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Local Expression of Mucosal YKL-40; Correlation of YKL-40 with Clinical Manifestations and Immunopathogenesis of Moderate/ Severe Persistent Allergic Rhinitis Patients

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ABSTRACT

YKL-40 is an important protein that plays a critical role in chronic inflammation in hypersensitivity disease. In this study, the expression of YKL-40 was investigated among patients with moderate/severe persistent allergic rhinitis (M/S PAR), patients with mild (M) PAR and healthy individuals. Moreover, the association between YKL-40 and immunopathogenesis of M/S PAR was meticulously surveyed. For this purpose, surgical samples were tested by real-time polymerase chain reaction to evaluate YKL-40 mRNA expression. The presence and location of YKL-40 protein in the tissue samples were determined by immunohistochemistry. Additionally, we measured the number of eosinophils per field in the tissue samples, blood eosinophils, total serum IgE, specific serum IgE, total nasal syndrome score (TNSS) and YKL-40 serum levels. The data indicated that production of YKL-40 in patients with M/S PAR increased significantly when compared with the control group. Furthermore, local production of YKL-40 correlated with specific IgE, nasal eosinophil count and TNSS. The results of the present study indicate that YKL-40, for its correlation with allergic clinical manifestations and symptom severity in M/S PAR patients, should be considered as a trigger factor in AR.

KEYWORDS

YKL-40; TNSS; disease severity; allergic rhinitis; M/S PAR

Introduction

As a common hypersensitive disorder, allergic rhinitis (AR) can be identified by symptoms such as sneezing, rhinorrhea and nasal congestion when susceptible individuals are exposed to inhaled allergens such as pollen, mold and dust mites. Mucosal inflammation is a prominent histological feature that is induced by type 2 helper T-cells (Bauchau and Durham, 2005; Pawankar et al., 2012; Skoner, 2001). AR, as an IgE-mediated chronic disease, has been observed with high frequency among children (Ciprandi et al., 2005;

Phipatanakul, 2005). Surprisingly, it often goes undiagnosed (Ciprandi et al., 2005). In addition to the high medical cost, this chronic disease decreases the quality of life and work efficiency for adults. It also decreases academic performance and the severe form reduces learning at school for children (Pawankar et al., 2011). In view of the frequency of the symptoms and nature of the allergens, AR is divided to two main forms: intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PAR) (Jun et al., 2014).

YKL-40 (chitinase-3-like-1; CHI3L1) is a human glycoprotein which binds to chitin and is primarily known as human cartilage glycoprotein 39 (HC gp-39). Although it binds to chitin, it does not exhibit chitin hydrolase activity. Some studies indicate that chitinase family members have an important role in the development of both fibrosis and remodeling of the airway (Konradsen et al., 2013). It has been indicated that the serum concentration of chitinase-like protein YKL-40 increases in patients with AR (Kwon et al., 2011). In asthmatic patients, the level of YKL-40 is a marker of disease severity (Chupp et al., 2007).

Recent experiments on airway allergies in mice models showed that YKL-40 has an initial function in immunoglobulin E (IgE) induction and antigen sensitization. It also stimulates dendritic cell accumulation and activation (Lee et al., 2009) and induces alternative activation of macrophages. Additionally, YKL-40 prevents cells from inflammation and apoptosis (Lee et al., 2009).

Except for asthma, data on how YKL-40 is related to allergic diseases are insufficient. The present study attempted to investigate serum levels of YKL-40 in patients with M/S PAR compared to patients with M PAR and a healthy control group. Evaluation of the expression of YKL-40 in the human inferior turbinate mucosa in patients with M/S PAR was compared with its expression levels in M PAR patients and the control group. The correlation between YKL-40 and disease severity was also examined.

Materials and methods

Patients and clinical specimens

The subjects were divided into three groups of 70 as moderate/severe persistent allergic rhinitis (M/S PAR), mild persistent allergic rhinitis (M PAR) and healthy ($n = 70$). Exclusion criteria included a background of nasal infection, recurrent infections of the respiratory tract, any history of allergies, smoking, systemic steroid treatment and continuous use of anti-allergic drugs or those who have used them in the previous four weeks. Inferior turbinate mucosal biopsies were obtained from the patients by a specialist. The diagnosis of AR was done by the specialist on the basis of the medical history and symptoms (sneezing, rhinorrhea, nasal congestion for at least 2 years), a positive skin test results and a positive dust mite-specific IgE test (Astra Biotec; Germany). The severity of total nasal symptom score or TNSS is based on the three symptoms (i.e., sneezing, rhinorrhea and nasal congestion) which were rated on a 4-point scale from 0 to 3 (Okuda et al., 1986) (Table 1). The normal nasal mucosa was collected from the inferior turbinate of 70 participants who had normal nasal mucosa and were admitted for augmentation rhinoplasty.

Before obtaining the tissue specimens, all protocols were approved after institutional review board of Shahrekord University of Medical Sciences and all participants provided

Table 1. TNSS symptom score and its components.

	Sneezing	Rhinorrhea	Nasal congestion
No symptoms	0	0	0
Minimal, well-tolerated symptoms	1	1	1
Bothersome but tolerated symptoms	2	2	2
Severe	3	3	3

completed and signed consent forms. Serum samples were obtained for the total and specific IgE measurement. Tissue specimens were divided into two parts: the first was used as the source of RNA extraction; therefore, it was immediately frozen in liquid nitrogen and kept at -70°C . The 2nd part was paraffinized for pathological examination and IHC. The pathological examinations were done by hematoxylin and eosin (H&E) staining. Biopsy specimens were immediately immersed in a 10% formalin solution and prepared for paraffin embedding. Next, the paraffin blocks were cut into $4\text{ }\mu\text{m}$ sections which were mounted on glass slides. The tissue slides were prepared for routine H&E staining for conventional histopathology and IHC to detect the local YKL40 expression.

Immunohistochemical analysis

IHC was used for the detection of expression levels of YKL-40. The labeled streptavidin-biotin complex method was used (Shohan et al., 2018). From each participant, two sections were prepared and were placed in an oven overnight at 70°C . Next, they were deparaffinized in xylene and re-hydrated using different series of alcoholic dilutions (100%, 100%, 80% and 70%). For antigen retrieval, the sections were put into citrate phosphate buffer (pH 6.0) and exposed to microwaves for 3 min at 100 W and then 25 min at 850 W microwave temperature.

Endogenous peroxidase activity was prevented by using 0.3% H_2O_2 in TBS for 15 min. The prepared sections were incubated with protein block (Abcam, England) for 10 min to reduce nonspecific background staining. Polyclonal anti-YKL-40 was generated by rabbit immunization (Abcam; England). Before conducting IHC the primary antibody was diluted 1:250 in TBS solution containing 1% BSA, according to the manufacturer's instructions (Abcam; England). The secondary antibody was ready to use. Next, 1 mg/ml was applied as the primary antibody against YKL40. The tissue sections were incubated overnight at 4°C . The negative control for IHC was normal goat IgG antibody instead of primary antibody.

The sections were washed with 1% BSA in TBS and biotinylated goat anti-rabbit IgG was applied as the secondary antibody. The sections were incubated again for 1 h at room temperature. Slides were developed with diaminobenzidine and counterstained with hematoxylin. The number of YKL-40+ cells was calculated in at least five fields at the high power field (10×40) by the pathologist where the highest number of positive-stained cells was observed. The mean number of positive cells was determined.

Assessment of serum YKL-40 levels by ELISA

Serum YKL40 levels were measured in all three groups by ELISA according to manufacturer protocol (Abnova; Taiwan). The protein concentration was determined using the STAT FAX 3200 ELISA reader (USA) and was stated as ng/ml.

RNA extraction, cDNA synthesis and real-time PCR

Total RNA was extracted from the nasal tissue samples using Biozol solution (Bioflux; Japan). The quantity and quality of the RNA were measured by NanoDrop at the wavelength absorption ratio (260/280). RNA samples (1 mg/ml) were mixed with DNaseI (10 u/ml) for 30 min in order to remove any DNA contamination. The cDNA was synthesized with random hexamers from 1 mg of total RNA (Thermo Scientific; Lithuania). The reaction tubes were incubated in a thermocycler at 25°C for 5 min, then at 42°C for 1 h and for another 5 min at 72°C. For real-time PCR, we performed an initial denaturation at 95°C for 10 min. Then, 40 cycles were conducted at 95°C for 15 s, 57°C for 20 s and 72°C for 25 s.

YKL-40 gene expression was measured by quantitative real-time PCR using SYBR Green master mix (Takara; Japan). The primer sequences which were used for real-time polymerase chain reaction (PCR) are listed in Table 2. β -actin was used as an internal control. The standard curves were drawn and the efficiency of each set of primers was determined. Primer efficiency was above 90%. The data were expressed as fold change using the comparative cycle threshold ($\Delta\Delta$ ct method). Relative gene expression was determined by the 2- $\Delta\Delta$ ct method (Bagheri et al., 2016).

Statistical analysis

Statistical analysis was conducted using SPSS 23.0 for Windows (IBM SPSS). The data from real-time PCR and IHC in the healthy control and M PAR and M/S PAR groups were compared by one-way ANOVA followed by the *post hoc* Tukey test. The student t-test was used to analyze the results of ELISA for detection of specific IgE between the M/S PAR and mild PAR groups. The correlations were assessed using the Pearson correlation test. A *p*-value of less than 0.05 was considered significant.

Results

Clinical characteristics of participants

The variables of this study are listed in Table 3. Healthy participants were age- and sex-matched with the patients. As the data showed, the duration of the disease did not significantly differ between groups (Table 3). The total IgE levels in the serum of the M PAR and M/S PAR groups were higher in comparison with the healthy control group (Table 3). The results are shown as mean $\pm$ SD.

Table 2. Sequences of PCR primers and size of amplicons.

Primer	Sequence	Size (bp)
β -actin	Forward primer: 5-AGCGAGCATCCCCAAAGTT-3	285
	Reverse primer: 5-GGGCACGAAGGCTCATCATT-3	
YKL-40	Forward primer: 5- ATACGACGACCAGGAAAGCGTCAA-3	158
	Reverse primer: 5- GTGCATCCTTGATGGCATTGGTGA-3	

Table 3. Participants' characteristics*.

Variables	Healthy control	mild persistent allergic rhinitis patients	moderate/severe persistent allergic rhinitis patients
Gender(male/female)	38/32	40/30	36/34
Age	25.8 ± (6.42)	26.7 ± (4.8)	26.0 ± (4.0)
Specific IgE for house dust mite(IU/mL)	Less than 0.01	4.5 ± (5.5)	0.5 ± (0.15)
Total IgE (IU/mL)	82.6 ± (43.8)	1061.1 ± (88.4)	236.3 ± (33.2)
Blood eosinophil count (absolute count)	74.5 ± (40.0)	618.9 ± (114.1)	255.7 ± (70.9)
The degree of eosinophil infiltration into the nasal mucosa (eos/HPF)	0.5 ± (0.5)	3.6 ± (1.8)	1.7 ± (0.59)
Disease duration (years)	-	17.1 ± (4.3)	15.1 ± (2.6)

*Results are shown as mean ± (SD)

Tissue distribution pattern of YKL-40

Local production of YKL-40 in the inferior turbinate of nasal mucosa was determined by immunohistochemical staining and shows the distribution of YKL-40 for all groups (Figure 1a–c).

The number of YKL-40 + cells in the nasal mucosa was significantly higher in the M/S PAR group compared to the control group ($p = .006$; Figure 2a; Table 4). There was no significant difference between the M/S PAR and M PAR groups ($p = .059$) or the M PAR and control groups ($p = .678$).

Serum YKL-40

YKL-40 levels were measured in serum obtained from all groups. Significantly higher levels of YKL-40 were found in serum the M/S PAR group compared with the healthy control ($p < .001$) and M PAR ($p = .001$) groups. The difference between YKL-40 in the M PAR and healthy control groups was also significant ($p = .003$; Figure 2b; Table 4).

Gene expression of YKL-40 in nasal mucosa

The gene expression levels of YKL-40 were determined in the nasal mucosa of all groups using real-time PCR. The expression levels of YKL-40 in the M and M/S PAR groups showed a significant increase when compared with the healthy control group ($p < .001$ and 0.022

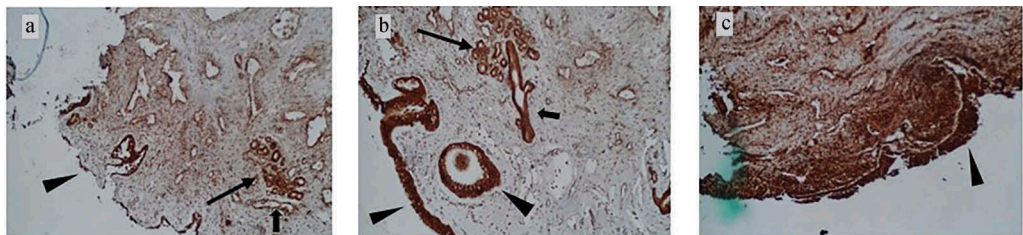


Figure 1. Local expression of YKL-40 using IHC in: (a) normal; (b) M and; (c) M/S PAR nasal mucosa. YKL-40 was detected in the surface epithelium (arrow head), submucosal glands (thin-long arrow) and vascular endothelium (thick, short arrow). YKL-40 staining was more intense in M/S PAR samples than the controls samples (magnification X40).

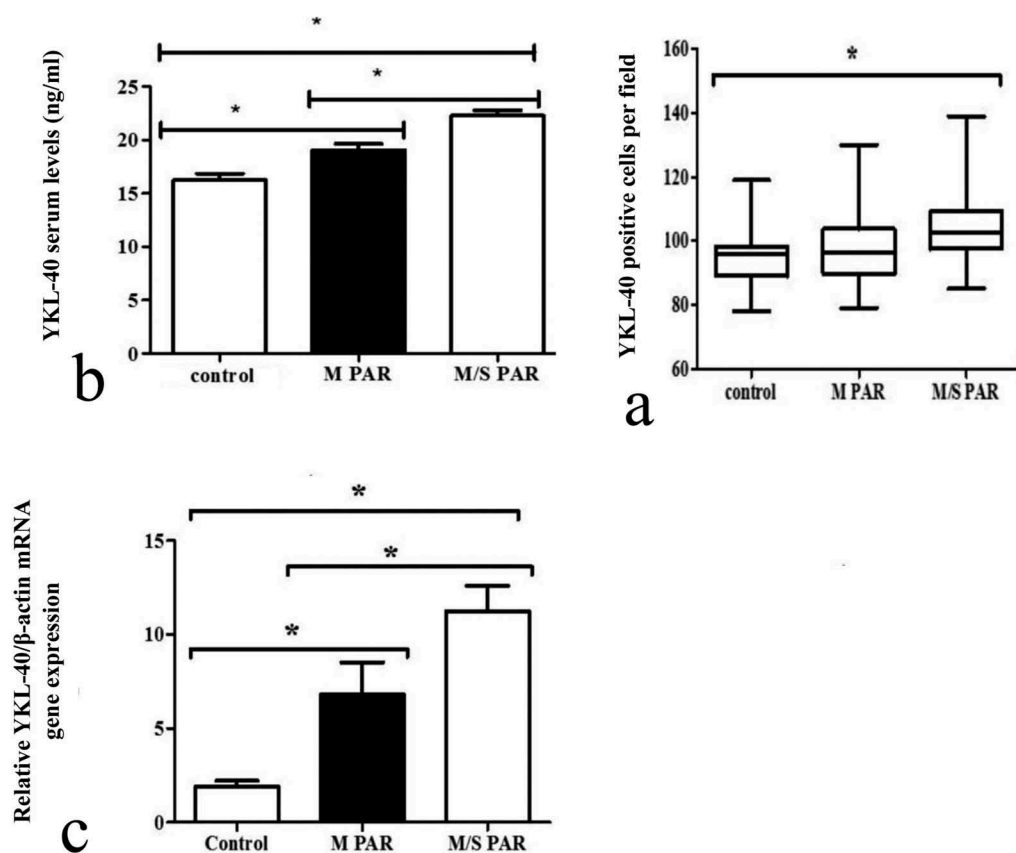


Figure 2. (a) Comparison of the number of YKL-40+ cells in nasal mucosa between groups ($p = 003$). (b) Comparison of serum levels of YKL-40 between groups ($p = 001$). (c) Real time-PCR analysis of YKL-40 mRNA expression showing the significant difference in YKL-40 between groups ($p < .001$). *significant difference.

Table 4. Comparison of all groups at baseline. YKL-40 gene expressions, serum levels of YKL-40 and YKL-40-positive cells per field*.

Variable	Control	M PAR	M/S PAR
YKL40 gene expression (relative to beta-actin)	1.88 ± (1.77)	6.8 ± (9.4)	11.23 ± (7.52)
Serum YKL-40 levels (ng/ml)	16.25 ± (3.39)	19.03 ± (3.44)	22.28 ± (2.72)
YKL-40-positive cells per field	95.66 ± (9.14)	98.16 ± (12.19)	105.03 ± (12.82)

*Results are shown as mean ± (SD)

respectively) (Table 4 and Figure 2c). Also, there is a significant difference in the mRNA expression levels of nasal mucosa YKL-40 between patients with M/S and M PAR ($p = .043$). Overall $p < 001$ (between the three groups).

YKL-40+ cells versus clinical manifestations in M/S PAR group

R represents the amount of correlation. A significant and positive correlation was seen between the number of YKL-40+ cells in the nasal mucosa and TNSS ($R = 0.822$; $p = .001$; Figure 3a). The

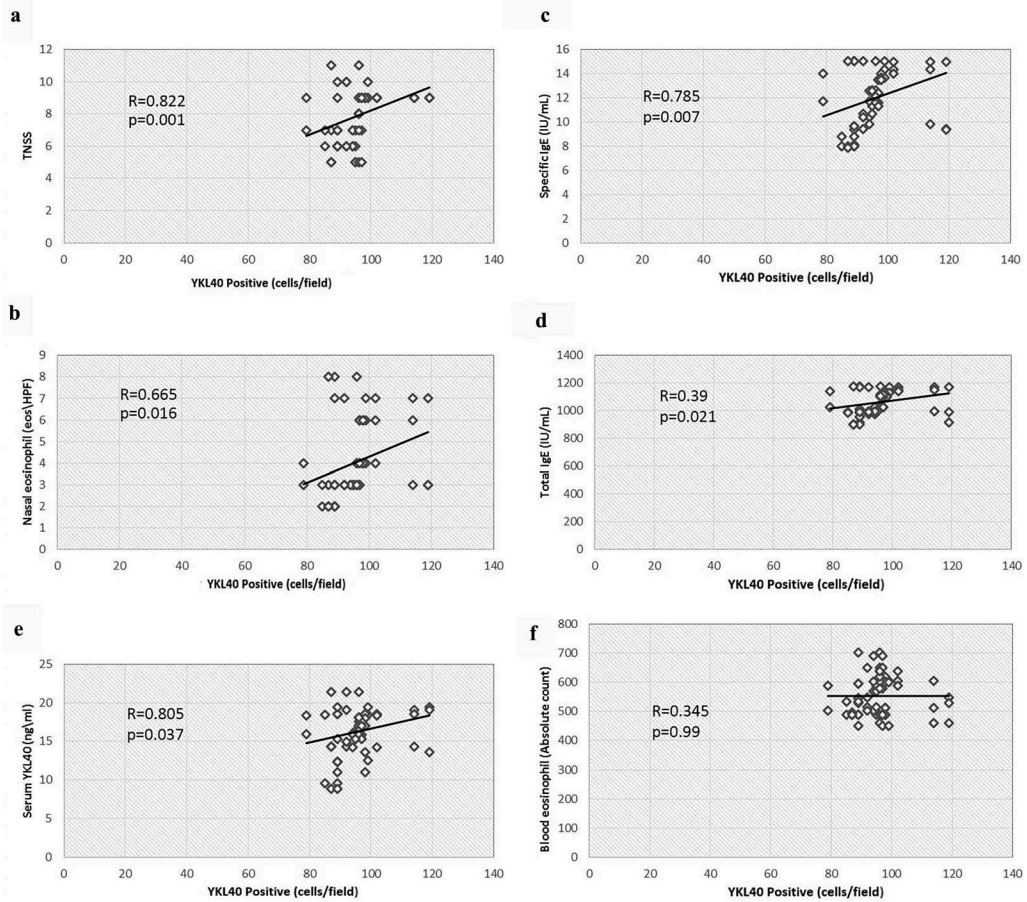


Figure 3. Number of YKL-40+ cells in nasal mucosa versus: (a) TNSS; (b) nasal eosinophil count; (c) specific IgE; (d) total IgE; (e) serum YKL-40; (f) blood eosinophil count.

congestion ($R = 0.621$; $p = .001$) and rhinorrhea ($R = 0.58$; $p = .001$) scores were significantly and positively correlated with the number of YKL-40+ cells. There was no significant correlation with sneezing ($R = 0.276$; $p = .072$). The degree of eosinophil infiltration into the nasal mucosa was positively correlated with the number of YKL-40+ cells ($R = 0.665$; $p = .016$; Figure 3b). There was a noticeable correlation between YKL-40+ cells and specific IgE ($R = 0.785$; $p = .007$; Figure 3c), total IgE ($R = 0.39$; $p = .021$; Figure 3d) and serum YKL-40 ($R = 0.805$; $p = .037$; Figure 3e). On the other hand, the number of YKL-40+ cells did not correlate with the blood eosinophil count ($R = 0.345$; $p = .99$; Figure 3f). Overall $p = .003$ (between the three groups).

Serum levels of YKL-40 versus clinical manifestations in M/S PAR group

The data revealed noticeable correlations between serum YKL-40 levels and the clinical manifestations of TNSS ($R = 0.846$; $p = .001$), eosinophil infiltration into the nasal mucosa

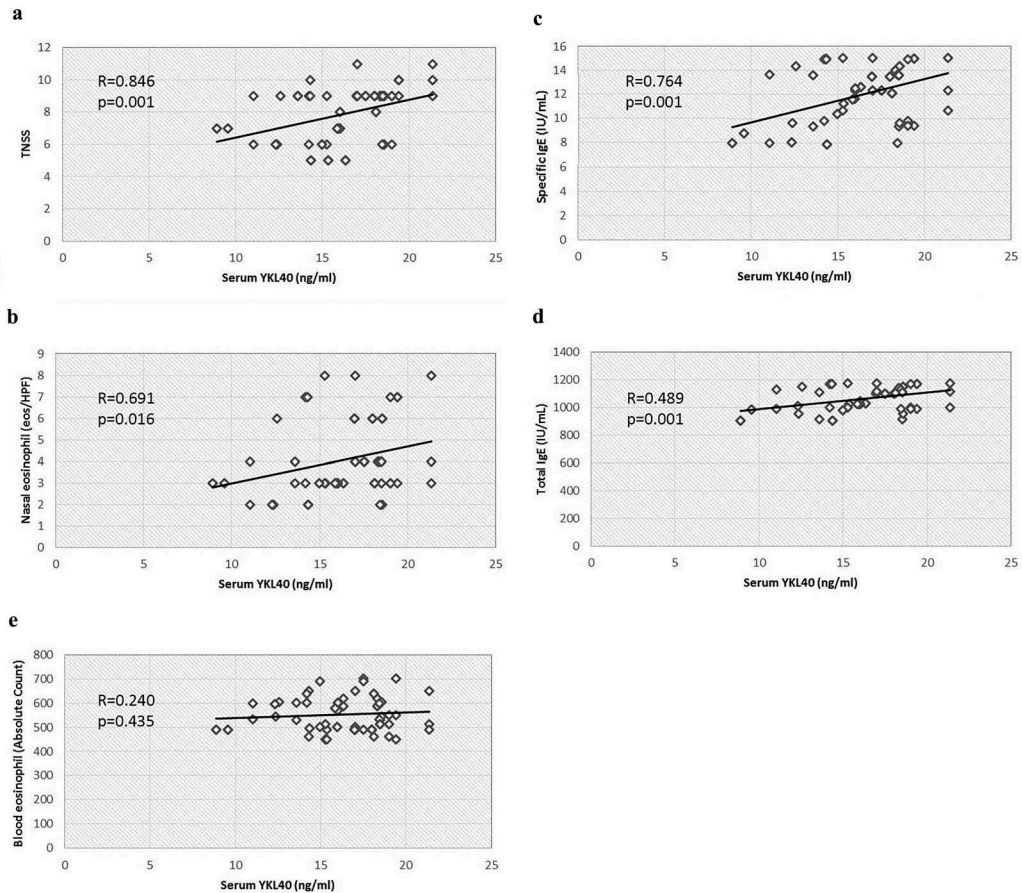


Figure 4. Serum levels of YKL-40 versus: (a) TNSS; (b) nasal eosinophil count; (c) specific IgE; (d) total IgE; (e) blood eosinophil count.

($R = 0.691$; $p = .016$), specific IgE ($R = 0.764$; $p = .001$) and total IgE ($R = 0.489$; $p = .001$). There was no significant correlation between serum YKL-40 levels and the blood eosinophil count ($R = 0.240$; $p = .435$) (Figure 4).

The mRNA levels of YKL-40 versus disease severity in M/S PAR group

According our results, there is a significant correlation between the mRNA levels of YKL-40 and the total nasal symptom score (TNSS) ($R = 0.534$; $p < .001$) which was obtained from the considering all criteria such as: sneezing ($R = 0.517$; $p < .001$), rhinorrhea ($R = 0.589$; $p < .001$), and congestion ($R = 0.306$; $p = .01$) scores (data not shown).

Discussion

YKL-40 is a chitinase-like protein that can bind with chitin but does not cause its degradation (Lee et al., 2012). Serum levels of YKL-40 have long been regarded as a biomarker of diseases characterized by inflammation and tissue remodeling; such as

cancer (Cintin et al., 2002; Johansen et al., 2003; Pelloski et al., 2005), inflammatory diseases (Johansen, 2006), hepatic fibrosis (Johansen et al., 2000) and atherosclerosis. In the current study, the cellular expression pattern of YKL-40 in the human nasal mucosa of the inferior turbinate has been described (Figure 1).

The correlation between the expression of YKL-40 and immunopathogenesis of patients with M/S PAR (disease severity and clinical characteristics) was the base of this study. Although the increased expression of YKL-40 in AR has previously been reported (Kwon et al., 2011), in this study, the patients were classified into subgroups and attempts were made to focus on pathological studies, especially the determination of local expression of YKL-40 and their relation to clinical manifestations.

The results showed that there was a significant increase in serum levels of YKL-40 in the M/S PAR group compared to the healthy control and M PAR groups. The difference between the serum levels of YKL-40 in the patients with M PAR and healthy control groups was also significant. Gene expression of YKL-40 in nasal mucosa was significantly higher in the M/S PAR group than in the healthy control and M PAR groups. A significant difference was also observed in the mRNA expression levels of nasal mucosa YKL-40 between the patients with M PAR and healthy control groups. The tissue expression of YKL-40 was higher for the M/S PAR group compared to the healthy controls, although the difference between the M/S PAR and M PAR groups and between the M PAR and healthy control groups were not statistically significant.

Previous studies show that the serum YKL-40 is noticeably associated with the disease severity and it can be considered as a prognostic or diagnostic marker or therapeutic targets in AR (Park et al., 2013). In another word, the serum levels of YKL-40 in the patients with allergic rhinitis positively correlate with symptom severity. In the present study, we investigated the mRNA expression levels, tissue distribution and serum level of YKL-40 in the normal, mild and moderate/severe persistent allergic nasal mucosa at the same time in order to understand the probable role of YKL-40 in AR.

Serum YKL-40 levels and YKL-40+ cells noticeably and positively correlated with the degree of eosinophil infiltration into the nasal mucosa and specific IgE. This was a remarkable finding of this study. Restricted persistent inflammation and the priming effect (enhancement in reactivity of the nasal mucosa following repeated exposure to allergens) were induced by eosinophil infiltration into the nasal mucosa, both of which can boost nasal hyperactivity (Canonica and Compalati, 2009). Thus, YKL-40 may induce inflammation through enhancement of eosinophilic inflammation. We also found out significant correlations between the mRNA levels of YKL-40 and the TNSS. However, the involved molecular mechanism in the induction of YKL-40 remains unknown.

In terms of clinical manifestations, there was also an interesting correlation between TNSS and serum YKL-40 levels, YKL-40 mRNA levels and YKL-40+ cells, suggesting that YKL-40 is closely associated with the disease severity of M/S PAR. Serum YKL-40 levels were associated with congestion, rhinorrhea and sneezing. The sneezing reflex following allergen challenge is a respiratory reflex which begins by the interaction between histamine and the H1 receptor at the sensory nerve terminals. Rhinorrhea can be considered as the mucosal gland secretion induced by parasympathetic stimulation synchronously with the sneezing reflex. The relaxation of the smooth muscle layer of capacitance vessels in the nasal mucosa and the interstitial edema induced by plasma exudation are the basic causes

of nasal congestion in the early phase of allergic rhinitis (Tang et al., 2013). Kwon et al. (2011) showed that serum YKL-40 levels correlated with congestion in patients with AR.

The results obtained in the current study suggest that YKL-40+ cells correlate with rhinorrhea and congestion, but not with sneezing. It would originate from this fact that up-regulation or down-regulation of the gen, necessarily, does not lead to increase or decrease in the protein related to same gen because various kinds of regulatory factors are controlling the process between protein translation from its gen. The data shows that YKL-40 serum levels and YKL-40+ cells were not associated with blood eosinophil counts. This finding highlights the suitability of counting eosinophils in mucosal tissue over blood. It would be interesting to determine whether or not there is a significant correlation between tissue expression levels and serum concentrations of YKL-40 in allergic patients. In view of the relationship between serum YKL-40 levels and tissue expression, it concludes that the serum level of YKL-40 would be considered as an allergy biomarker. In short, blood measuring of YKL-40 could be considered to be a worthy test for precise allergy monitoring.

Furthermore, increased concentrations of YKL-40 which positively correlate with the progression of asthma. Gomez et al. reported a positive association between an increase in the serum YKL-40 levels and asthma severity. The same research group also observed a close correlation between genetic variation in YKL-40 encoding gene, serum levels of YKL-40 and asthma morbidity (Gomez et al., 2015). In addition, an allergic phenotype is associated with a single nucleotide polymorphism which is found in the promoter region of YKL-40 gene (Hansen et al., 2015). Hao Tang et al, found that, in the airways during an asthma attack, YKL-40 can contribute to IL-8 expression and stimulate the epithelial cells as their cellular targets. It is probable that YKL-40 may act in dissimilar ways depending on the cell type (Tang et al., 2013). This stimulation is promoted by YKL-40 and may be mediated through differential signaling pathways. Despite the fact that the activation of these pathways is triggered by ligand attaching to cell-surface receptors, no cell-surface protein that binds to YKL-40 has been recognized (Coffman, 2008; Lee et al., 2010). It appears that the dysregulation of YKL-40 results in greater vulnerability for AR, but neutralization of YKL-40 in an attempt to relieve AR symptoms requires more study. It must be determined which allergic diseases would benefit most. The results of the present study demonstrate that high levels of YKL-40 in patients with M/S PAR are associated with disease severity and increased markers of inflammation, especially specific IgE and the number of eosinophils infiltrating the nasal mucosa. Overall, these findings support the notion that YKL-40 is a worthwhile biomarker of AR. It can be considered as an active trigger, at least in boosting symptom severity through specific mechanisms.

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Disclosures

The authors have no conflicts of interest.

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