



Serum level of stem cell factor and its soluble receptor in aspirin-exacerbated respiratory disease

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Aim: Stem cell factor (SCF) may be associated with inflammatory processes leading to aspirin-induced asthma. This study evaluated the relationship between serum level of SCF and its soluble receptor with aspirin-induced asthma. **Methods & materials:** Twenty-five patients and 25 healthy controls were enrolled in this study. The concentration of SCF and mast/stem cell growth factor receptor (C-kit) was determined in serum samples. Spirometry and rhinometry were performed to determine the severity of the disease. $p < 0.05$ were considered significant. **Results:** The serum levels of SCF and C-kit receptor were significantly higher in the case group. The serum SCF and C-kit level had a significant positive correlation with the severity of asthma, disease duration and nasal obstruction. **Conclusion:** Our findings suggest that SCF and C-kit receptors have a direct effect on the severity of aspirin-induced asthma.

First draft submitted: 26 February 2019; Accepted for publication: 24 July 2019; Published online: 18 September 2019

Keywords: aspirin-induced asthma • C-kit receptor • inflammation • NSAID • SCF • severity of disease

Aspirin, which is also named as acetylsalicylic acid, is one of the greatest recommended and recurrently used prescriptions in treatment of diseases. Aspirin-induced asthma, also called aspirin-exacerbated respiratory disease, is characterized by sensitivity to NSAIDs and nasal polyps. This condition was first described in 1968 as the Samter's triad. It can aggravate airway disorders and lead to refractory asthma. The prevalence of this condition depends on the diagnostic method used. Relying solely on patient history for the diagnosis of aspirin-induced asthma results in a much lower prevalence rate (2.7%) in adults and children (2%). Vally *et al.* described that the outbreak of respiratory signs initiated via aspirin in three different asthma study cases plotted in Australia was 10–11%. Recent studies indicate that about 7% of asthmatic patients show allergic response to aspirin. The rate goes up to about 14% in patients with severe asthma. Individuals with aspirin-induced asthma commonly show modest to intense determined asthma and often high-dose breathe in corticosteroids was needed in these cases and even systemic corticosteroids in some instances. Rhinitis observed in women 2.5-times more than men and indicators arise during the third decade of life. After a few months, problems such as chronic nasal congestion, anosmia and rhinorrhoea are seen in patients, and nasal polyps regularly can be seen via physical check. The etiology of aspirin-induced asthma is multifaceted and not completely clear; however, a disorder in arachidonic acid metabolism is suggested in most documents. COX is an important enzyme in arachidonic acid metabolism, which has two isoforms: COX-1 and COX-2. Production of COX-2 is prompted in inflammatory disorders. Several models about the role of COX2 in pathogenesis of inflammatory illness such as rhinitis have been suggested. Furthermore, recent advancements

have identified the role of increased inflammatory markers including COX-1, interleukins, eosinophils and mast cells in aspirin-induced asthma [1–5].

The main growth factor in mast cells is the SCF (stem cell factor), also named Kit ligand, is a cytokine involved in the inflammatory processes, which increase the number and activity of mast cells, including in asthma. It is also known as an important hematopoietic factor that plays an important role in the development of leukocytes and erythrocytes. The SCF gene is encoded at the steel (Sl) locus on human chromosome 12q22–q24 and murine chromosome 10 [6]. SCF is a cytokine, which exerts its role through binding to C-kit receptor [5], which can be shed from the cell surface and is detected in serum as soluble C-kit [7].

Gene location of C-kit tyrosine kinase receptor is at the white spotting (W) locus on chromosome 4q11–q12 and chromosome 5, respectively, in human and mouse. The cells that expressed C-kit include hematopoietic stem cells, human lung mast cells in the airways, peripheral blood eosinophils and circulating basophils [8]. Also, C-kit expression has been described on some organizational cells, including vascular smooth muscle cells, epithelial cells and umbilical vein endothelial cells in human. SCF is also produced by C-kit expressing cells, which may therefore induced via an autocrine pathway [9].

Binding of SCF to C-kit leads to activation of multiple pathways, including phosphatidyl-inositol-3-kinase, phospholipase C- γ , Src kinase, Janus kinase/STAT and MAPK pathways [10]. SCF is released by many airway cells including bronchial epithelial cells, lung fibroblasts, bronchial muscle cells, endothelial cells and eosinophils, as well as mast cells in the peripheral blood. SCF can affect the cells that express C-kit receptors, such as progenitor cells, melanocytes, germinal cells, eosinophils in peripheral blood, basophils and mast cells. SCF can stimulate immature mast cell to growth and differentiation [11]. Moreover, SCF can suppress apoptosis in mast cell and involve in survival in these cells [6]. Also, SCF acts as effective chemotactic agent for mast cells [12], and stimulates their connection to the extracellular matrix [8]. Additionally, studies showed that SCF subcutaneous injection in humans prompts mast cell hyperplasia [13]; and mast cell hyperplasia detected in systemic mastocytosis is related to increased SCF expression [10]. Last, SCF significantly increases degranulation of lung-derived mast cells induced via antigen [11], and induces mast cell degranulation both *in vitro* [12] and *in vivo* [13].

Consequently, SCF leads to degranulation of mast cells and release of histamine, proinflammatory cytokines and chemokines. Moreover, it induces the adhesion and activation of eosinophils [14–17].

Studies have reported that the SCF and C-kit receptor were high in the serum and lung of the asthmatic patients, as well as the nasal epithelium and skin of the allergic patients. Animal studies have proven that SCF can initiate several inflammatory reactions that intensify airway response, which can be inhibited by anti-SCF treatments [16,18–20]. The comparison between aspirin hypersensitive patient and aspirin tolerant patients shows that SCF expression is greater in nasal polyp epithelial cells of aspirin hypersensitive patients, and a correlation was observed with tissue eosinophils and polyp relapses [21]. Researches on anti SCF treatment on asthma in mice model revealed that reservation of SCF causes a discount in airways eosinophil, lessening of peribronchial altering and reduction in bronchial reactivity [19,22,23].

A higher expression of SCF and its receptor C-kit gene was observed in airway epithelium of patients with asthma in comparison with healthy control [18]. The results of researches on expression of SCF in nasal mucosa are controversial; a study revealed high expression of SCF gene in the nasal mucosa of patients with allergic rhinitis [24,25] whereas another one showed no alteration in the SCF mRNA expression between patients and healthy control. Studies on anti SCF treatment in mice with asthma showed that suppression of SCF causes decrease in eosinophil gathering in the airways, lessening of peribronchial transformation and reduction in bronchial hyperactivity.

These promising results indicate the importance of research on SCF and its probable role in new treatments for asthmatic patients. As mentioned before, the role of SCF and its receptor in the development of inflammation and allergic responses through the effects on the production of cytokines and eosinophils has been identified and studies have been conducted on this topic. It has also been shown that inhibition of this molecule and its receptor in the process of treatment can be effective, but so far no study has been conducted to assess the role of SCF and its receptor in aspirin-induced asthma. Considering the prevalence of aspirin-induced asthma in the society, we conducted this study to measure the serum concentration of SCF and C-kit in these patients, in comparison to healthy controls, and assess the relationship between these variables and the disease severity.

Methods

Design & ethical consideration

This case-control study was conducted in the Asthma and Allergy Clinic of Besat Hospital in Sanandaj from September 2017 to September 2018. The study protocol was approved by the Ethical Committee of the Kurdistan University of Medical Sciences (Approval code: IR.MUK.REC.1397.108). Patients or their representatives gave written consent before participating in the study.

Population

Twenty-five patients, who were referred to Asthma and Allergy Clinic of Besat Hospital in Sanandaj and were attested as having aspirin-induced asthma by an allergist, were included in the study as the case group. The diagnosis of asthma was made based on medical history and aggravation of symptoms after the administration of NSAIDs. The clinical and paraclinical (CT scan) findings indicated polyposis. The control group comprised of 25 age- and sex-matched healthy subjects without any pulmonary disease or family history of allergic diseases.

The patients with suspicion of aspirin-induced asthma underwent acetyl salicylic acid challenge test in the clinic. Patients were told to cease all medications 72 h prior to the procedure. After the placebo challenge, an acetyl salicylic acid tablet (500 mg) was administered and patients were monitored every 30 min in the next 4 h in terms of urticaria and altered pulmonary functions. Development of urticaria without any changes in FEV₁ was considered as a positive result [26]. In case of positive outcome, patients were included in the case group.

Inclusion criteria

Inclusion criteria for the case group was being older than 20 years, history of more than one experience of severe acute asthma attacks, chronic rhinosinusitis, and presence of skin or ocular manifestations.

Exclusion criteria

Patients with pulmonary disease other than aspirin-induced asthma or those with history and symptoms of any infectious, autoimmune, inflammatory or neoplastic disorders were excluded. Patients who had aspirin-sensitive wheal were also excluded.

Data collection

The patients who were referred to our asthma and allergy clinic were first thoroughly evaluated based on medical history and physical examination by an allergist and clinical immunologist to confirm the diagnosis of aspirin-induced asthma. Then, the baseline and demographic characteristics of the patients were collected using a checklist.

Blood samples (5 ml) were collected using standard and sterile techniques by a single operator from all the participants to measure white blood cell count and absolute eosinophil count (AEC). An AEC of ≥ 450 was considered as eosinophilia. Blood samples were then centrifuged to separate the serum and were kept at -80°C . The serum levels of IgE, SCF and C-kit receptor were measured by ELISA reader Dana[®]-3200 (Garni Medical Eng. Co., Iran) analyzer using sandwich ELISA method. Briefly, we kept all reagents and samples to room temperature ($18\text{--}25^{\circ}\text{C}$) before use. First, 100 μl of each standard and sample was added into appropriate wells and were covered and incubated for 2.5 h at room temperature with gentle shaking. Then, the solution was discarded and the wells were washed four-times with 300 μl 1 $\times$ wash buffer by filling each well with wash buffer. Then, 100 μl of 1 $\times$ prepared biotinylated antibody was added to each well. After discarding the solution, samples were incubated for 1 h at room temperature with gentle shaking. The washing process was repeated as previously mentioned. Then, 100 μl of prepared streptavidin-horseradish peroxidase (HRP) solution was added to each well and the wells were incubated for 45 min at room temperature with gentle shaking. After that 100 μl of TMB substrate was added to each well and the wells were incubated for 30 min at room temperature in the dark with gentle shaking. In the final step, the absorbance was read in 540 nm with an ELISA reader. An IgE level of ≥ 100 IU/ml was considered as abnormal.

Spirometry test was performed under standard settings using the Spirolab III[®] (Mir Company, Italy) by a specialist for all the participants to assess their respiratory function. Prior to performing spirometry, the patient's identification was checked, their height without shoes or boots and weight were measured, and their age and sex were also recorded. If a patient was unable to stand to have his/her height measured, the arm span was measured. The important parameters measured by spirometry were forced vital capacity (FVC; Lit), forced expiratory volume

Table 1. Laboratory results of the two groups.

Variable	Case group	Control group	p-value
WBC ($10^3/\mu\text{l}$)	7447.2 $\pm$ 1448.8	6048.0 $\pm$ 553.1	< 0.0001 [†]
AEC ($10^3/\mu\text{l}$)	450.2 $\pm$ 301.1	114.2 $\pm$ 52.6	< 0.0001 [†]
IgE (IU/ml)	166.1 $\pm$ 78.5	15.2 $\pm$ 12.8	< 0.0001 [‡]
SCF (pg/ml)	516.1 $\pm$ 202.7	416.4 $\pm$ 119.6	0.039 [‡]
C-kit receptor (pg/ml)	93.2 $\pm$ 30.6	91.1 $\pm$ 24.5	0.785 [‡]

[†]Mann–Whitney test was used.

[‡]Independent samples *t*-test was used.

AEC: Absolute eosinophil count; SCF: Stem cell factor; WBC: White blood cell.

in 1 s (FEV₁; Lit) and FEV₁/FVC ratio. The severity of asthma was categorized into mild, moderate and severe according to the Global Initiative for Asthma (GINA) classification, based on the results of spirometry [27,28].

In addition, we performed rhinometry for all participants based on the rhinomanometry method by a single operator using Rhino 4000M[®] rhinometer (Homoth Medizinelektronik GmbH & Co Kg, Germany). A translucent airtight face mask with one nostril sealed off with adhesive tape was used. A hard plastic tube was putted over the tape to measure the nasopharyngeal pressure. This is a dynamic examination that investigated nasal ventilation, and illustrations the environment of the air stream. Pressure is documented in one nostril while the patient breathes over the other. Based on the total nasal flow (Lit/min), we classified the severity of participants' nasal obstruction into mild, moderate, severe and completely closed airway.

Statistical analysis

Data were analyzed using the statistical package for social sciences (SPSS) software version 22 for Windows (IBM Statistics, IL, USA). Kolmogorov–Smirnov test was used to assess the normal distribution of data. Independent sample *t*-test, Mann–Whitney test, Kruskal–Wallis test, Pearson and Spearman correlation coefficient, as well as Chi-square test, or Fisher exact test were used when appropriate to compare different variables within and between study groups. The *p* < 0.05 were considered as statistically significant.

Results

Overall, 50 patients (25 in the case group and 25 healthy controls) were studied, of whom 44% were men and 56% were women in both groups. The mean age of the patients was 34.4 $\pm$ 7.5 years in the case group and 33.2 $\pm$ 4.5 years in the control group. There was no significant difference between groups regarding age (*p* = 0.661) and sex (*p* > 0.999).

The mean duration of disease in the asthmatic patients was 6.6 $\pm$ 2.1 years. The spirometry test in asthmatic patients in the case group showed that the mean values of FEV₁, FVC, FEV₁/FVC and total nasal flow were 68.6 $\pm$ 17.1 Lit, 70.7 $\pm$ 17.1 Lit, 62.9 $\pm$ 9.9%, and 408.6 $\pm$ 217.7 Lit/min, respectively.

The severity of asthma in the case group was defined based on the results of spirometry testing: five patients (20%) had mild asthma, 12 (48%) had moderate asthma and the remaining 8 patients (32%) had severe asthma. Regarding the nasal flow, one patient (4%) in the case group showed complete nasal obstruction, while nine (36%) had severe obstruction, nine (36%) had moderate obstruction and four (16%) had mild nasal obstruction.

The basic laboratory results including the total white blood cell count, AEC and serum level of IgE were significantly higher in the case group, compared with the control group. The mean serum levels of both SCF and C-kit receptor were higher in the case group, compared with the control group. However, this difference was statistically significant only for SCF and the difference in C-kit concentrations did not reach the level of significance (Table 1).

In the case group, 12 patients (48%) had eosinophilia and 21 (84%) had abnormally high IgE levels, while all subjects in the control group (100%) showed normal AEC and IgE levels (*p* < 0.0001).

There was a significant difference regarding the serum levels of SCF and C-kit receptor between the patients who had asthma for 6 years or less, and those who had asthma for >6 years (*p* < 0.0001 and *p* = 0.003, respectively) (6 years is the best period for incidence of polyposis in patients).

There was also a significant difference between the patients with different severities of asthma in terms of these two biomarkers (*p* < 0.0001). Table 2 shows the details regarding these comparisons.

The correlations between studies parameters are shown in Table 3. As the Table implies, there was a significant

Table 2. Comparison of the main outcomes between severity categories and duration of the disease in the case group.

Variable		SCF		C-kit receptor	
		Mean $\pm$ SD	p-value	Mean $\pm$ SD	p-value
Severity	Mild	247.4 $\pm$ 133.6	< 0.0001 [†]	48.8 $\pm$ 28.6	< 0.0001 [§]
	Moderate	506.3 $\pm$ 44.2		96.7 $\pm$ 13.5	
	Severe	698.7 $\pm$ 194.3		115.9 $\pm$ 21	
Duration	≤ 6	402.5 $\pm$ 154.3	< 0.0001 [‡]	77.1 $\pm$ 30.5	0.003 [¶]
	>6	639.1 $\pm$ 178.6		110.8 $\pm$ 19.5	

[†]Kruskal–Wallis test was used.
[‡]Mann–Whitney test was used.
[§]One-way ANOVA test was used.
[¶]Independent samples t-test was used.
 SCF: Stem cell factor; SD: Standard deviation.

Table 3. Correlations between studied parameters in the asthmatic patients.

Variable	SCF	C-kit	WBC	AEC	IgE
SCF		r = 0.677 p < 0.0001	r = 0.320 p = 0.119	r = 0.755 p < 0.0001	r = 0.893 p < 0.0001
C-kit	r = 0.677 p < 0.0001		r = 0.346 p = 0.090	r = 0.518 p = 0.008	r = 0.488 p = 0.013
Disease duration	r = 0.822 p < 0.0001	r = 0.685 p < 0.0001			
Disease severity	r = 0.914 p < 0.0001	r = 0.714 p < 0.0001			
FEV ₁	r = -0.823 p < 0.0001	r = -0.763 p < 0.0001			
FVC	r = -0.853 p < 0.0001	r = -0.702 p < 0.0001			
FEV ₁ /FVC	r = -0.806 p < 0.0001	r = -0.722 p < 0.0001			
Total nasal flow	r = -0.875 p < 0.0001	r = -0.733 p < 0.0001			

Pearson or Spearman correlations were used.
 AEC: Absolute eosinophil count; FVC: Forced vital capacity; SCF: Stem cell factor; WBC: White blood cell.

and strong correlation between the levels of SCF and C-kit receptor, and several indicators of disease severity, duration and stage as well as rhinometry findings (Table 3). As Table 3 demonstrates, the rhinometry index of total nasal flow had a significant negative correlations with the SCF and C-kit levels ($p < 0.0001$).

Discussion

Conceivably aspirin-induced asthma is the most well-known asthma in comparison with other asthma phenotypes, including allergic, nonallergic, exercise-induced and infectious asthma. It is a quite regular phenotype of asthma, disturbing mainly in grownups nevertheless possibly can be observed among children with physician-diagnosed asthma and also cases with no prior history of asthma. Previous studies have established a significant role for SCF during the development of allergic airway inflammation, which was associated with disease severity and progression. Furthermore, SCF and its soluble receptor, C-kit, have been linked to asthma, especially allergic types like aspirin-induced asthma [14,15,18,21]. Management and control of asthma has always been a challenge for physicians, especially in nonadherent and noncompliant children [29]. Patients with modest to drastic asthma who have drastic nasal crumpling, nasal polyposis and radiologic confirmation of pacification of sinuses and who need necessary treatment should be supposed to have this kind of asthma. One of the diagnostic criteria for these patients can be a history of allergy aspirin or other COX-1 NSAIDs. Two to four days of a refractory period may be existing following aspirin test, through which no extra signs arise with further aspirin or other COX-1 [30]. Our study provides several insights toward the role of SCF and C-kit receptor in the pathophysiology of aspirin-induced asthma.

Our results showed that the mean serum level of SCF was significantly higher in the case group compared with the control group. The SCF and C-kit was found to be significantly higher in the sera of patients with severe

asthma, compared with moderate and mild cases. In addition, the serum SCF and C-kit level had a significant positive correlation with the severity of asthma, disease duration, nasal obstruction, AEC and IgE level in asthmatic patients, while there was no such correlation in the control group. All spirometry indices including FEV₁/FVC, FEV₁, FVC and rhinometry index of total nasal flow were negatively correlated with the SCF and C-kit levels.

Tayel *et al.* conducted a study on 50 asthmatic and 30 healthy subjects to evaluate the association between SCF gene expression and the severity of bronchial asthma. Their results revealed that the asthmatic patients had significantly lower pulmonary function and higher SCF gene expression in comparison with the control group. Furthermore, among the asthmatic patients, SCF expression was significantly higher in those with a history of atopy and those with severe asthma, compared with nonatopic and mild asthmatic cases. Besides, SCF gene expression had a significant positive correlation with serum IgE level and a significant negative correlation with the dose of budesonide consumed in asthmatic patients [31]. These results were in line with our findings; however, we did not categorize our asthmatic patients based on the history of atopy and drug use. The findings of our study together with the previous studies show a promising diagnostic and even prognostic role for SCF in patients with asthma.

Makowska *et al.* studied the correlation of SCF and C-kit receptor with disease severity in asthmatic patients. Their results indicated that SCF level was significantly higher in asthmatic patients compared with the control group and in subjects with severe asthma, compared with those with mild disease. However, the C-kit level was not significantly different between the asthmatic and healthy subjects. Among patients with severe asthma, those taking oral corticosteroids had no significant difference in SCF levels compared with those not taking the drug. They also found that SCF levels did not correlate with the number of peripheral blood eosinophils. No significant correlation was found between C-kit and SCF levels in asthmatic patients and control group. In addition, there was no significant difference in serum C-kit and SCF levels among asymptomatic aspirin-sensitive and nonaspirin-sensitive patients [24]. These results were mostly consistent with the findings of our study. However, unlike Makowska *et al.*, we found that SCF level was strongly correlated with AEC and IgE level. Contrary to Makowska *et al.*, we did not investigate the effect of corticosteroid therapy on serum SCF levels. Moreover, in contrast to Makowska's study, we found that the serum level of SCF was significantly correlated with that of C-kit receptor in aspirin-induced asthma patients. Makowska *et al.* study results may be due to a small sample size, or it may have been negatively affected by the increase in the amount of SCF and a negative feedback has happened, although identifying the exact cause requires further investigation. Our observations were in line with the findings of the study on patients with atopic dermatitis [32], which indicated advanced serum amount of both SCF and C-kit in comparison with healthy persons and also a positive correlation was observed between C-kit amount and atopic dermatitis severity index (SCORAD). On the other hand, C-kit was reduced in cases with systemic lupus erythematosus and a negative correlation was observed with disease severity.

In an animal study by Berlin *et al.*, allergic rats were exposed to intranasal allergens and then received anti-SCF injection. The results revealed that the monoclonal anti-SCF inhibits hyperactivity and number of eosinophils after the administration of allergens. They found that peribronchial infiltration of eosinophils was significantly reduced by high doses of anti-SCF, which also led to significant reduction in IL-5 and TNF- α [19]. These findings were consistent with the results of our study regarding the correlation between SCF level and eosinophilia. It is expected that the use of monoclonal anti-SCF can reduce the number and activity of eosinophils in the airways of the asthmatic patients and thus reduce the severity of asthma.

In another study, Al-Muhsen *et al.* investigated bronchoalveolar lavage samples and bronchial biopsy of asthmatic and healthy subjects and found that the SCF and C-kit mRNA expression in the epithelial and subepithelial airways cells in asthmatic patients was significantly higher compared with the control group [18]. These findings were completely consistent with the results of our study. These findings along with the findings of our study enforce the evidence behind the role of mast cell cytokine, SCF and its soluble receptor in the pathophysiology of asthma.

Lei Z *et al.* stated that SCF, B-cell-activating factor (BAFF) and cytokines, comprising IL-17 and -31, are applied factors for the identification of allergic asthmatics. The results of Lie *et al.* propose that allergic asthma is described via an increase of cytokines, SCF and IL-31, and that assessing their expression at protein level in serum or mRNA assay in Peripheral blood mononuclear cells (PBMCs) will be an appreciated factor for the identification of allergic asthma [20]. In accordance with these results, the results of our study also showed a higher level of SCF in aspirin-induced asthma patients in comparison with healthy controls.

Kowalski *et al.* studied the expression of SCF in nasal epithelial cells of 29 patients with nasal polyps, of whom 9 had aspirin-induced asthma and 12 had bronchial asthma. They found that SCF level was significantly higher in nasal epithelial cells of patients with aspirin-sensitive asthma compared with aspirin-tolerant patients, which was

consistent with the findings of our study [21]. However, Makowska *et al.* failed to identify a correlation between the level of SCF and aspirin hypersensitivity or concomitant nasal polyposis [24]. This outcome proposes that serum amount of SCF may not completely reveal local secretion of SCF in the inflammatory tissue. In contrast to a prior study, that described SCF levels in peripheral blood were considerably greater than healthy subjects, only in a group of allergic asthma subjects, SCF amount did not vary considerably between subjects with and without allergic asthma [20], which was also observed by Makowska *et al.* An animal study by Krishnamoorthy *et al.* revealed that contact with home mites increases the expression of C-kit and its ligand (SCF) through stimulation of IL-6 production in dendritic cells, which in turn induces Th-2 and Th-17 responses. They found that dendritic cells with no C-kit function or those unable to express SCF secrete less IL-6 against allergens and are unable to induce a strong Th-2 and Th-17 response. These findings provide more insight into the underlying mechanisms behind the role of SCF and C-kit receptor in asthma [33].

Researchers have also initiated observing the action of SCF on eosinophil gathering and motivation. Especially, the most latest research has revealed that SCF facilitates eosinophil-induced degranulation, cytokine creation and inhibition of apoptosis [12,19]. In addition, *in vivo* models of chronic allergen-induced response confirmed that SCF has function in production of cytokine by Th2 in the lung and mucus extra expression and airway alteration. Use of an inhibitor that suppressed C-kit receptor tyrosine kinase activation such as imatinib, repeated alike consequence as anti-SCF therapy in mice. In conclusion, these data were suggested that SCF or its receptor may be an operative objective for prospect treatment mediations [34]. One of the limitations of this study was the small sample size. It is also advisable to measure the values of other parameters, including interleukins and TNF α , as well as molecular signaling pathways at the gene and protein levels in future studies. Furthermore, considering that SCF has different isoforms, it would be better to examine the various isoforms and to determine which isoform has a more important role in the pathogenesis of these patients.

Conclusion

In this study, the relation between SCF, its soluble receptor and the severity of aspirin-induced asthma in patients older than 10 years of age was investigated. Evaluations revealed that the level of SCF and its receptor was associated with the severity and duration of the disease, and the inflammatory and immunological factors. These findings confirmed positive effects for anti-SCF therapy and reveal the necessity for further studies on these drugs. Furthermore, it seems that physiological downregulation of this cytokine by soluble kit receptor is also impaired in patients with severe aspirin-induced asthma, thus modifying the SCF/C-kit interaction in aspirin-induced asthma subjects.

Summary points

- Aspirin-induced asthma is a form of asthma characterized by allergy to NSAIDs and nasal polyps.
- Stem cell factor (SCF) may be associated with inflammatory processes leading to an increase in the number and activity of mast cells. SCF has also been linked to increased inflammatory airway response.
- This study aimed to evaluate the relationship between serum level of stem cell factor and its soluble receptor with aspirin-exacerbated respiratory disease. In this case-control study, 25 aspirin-induced asthma patients (case group) who were referred to the asthma and allergy clinic of Besat Hospital in Sanandaj, between September 2017 and September 2018 were enrolled.
- The control group consisted of 25 healthy age- and sex-matched people.
- The serum samples were obtained to assess the concentration of SCF and C-kit receptor. Spirometry and rhinometry were performed to determine the severity of the disease.
- Data were analyzed using the statistical package for social sciences (SPSS) software. $p < 0.05$ were considered significant. Out of 50 patients, 22 (44%) were males. The mean age of the subjects was 33.78 ± 6.19 years.
- The IgE level, leukocyte count and absolute eosinophil count, as well as the mean serum levels of SCF and C-kit receptor were significantly higher in the case group compared with the control group.
- In both groups, the serum level of SCF was significantly correlated with its soluble receptor.
- The serum SCF and C-kit level had significant positive correlations with the severity of asthma, disease duration and nasal obstruction (based on spirometry and rhinometry findings).
- Our findings suggest that SCF and C-kit receptor have a direct effect on the severity of aspirin-induced asthma.
- Therefore, the use of medications that inhibit this factor and its receptor in patients can play a key role in reducing the severity of the symptoms of the disease.

Financial & competing interests disclosure

This article was the result of specialist resident thesis, which was approved by the Research Deputy of Kurdistan University of Medical Sciences (with code 1396.206). This study was financially supported by the Kurdistan University of Medical Sciences. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved. The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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