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Immunological Value of Periostin, Amphiregulin, IL-33 and sST2 Markers in Rhinosinusitis Patients

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Abstract

Background: Rhinosinusitis is an inflammatory disorder that refers to inflammation of the nose and paranasal sinuses. Recent studies show that serum IL-33, periostin, ARGE and sST2 had the role in the pathogenesis of chronic rhinosinusitis as an easy, non-invasive and readily available (biomarker) for diagnosis of chronic rhinosinusitis. We tested for correlations of IL-33, periostin, ARGE and sST2 between acute and chronic rhinosinusitis in compare to healthy people. This study aimed to Measure serum levels of periostin, IL-33, sST2, and ARGE biomarkers in patients ARS and CRS.

Materials and Methods: We collected serum of 30 patients with acute rhinosinusitis, 30 with chronic rhinosinusitis, and 30 controls to examine serum levels of IL-33, periostin, ARGE, and sST2 by enzyme-linked immunosorbent assay method (ELISA) **Results:** serum periostin had significance (p=0.001) with the chronic rhinosinusitis group and significantly higher in patients with CRSwNP(p=0.000). Serum ARGE and sST2 levels significantly higher in patients groups (p=0.01; p=0.001; p=0.03; respectively), serum sST2 levels in CRSwNP(p=0.000). No difference in serum levels of IL-33. **Conclusions:** Our results show increased serum levels of periostin among chronic rhinosinusitis patients also especially with nasal polyps. Serum ARGE and sST2 levels significantly increased among patients with acute and chronic rhinosinusitis also serum sST2 levels found to be with CRSwNP, and no statistical significance was detected in serum IL-33.

Keywords: Acute and Chronic Rhinosinusitis, Nasal Polyps, IL-33, sST2, ARGE, Periostin**.**

Introduction

Rhinosinusitis(RS) is one of the airway diseases and the most common health care complaints affecting by nose mucosal inflammation and the paranasal sinuses (Rosenfeld et al., 2007). RS is classified clinically to acute Rhinosinusitis (AR) is an upper respiratory tract infection that persists for

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up to four weeks can be divided into acute bacterial and viral rhinosinusitis (Sharp et al., 2015). Chronic Rhinosinusitis is a frequent disorder that persists at least 12 weeks or longer characterized by inflammation of paranasal sinus and the nasal mucosa (Chong et al., 2020).

Periostin is a protein belonging to the fasciclin family described as an extracellular matrix protein (Lehmann et al., 2019). Though, in several allergic diseases including asthma, atopic dermatitis, chronic rhinosinusitis serum periostin has been elevated (Ono et al., 2020). The immune response of IL-13 and IL-4 induces the production of periostin by fibroblasts, overexpression of periostin associated with up-regulation in the Th-2 immune response, given that signals for tissue development and remodeling by deposition of periostin in thickened basement membranes (Passali et al., 2020). Amphiregulin(AREG) is a protein primarily produced by ILC2s, Tregs, and Th2 cells, it part of the epidermal growth factor (EGF) family, AREG interacts with EGFR to promote the growth of epithelial cells (Dogan et al., 2019). Whereas after influenza virus infection shows the role of AREG in lung repair (Guo & Thomas, 2017), also, revealed the role of amphiregulin in the tissues repair of chronic inflammation in the respiratory system (Okumura et al., 2005).

An over-expression of AREG was reported in the epithelium in patients with CRS (S. Wang et al., 2020). IL-33 is a protein that belongs to the IL-1 cytokine family and acts as a ligand to receptor ST2, When IL-33 is bound to the ST2 receptor that's probably led to induce a Th2 inflammatory response (Rogala & Glück, 2013). IL-33 plays important roles to regulate the immune response in inflammatory diseases such as asthma, Rhinosinusitis, Recently, the soluble ST2 isoform was formally shown to function as an antagonistic decoy-receptor used for IL-33, in patients with different disorders correlated with abnormal Th2 responses, the serum sST2 levels are increased, IL-33/ST2 axis paly the important role in the pathogenesis of chronic rhinosinusitis (C. Wang et al., 2020) (Article, 2020). This study aimed to investigate the role of these cytokines in the pathology of acute and chronic rhinosinusitis when examined the serum levels of (periostin, IL-33, sST2, and ARGE) and compared with the healthy control group, Find out the association of biomarkers levels (periostin, IL-33, sST2, and ARGE) in patients with acute and chronic rhinosinusitis

Patients and Methods

This study was performed between January and April 2020 at the Department of otolaryngology, an outpatient clinic in Baghdad teaching hospital, and approved by the ethics committee of the

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Department of Microbiology, College of medicine, University of Baghdad. The study included thirty (30) patients with acute rhinosinusitis and thirty (30) with chronic rhinosinusitis(15 cases with nasal polyps) with ages ranged 13-62 years old compared to thirty (30) healthy individuals as a control group with 14-58 years old. Samples were taken from each individual include 5ml Blood by vein puncture, the tube with clotted blood was centrifuged under 1000x g for 20 minutes, and extracted serum collected in Clean tubes then stored under -20ºC.

Detection of cytokines: serum markers will be detected by using enzyme-linked immune sorbent assay (ELISA) kit. Four kits used (AL-shkairate establishment for medical supply, Jordon, Catalogue No (IL-33); RDEEH0198, (Periostin); RDEEH0255, (ARGE); RDEEH6284, (SST2); RDEEH0188).

Statistical Analyses: Statistical analysis was performed by using SPSS (IBM-statistical package for windows version 23.0 computer software). Kolmogorov–Smirnov and Shapiro-Wilk tests were used for the normal distribution of the quantitative data. Mann-Whitney U test was assessed to comparison the median with an interquartile range of two non-normally distributed data and Kruskal-Wallis H for three groups. An estimate of the correlation coefficient between variables. Receiver operating characteristics (ROC) was used. P-value less than <0.05 was considered to be statistically significant.

Results : Data of 88 individuals were investigated.

Table (1) describes the demographic distribution of study groups.

Factors		**Groups**		
		Acute No=30	**Chronic No=30**	**Control No=30**
Sex	**Male**	17 (56.67%)	21 (70.00%)	15 (50.00%)
	Female	13 (43.33%)	9 (30.00%)	15 (50.00%)
Age Mean ± SE (year)		31.03 ±1.88	39.07 ±2.74	37.20 ±2.51

Mann-Whitney test demonstrated the median of serum periostin (0.53ng/ml) significantly higher among chronic rhinosinusitis in comparison to both acute and control group (p= 0.001) and no difference between acute rhinosinusitis and control group (p= 0.286), while significant difference was observed among both acute and chronic rhinosinusitis for serum amphiregulin and soluble ST2 levels

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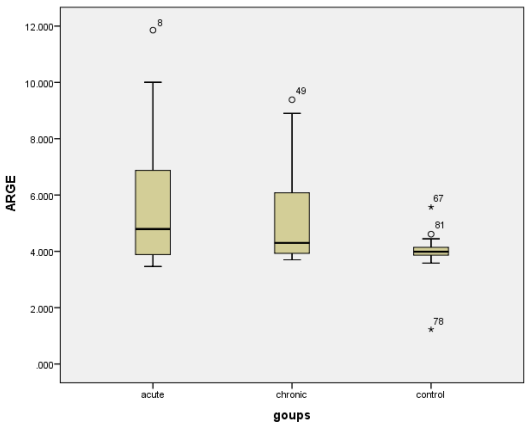
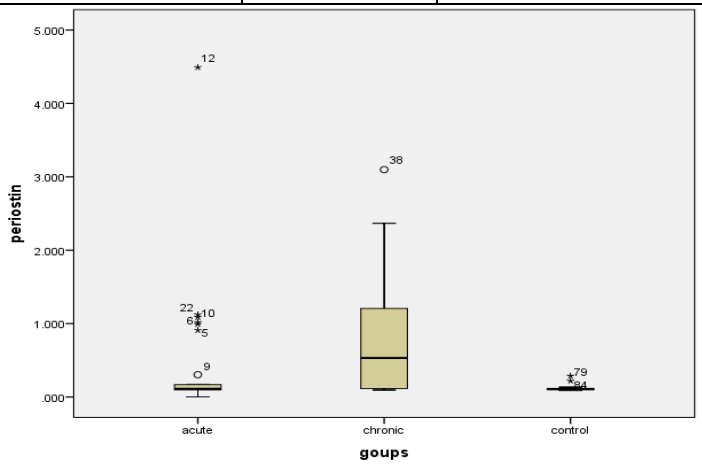
in compared to control group (p= 0.01, p= 0.01, p= 0.001 and p= 0.03 respectively), no difference detected in serum IL-33 levels among acute and chronic rhinosinusitis groups and control group (p= 0.791 and p= 227). The median of serum sST2 (1.79pg/ml) and serum periostin (1.20ng/ml) significantly higher in patients with CRSwNP than CRSsNP and no difference in serum ARGE and IL-33 levels (p= 0.000, p= 0.000, p= 0.934 and p= 0.395 respectively). No statistical significant correlation was found between serum markers (IL-33, sST2, ARGE and periostin) and smoking (p=0.429, p=0.319, p=0.513 and p=0.230 respectively) and gender (p=0.544, p=0.256, p=0.471 and p=0.247 respectively).

Table (2): compression of serum cytokines in study groups.

Cytokines	Study groups	Mean ± SE	Median	P(kruskal- wallis)
periostin	**Acute**	0.411± 0.154	0.12	0.001
	Chronic	0.837± 0.154	0.53	
	Control	0.117 ± 0.01	0.10	
ARGE	**Acute**	5.552± 0.401	4.79	0.01
	Chronic	5.191± 0.322	4.29	
	Control	3.969± 0.124	3.98	
IL-33	**Acute**	8.958± 0 .907	7.60	0 .428
	Chronic	9± 1.238	7.10	
	Control	8.537± 0 .500	9.10	
sST2	**Acute**	2.302± 0 .208	2.03	0.001
	Chronic	1.357± 1 .174	1.31	
	Control	0.978± 0 .222	0.59	





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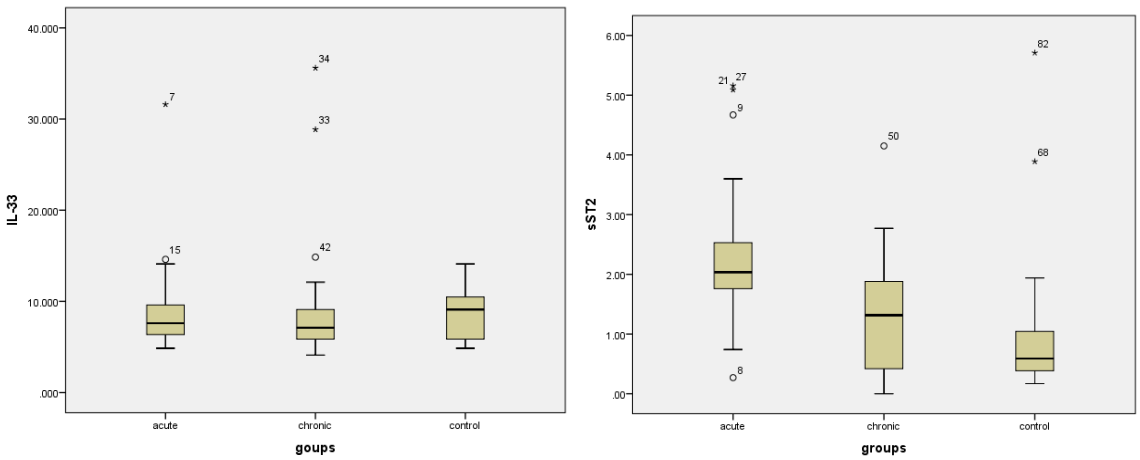

Dot diagram with error bars graphics showing the distribution of levels of IL-33, sST2, ARGE and periostin.

Discussion

Recent studies shown that (periostin, AREG, IL-33, sST2) plays the central role in the recruitment of inflammatory cells, and have the mechanisms which can regulate different important Immune cells in chronic rhinosinusitis. Since the periostin induces inflammation and fibrosis of many organs in various disease states, and the up-regulation of TH2 which mainly responsible for the stimulation of periostin(Conway et al., 2014). In this study, the median value of serum periostin shows that (0.53ng/ml) of the CRS group has a strong difference (p= 0.001) more than both acute rhinosinusitis and control groups. the statistical significance was agreed with (Maxfield et al., 2018) which showed a high level of serum periostin in patients with chronic rhinosinusitis that's explain the up-regulation of the immune response of Th2 and the role of periostin as the best sense for Th2 driven in such inflammation disease.

Otherwise, no difference in serum periostin between ARS and control groups that's demonstrate production and stimulation of periostin only happened in chronic inflammatory sites after inducing of IL-4 or IL-13 in tissue destruction (Izuhara et al., 2019). Periostin level found to be with strong significance (p=0.000) in chronic rhinosinusitis patients with nasal polyps, which agreed with other studies that are revealed the role of periostin in the formation of nasal polyp and elevated serum periostin in CRSwNP more than CRSsNP which considered the periostin as a marker in the description of the mechanism of Th2 driven in CRSwNP and suggest the possibility of periostin to stratify chronic Rhinosinusitis to at least two molecular endotypes (Maxfield et al., 2018). Also,(Ninomiya et al.,

2018) reported increased serum levels of periostin in chronic rhinosinusitis patients with nasal polyp made the periostin biomarker ideal for predicting CRSwNP. Furthermore, previous studies, reported increased serum level of periostin in CRS patients and using serum periostin as a marker for predicting eosinophilic CRSwNP (Asano et al., 2017).

In our findings there was statistical significance in serum ARGE between patients groups and control group. Since the role of amphiregulin in tissues remodeling and repair as an immune response, the older studies did not describe the role of ARGE in acute rhinosinusitis, and in our study, we investigate the elevated serum ARGE level in the acute group with statistical significance (p= 0.01), ARGE maybe contribute in pathogenesis of ARS as an immune response. To the best of our knowledge, there were no other studies explain the relation of ARGE and acute rhinosinusitis, may be suitable to use results of studies in acute respiratory infection to explain the role of ARGE in acute rhinosinusitis pathophysiology, that was revealed after a viral infection of upper respiratory the stimulation of IL-8 due to the expression of ARGE which activate IL-8 as a pro-inflammatory and summarize the role of ARGE in the pathogenesis of inflammation and obstruction upper respiratory (Val et al., 2012). Also after bacterial infection, the TLRs will be activated EGFR which induced ARGE in airway epithelium (Avila et al., 2005). So increased serum level of ARGE in acute rhinosinusitis group may be demonstrating mixed Th1 and Th2 immune response can occur in ARS patients, and this agreed with (Scheckenbach & Wagenmann, 2016), and that was based on the methods and materials, which can differ in results and interpretation. Whilst elevated serum level of ARGE in chronic rhinosinusitis group with statistical significance (p= 0.01), agreed with later authors which reported the role of ARGE in the pathogenesis of chronic airways and expression in the upper respiratory epithelium in asthmatic patients (Okumura et al., 2005), also shown increased expression level of ARGE in the tissue of patients with CRSwNP and the role of ARGE in the aetiopathogenesis of CRSwNP (Dogan et al., 2019).

The serum level of IL-33 between the patient's groups had no difference with the control group (p= 0 .428). On the contrary, recent studies indicated that the IL-33 also can express from Th1 cells and Treg cells after viral and bacterial infection (Bell & Gern, 2012)(C. Baumann et al., 2015). Additionally, IL-33 mediated by Th2 in chronic rhinosinusitis, later authors showed elevated serum level of IL-33 in patients of chronic rhinosinusitis with nasal polyps more than patients without nasal polyps and control group (Ozturan et al., 2017).

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The low concentration of serum IL-33 in patients' groups and without significance in comparison with the control group that was may be affected by the time of sample taken from the patient. Did the sample taken at the beginning of the rhinosinusitis? Or was it happening? Or later it can occur? This is because interleukin 33 acts as a pro-inflammatory cytokine, might function as an alarmin out from damaged cells respiratory system, exposure to allergic and infectious stimuli(Cayrol & Girard, 2018). Also may be due to the type of kit for measure the serum level of IL-33, also, the presence of interfering factors in serum such as IL-1RL1-a may be explained the low IL-33 level in serum, as Ketelaar et al, 2016 find that the measurement of IL-33 as accurate quantification by ELISA kits affected by both serum and recombinant IL-1RL1-a (sST2).And that's been achieved in our finding where increased serum level of (sST2) in patients groups and explain the negative role of soluble ST2 in suppressing and inhibition of active IL-33(Arend, 2008). Also, the median value of serum soluble ST2 in acute and chronic rhinosinusitis groups were statistically significance compared to control group. Soluble ST2 is a key molecule that controls the immune system and the proliferation of cells, likewise, increased serum level of (sST2) in the acute rhinosinusitis group maybe explain the role of the soluble receptor of IL-33 in the pathology of acute rhinosinusitis, the negatively regulation make the soluble ST2 act as an inhibitor mediator in the suppression of IL-33 and that was maybe achieved in our finding by reducing the serum level of IL-33. Increased serum level of sST2 in acute face of rhinosinusitis was agreed with other studies which expected increased soluble ST2 in acutely face to moderate the expression of immune mediators also in airway epithelium (Smith, 2010).

These findings may be indicating the possibility of soluble ST2 to participate and immune regulation of acute rhinosinusitis after viral or bacterial nasal infection. Otherwise, elevated serum level of sST2 in the CRS group illustrated the up-regulation of Th2 cells, and that was agreed with previous studies when show increased expression of mRNA ST2 protein in nasal mucosae of CRS patients (Baba et al., 2014). Likewise, (Oshikawa et al., 2001) reported elevated serum levels of sST2 in asthmatic patients and summarize the role of sST2 in Th2 mediated chronic airway inflammation. Later authors, concluded the role of ST2 in chronic rhinosinusitis in patients with nasal polyps as an expression in the mucosa of Ethmoid Sinus with statistical significance compared with CRSwNP group and healthy control, while, no significance observed in IL-33 between groups.

Moreover, these results agreed with other studies when elevated serum levels of sST2 in other inflammation diseases like, Allergic rhinitis which typically precedes additional co-morbidities such as

CRS, atopic dermatitis, and asthma (R. Baumann et al., 2013). Otherwise, statistical significance observed in our results (p=0.000) between patients with a nasal polyp and without nasal polyps which may summarize the role of soluble ST2 in the pathogenesis of CRSwNP and that was found in previous studies, when an increased expression of ST2 in patients with eosinophilic chronic rhinosinusitis to prevent the activation of IL-33/ST2L pathway in eosinophilic CRSwNP (Liao et al., 2015).

Conclusions

The serum periostin levels were significantly higher in the chronic rhinosinusitis demonstrate the role of periostin in chronic sites, especially in CRSwNP. Also increased serum levels of ARGE and sST2 among acute and chronic rhinosinusitis patients groups explain their role in the pathology of rhinosinusitis. As well increased statistical significance of serum sST2 in patients of chronic rhinosinusitis with nasal polyps maybe is another potential target to discriminate the patients with CRSwNP. No statistical significance of serum IL-33 was observed between patients groups.

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