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Original article

Plasma levels of BAFF and APRIL are elevated in patients with asthma in Saudi Arabia

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ABSTRACT

B-cell activation factor (BAFF) and a proliferation-inducing ligand (APRIL) are members of the tumor necrosis factor superfamily of cytokines and can induce B cell activation, differentiation, and antibody production via interaction with their receptors, including transmembrane activator, calcium modulator, and cyclophilin ligand interactor (TACI), B-cell maturation antigen (BCMA), and B-cell activating factor receptor (BAFF-R). Herein, we assessed the plasma protein levels of BAFF and APRIL in patients with asthma to determine whether their expression is correlated with total IgE production and examined the surface expression of BAFF/APRIL receptors on B cells. Blood samples were collected from 47 patients with controlled asthma symptoms and 20 healthy normal controls, and plasma levels of APRIL, BAFF, and total IgE protein were quantified by corresponding ELISA assays. Furthermore, lymphocytes were isolated and B cells were analyzed for the presence of BAFF-R, BCMA, and TACI receptors using flow cytometry. Our results showed that IgE, BAFF, and APRIL plasma levels were markedly increased in patients with asthma compared with healthy controls. Moreover, expression of BAFF-R and BCMA, but not that of TACI, was significantly increased in patients with asthma compared with healthy controls. Overall, the findings suggest BAFF and APRIL as key mediators of asthma, and determination of their plasma levels may be useful in monitoring asthma symptoms and treatment response.

1. Introduction

Asthma, a chronic inflammatory disease with an increasing prevalence worldwide, mainly affects the lungs, causing airway constriction and difficulty breathing (Alturaiki, 2020a). In Saudi Arabia, the prevalence of adolescent asthma has increased from 4.02% to 8.2% since the previous national survey (Musharrafieh et al., 2020). While the precise genetic and environmental causes of asthma are not fully understood, it is recognized that asthma represents a set of diseases with distinct inflammatory types, leukocyte activation, and recruitment patterns (Ishmael, 2011). It is nevertheless important to understand the immune changes underlying the types of asthma and identify effective markers of disease development, progression, and exacerbation.

The allergen-specific production of IgE antibodies, which typifies many cases of allergic asthma, depends on B cell maturation and differentiation and plasma cell formation (Lemanske and Busse, 2003; Jee et al., 2010). Other roles of B cells include cytokine production, regulatory cell activation, and the presentation of antigenic peptide to T helper cells (Kato et al., 2009). Identifying molecules that regulate B cell activation and their differentiation is

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important, at least in allergic asthma, as these molecules may be potential markers of disease activity. Asthma is a complex disease and several molecules, including those expressed on immune and non-immune cell surfaces, contribute to pathogenesis of asthma (Alturaiki, 2020b, 2020c). Furthermore, several cytokines, including IL-4, IL-6, and IFN-γ are known to influence B-cell response and enhance antibody class switching recombination (CSR), a process by which the antibody subclass, such as IgG, IgA, and IgE, is changed (Vazquez et al., 2015).

B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), members of the tumor necrosis factor superfamily, play essential roles during B-cell development. Both proteins are ubiquitous in the body (Mackay and Schneider, 2009); BAFF can be found in several cell types, such as neutrophils with fibroblast-like synoviocytes, dendritic cells, astrocytes, monocytes, salivary gland epithelial cells, and bronchial epithelial cells (Kato et al., 2009), whereas APRIL is expressed by several cells, including monocytes, activated T cells, neutrophils, dendritic cells, macrophages, and airway epithelial cells (Stein et al., 2002; Mackay and Ambrose, 2003; Kato et al., 2006; Huard et al., 2008). BAFF exists as a membrane-bound protein and can be secreted as a soluble molecule upon cleavage by furin protease (Nardelli et al., 2001). Unlike BAFF, APRIL is cleaved intracellularly by furin convertase inside the Golgi apparatus, and is then secreted (López-Fraga et al., 2001).

BAFF and APRIL mediate their biological functions through receptor binding, which include transmembrane activator, calcium modulator, and cyclophilin ligand interactor (TACI), B-cell maturation antigen (BCMA), and B-cell activating factor receptor (BAFF-R) (Vincent et al., 2013). BAFF and APRIL ligands are mostly found on the surface of B cells; however, their expression varies in diverse cell types (Vincent et al., 2013). The binding of both BAFF and APRIL to their ligands leads to B-cell activation and differentiation as well as antibody production by B cells (Schuepbach-Mallepell et al., 2015; Smulski et al., 2017).

Several studies have examined the role of BAFF and its ligands in the development of asthma (Samitas et al., 2016; Dilidaer et al., 2017; Oliveria et al., 2017). However, the exact role of the APRIL protein in asthma has not been previously examined. In the present study, we aimed to investigate whether APRIL and BAFF plasma levels and surface expression of their ligands are increased in allergic asthma and determine the association between APRIL/BAFF levels and total IgE levels.

2. Material and methods

2.1. Subjects

Forty-seven patients diagnosed with chronic stable asthma in Saudi Arabia, according to the Saudi Initiative for Asthma guidelines (Al-Moamary et al., 2019), and 20 healthy controls were included in the experiments. The characteristics of patients with asthma and healthy controls are listed in Table 1.

The selection criteria for patients with asthma included a clear diagnosis of chronic bronchial asthma based on symptomatology, clinical course, and response to treatment after a review of their medical record files and electronic data. Furthermore, only patients with controlled asthma symptoms at the time of their appointment were included in this study. Asthma stabilization was ascertained by clinical evaluation of patient symptoms and through the use of an Asthma Control Test questionnaire based on the Saudi Initiative for Asthma guidelines. Patients with a test score of 20 or more were considered to have chronic stable asthma (controlled asthma) (Al-Moamary et al., 2019).

Table 1
Characteristics of subjects in the healthy control and patients with asthma groups.

Category	Control group	Asthma group
Subjects	20	47
Gender (male/female)	12/8	23/24
Mean age (years)	33.06	36.97
Mean disease duration (years)	–	7.95
Anti-asthma treatment		
SABA (salbutamol inhaler) on an as-needed basis	–	10
ICSs and salbutamol inhaler	–	37

Note: Patients with chronic stable asthma were selected by a consultant physician based on their follow up appointment at the chest clinic department of internal medicine at Alzulfi General Hospital.
ICSs, inhaled corticosteroids; SABA, short-acting beta agonists.

Exclusion criteria included patients with asthma and additional diagnosis of diabetes mellitus, hypertension, or obesity [body mass index (BMI) > 30], pregnancy, the presence of any chronic disease, a recent hospital admission for asthma and/or acute respiratory infection, or a history of smoking.

Ten patients with asthma were subjected to stabilization or control via a salbutamol inhaler (short-acting beta agonist, SABA) only on an as-needed basis. Additionally, 37 patients with asthma reported the usage of low-dose inhaled corticosteroids (ICSs), including a budesonide inhaler (200 μg/day) or beclomethasone dipropionate inhaler (100 μg twice per day), along with a salbutamol inhaler.

The healthy controls comprised voluntary blood donors of the Alzulfi General Hospital blood bank who were selected based on the following criteria: no recent respiratory infection, no chronic diseases, non-smoking individuals, no recent vaccines administered, no recent use of any drugs (especially corticosteroids or non-steroidal anti-inflammatory drugs), and no history of allergies. Written and signed informed consent was obtained from all participants of the study. The study was approved by the ethics committee at the author's University (MUREC-April.01/COM-206).

2.2. Collection of plasma samples and isolation of peripheral blood mononuclear cells

Samples of peripheral blood (5 mL) were collected from all participants. Blood was gently added to tubes containing an equivalent volume of Ficoll®-Paque Premium (cat. no. GE17-5442–02; Sigma-Aldrich, St Louis, MO, USA) and centrifuged at 398*g* for 30 min at 25 °C. Following centrifugation, plasma was carefully aspirated from the upper layer and aliquoted into Eppendorf tubes (1.5 mL; cat. no. 0030 120.086; Eppendorf, Hamburg, Germany). Lymphocytes, found in the interface layer, were collected, washed with phosphate buffered saline (PBS), and counted using a hemocytometer. The lymphocytes were subsequently resuspended in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 12.5% fetal calf serum and 20% DMSO and stored at −20 °C until further cytometric analysis.

2.3. Measurement of total IgE, APRIL, and BAFF levels

The levels of IgE, BAFF, and APRIL in the plasma samples were determined using the corresponding ELISA kits (cat. no. ab108650, Abcam, Cambridge, UK; cat. no. DBLYS0B, R&D Systems, Minneapolis, MN, USA; and cat. no. DBLYS0B, R&D Systems, respectively) per the manufacturer's instructions. The optical density was measured at 450 nm for each protein using an ELISA plate reader ELx800 (BioTek, Winooski, Vermont, USA). The lower limit of detection for total IgE, BAFF, and APRIL was 5 IU/mL, 62.5 pg/mL,

and 31.5 pg/mL, respectively. The protein levels were calculated using the KC Junior software (BioTek).

2.4. Flow cytometric analysis of BAFF/APRIL receptors

Lymphocytes (2×10^5) isolated from the samples were washed with PBS containing 0.02% bovine serum albumin (BSA) to prevent the binding of non-specific antibodies and then incubated with specific conjugated antibodies, including PerCP anti-human CD19 (cat. no. 363014; BioLegend, San Diego, CA, USA) as a B-cell marker, FITC anti-human CD268 (BAFF-R; cat. no. 316904; BioLegend), PE anti-human CD269 (BCMA; cat. no. 357504; BioLegend), and APC anti-human CD267 (TACI; cat. no. 311912; BioLegend) for 30 min at 4 °C in the dark. Following incubation, the cells were washed with PBS supplemented with 0.02% BSA. In each experiment, non-stained cells were included as a negative control. The cells were then resuspended in 500 μL PBS and flow cytometric analysis was performed using FACSCanto II (BD Biosciences, Franklin Lakes, NJ, USA). The data were analyzed, and the fluorescence intensity was measured using BD FACSDiva™ software (BD Biosciences).

2.5. Statistical analysis

The data are expressed as the mean ± standard deviation (SD) and were analyzed using the Mann-Whitney *U* test with GraphPad Prism v. 6.0 (GraphPad Software Inc, La Jolla, CA, USA). The correlation between the BAFF/APRIL levels and total IgE level was assessed using Pearson's correlation coefficient test. Results with p values < 0.05 were considered statistically significant.

3. Results

3.1. Total IgE protein levels are significantly increased in patients with asthma

Allergic asthma is characterized by elevated levels of IgE antibody. To ensure that samples were collected from patients with allergic asthma, the total IgE level was measured in patients with asthma and in healthy controls. Patients with asthma had significantly increased total IgE levels (405 IU/mL) compared with those in the healthy controls (185 IU/mL; $p = 0.003$; Fig. 1).

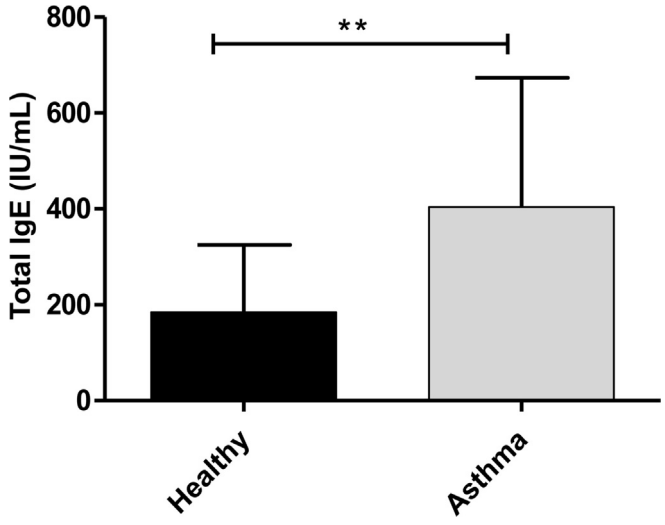

Fig. 1. Total IgE protein in patients with asthma and healthy subjects, as determined by ELISA. Data are presented as the mean ± SD. $p = 0.003$.

3.2. Protein levels of BAFF and APRIL are significantly elevated in patients with asthma

Plasma BAFF and APRIL levels were found to be significantly increased in patients with asthma (735 and 245 pg/mL, respectively) compared with those in healthy controls (458 and 135 pg/mL; $p = 0.0003$ and 0.008, respectively; Fig. 2A, B). The total IgE level was not associated with BAFF and APRIL levels (Fig. 2C, D).

3.3. BAFF-R and BCMA expression is increased in patients with asthma

We performed flow cytometric analysis to determine the surface expression of BAFF-R, BCMA, and TACI on human peripheral blood $CD19^+$ B cells (Fig. 3). The expression of BAFF-R and BCMA was significantly increased in patients with asthma (6.01×10^3 and 4.7×10^3 MFI, respectively) compared with that in healthy controls (3.40×10^3 and 2.61×10^3 MFI; $p = 0.01$ and 0.03, respectively). TACI expression was comparable between individuals with and without asthma ($p = 0.77$).

4. Discussion

In this study, we examined the expression levels of BAFF and APRIL as well as their ligands (BAFF-R, BCMA, and TACI) in patients with asthma and in healthy controls and evaluated the correlation between plasma BAFF/APRIL levels and total IgE levels. We found that the plasma levels of total IgE were significantly higher in patients with asthma than in healthy controls, which is in agreement with a previous study (Stokes and Casale, 2016). Patients with asthma also presented with higher BAFF levels than the controls despite receiving treatment during the study period; this is consistent with the observations reported by Samitas et al. (2016), where BAFF levels in bronchoalveolar lavage fluid were found to be elevated in patients with acute asthma undergoing treatment compared with healthy controls. Furthermore, studies have reported that BAFF levels show an increase in the plasma and sputum of patients with asthma and decrease after treatment, suggesting that BAFF may serve as a biomarker for predicting the severity of asthma symptoms (Kang et al., 2006; Jee et al., 2010).

Although increased expression of APRIL has been reported in other allergic diseases, including atopic dermatitis (AD) (Matsushita et al., 2006), to our knowledge, such a finding has

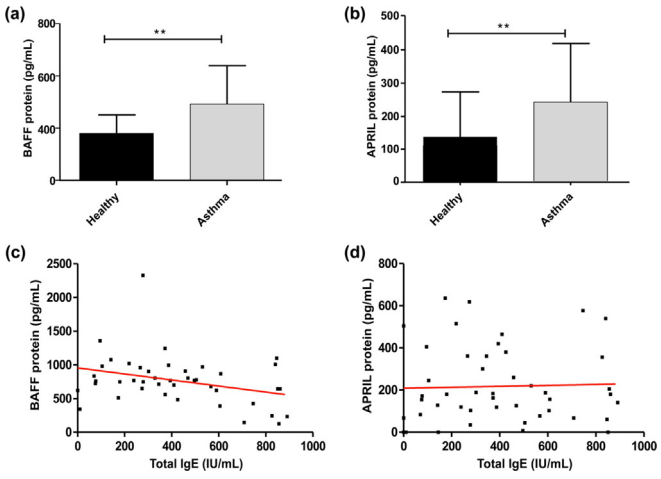

Fig. 2. Plasma levels of BAFF and APRIL in patients with asthma and healthy controls. (a) BAFF and (b) APRIL plasma levels determined by ELISA. The relationship of total IgE level with (c) BAFF (r = -0.048, $p = 0.74$) and (d) APRIL levels (r = 0.034, $p = 0.82$) was assessed using Pearson's test. The data are expressed as the mean ± SD. $^{**}p < 0.01$, $^{***}p < 0.001$.

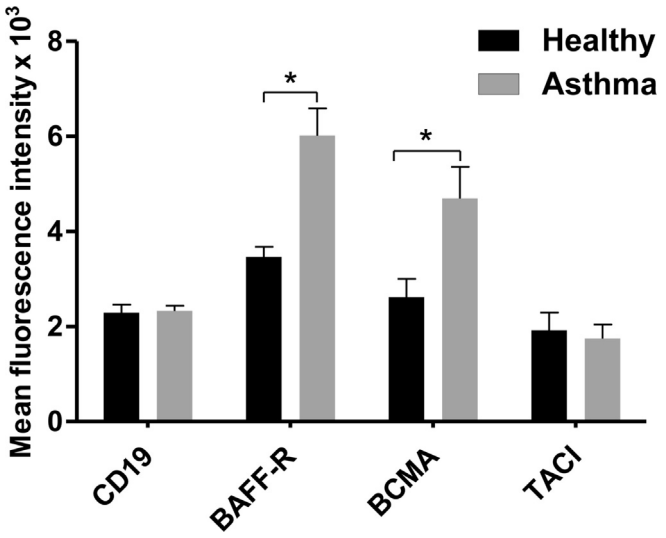

Fig. 3. Surface expression data of BAFF/APRIL receptors present on peripheral blood B cells. Flow cytometry was performed using samples obtained from patients with asthma and the healthy controls. Data are expressed as the mean ± SD of seven independent experiments. Unstained cells were used as negative controls for each experiment. $^{*}p < 0.05$.

not been reported in asthma (Alturaiki, 2020a). Here, we found that APRIL protein levels in plasma is significantly increased in patients with asthma compared with healthy normal controls. APRIL-deficient mice develop considerable airway inflammation compared with control mice (Xiao et al., 2011), suggesting the importance of APRIL expression in alleviating airway inflammation in the lungs.

Both BAFF and APRIL can influence the CSR process, which can produce various classes of antibody, including IgG, IgE, and IgA (Litinskiy et al., 2002; Castigli et al., 2004; Castigli et al., 2005). Matsushita et al. (2006) showed that increased APRIL protein levels in the serum are associated with elevated levels of IgE and total eosinophil counts, and are closely correlated with the severity of AD. Furthermore, BAFF protein levels are increased in the nasal polyp tissues of patients with asthma and are associated with the production of local IgE as well as elicitation of a Th2 response (Dilidaer et al., 2017). BAFF protein levels in the sputum are also significantly elevated in patients with asthma and are positively correlated with B-cell and eosinophil counts and total IgE levels (Oliveria et al., 2017). However, in the present study, significant associations between total IgE and BAFF or APRIL levels were not detected.

It has also been shown that corticosteroids can inhibit the expression of several cytokines, including BAFF (Reyes et al., 2008; Barnes, 2010); however, in the present study, plasma BAFF and APRIL levels in patients with asthma remained higher than those in healthy controls, despite the use of ICSs. This indicates that patients with asthma require high doses of ICSs, which is consistent with the report that not all patients respond equally to ICSs (Szefler, et al., 2002). Thus, plasma levels of BAFF and APRIL in patients with asthma may be used as potential biomarkers to assess the success of ICS therapy.

Stimulation of murine models of allergic airway inflammation with specific allergens revealed that BAFF plays an important role in the induction of B cells in the lungs and increased the expression of BAFF-R, BCMA, and TACI on B cells (Samitas et al., 2016). However, BAFF and APRIL receptors have not been previously investigated in patients with asthma. Flow cytometric analysis of the surface expression of BAFF/APRIL receptors showed that BAFF-R and BCMA expression levels were elevated in patients with asthma compared with healthy controls. BAFF and APRIL strongly interact with BAFF-R and BCMA (Vincent et al., 2013), respectively; thus, increased expression of BAFF and APRIL is coupled with elevated expression of these receptors. This finding indicates the potential for an increased B-cell response to these cytokines. In contrast, surface expression of TACI did not differ significantly between the two study groups. TACI is abundantly expressed on T2 and marginal zone B cells (Seshasayee et al., 2003; Guinamard et al., 2000) and plays an essential role in the maturation and function of B cells in the spleen, which may explain the lack of TACI expression in the blood of patients with asthma and the control group.

The limitation of the current study is the small sample size. Consequently, larger study groups are necessary to ascertain if expression levels of BAFF and APRIL and their ligands are linked with disease progression in patients with mild, moderate, and severe asthma. Furthermore, whether these cytokines can drive the overproduction of IgE and whether expression inhibition of BAFF and APRIL as well as their ligands can offer new treatment options for asthma should be analyzed in the future.

5. Conclusions

Our results revealed that plasma BAFF and APRIL protein levels are markedly increased in patients with asthma compared with healthy subjects and that BAFF-R and BCMA, but not TACI, are overexpressed in the former group. These findings suggest that determination of BAFF and APRIL protein levels may be useful for evaluating disease symptoms and monitoring response to treatments. Additional studies are necessary to clarify the exact roles of BAFF and APRIL in the induction of local IgE production in the airways as well as the activation of a Th2-cell response that mediates airway inflammation in the lungs.

CRediT authorship contribution statement

Wael Alturaiki: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing–original draft, Visualization, Supervision, Project administration, Funding acquisition. **Ayman Mubarak:** Validation, Formal analysis, Data curation, Writing–original draft. **Sajad Ahmad Mir:** Methodology, Formal analysis, Resources. **Adnan Afridi:** Methodology, Formal analysis, Resources. **Mariappan Premanathan:** Methodology, Validation. **Suresh Mickymaray:** Methodology, Data curation. **Rajendran Vijayakumar:** Data curation. **Suliman A. Alsagaby:** Methodology, Resources. **Sami G. Almalki:** Methodology. **Fayez Alghofaili:** . **Ahmad K. Alnemare:** Data curation. **Brian F. Flanagan:** Investigation, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Unblinded ethics statement

All subjects provided their informed consent for inclusion before participation in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Majmaah University (approval number MURECApril.01/COM-2).

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