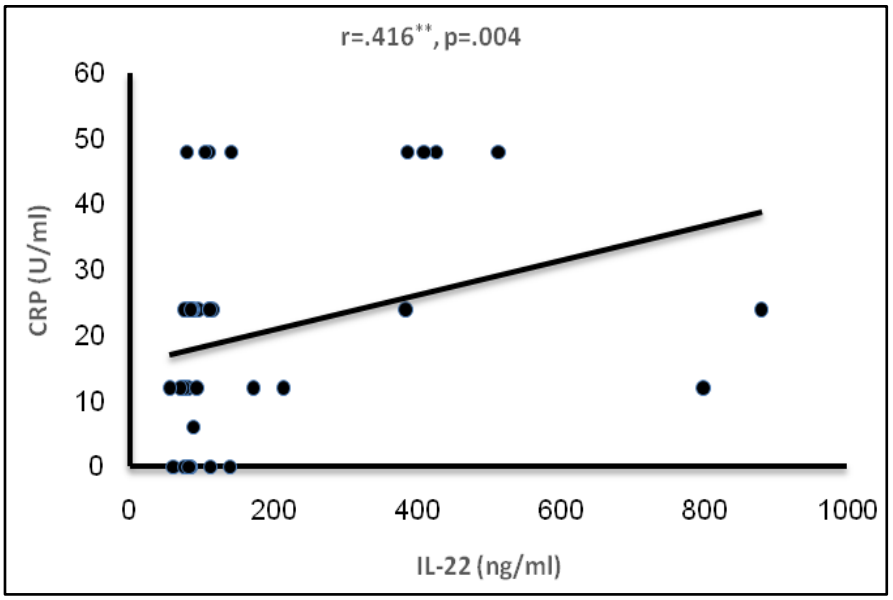

Figure 1: The correlation between serum levels of IL-22 and CRP in RA patients.

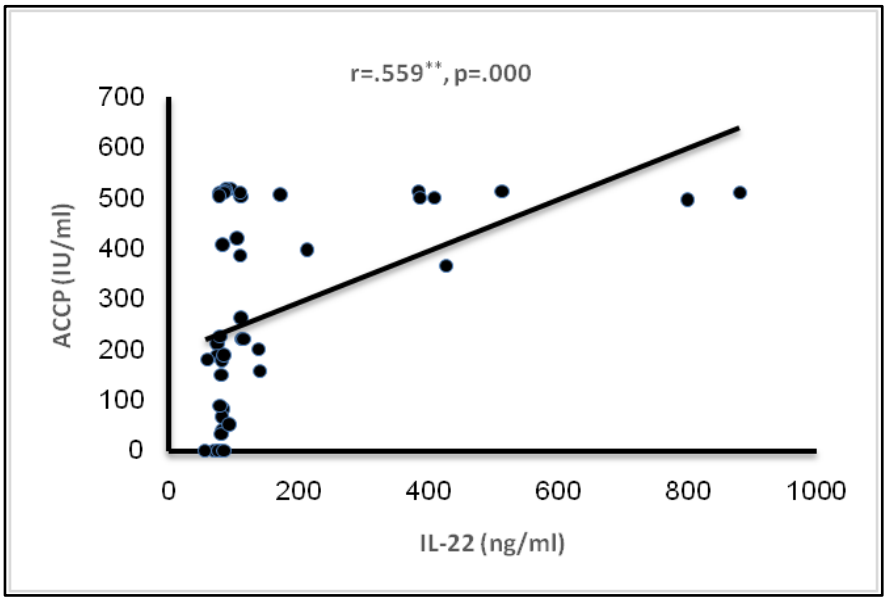

Figure 2: The correlation between serum levels of IL-22 and ACCP in RA patients.