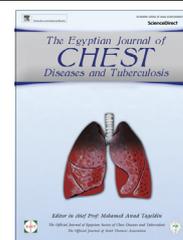




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ORIGINAL ARTICLE

Serum levels of angiotensin-2 and vascular endothelial growth factor in severe refractory asthma



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KEYWORDS

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Abstract *Background:* Airway and vascular remodeling may play a prominent role in the clinical severity of severe refractory asthma (SRA). Angiotensin-1 (Ang-1) is an essential mediator of angiogenesis by establishing vascular integrity, whereas angiotensin-2 (Ang-2) acts as its natural inhibitor. Vascular endothelial growth factor (VEGF) is considered to be the most important angiogenic factor, which induces vascular endothelial cell proliferation, tubule formation and increases microvascular permeability.

Objective: In the present study, we aimed to determine the serum levels of angiotensin-2 and VEGF in patients with SRA as both are involved in remodeling and angiogenesis occurring in SRA leading to resistance to inhaled steroid.

Methods: Twenty five patients with SRA, 25 patients with moderate asthma, and 20 healthy subjects are included in this study. Serum Angiotensin-2 and vascular endothelial growth factor were estimated in all groups.

Results: Ang-2 (pg/ml) levels were significantly higher among patients with SRA compared to patients with moderate asthma and healthy control. Vascular endothelial growth factor was significantly higher in patients with SRA compared with the other two groups.

Conclusion: Results provide suggestion for possible mechanisms involving angiotensin-2 and VEGF in the pathogenesis of SRA.

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Introduction

Severe refractory asthma (SRA) is a heterogeneous disorder that is characterized by persistent asthma symptoms despite treatment with high-dose inhaled steroids (ICS) [1]. Increased angiogenesis has been observed in SRA [2], and along with

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other components of tissue repair and airway inflammation, they may account for the poor steroid response in SRA [3].

Angiogenesis is a complex multiphase process, potentially involving a great number of growth factors, cytokines, chemokines, and numerous other mediators but the specific role of each molecule has not been clearly defined [4]. Vascular endothelial growth factor (VEGF) is considered to be the most important angiogenic factor [5,6], which induces vascular endothelial cell proliferation, tubule formation and increases microvascular permeability [7]. The latter is a common feature of vascular remodeling in asthma and is modulated by the release of different inflammatory mediators, cytokines, proteases, and growth factors [4,8].

Angiopoietins 1 and 2 (Ang-1, Ang-2) are both ligands for the endothelial cell-specific Tie-2 surface receptor and may act in a complimentary and coordinated manner along with VEGF in airway microvascular process. Ang-1 is known to promote sprouting and stabilizing of nascent vessels by promoting interactions between endothelial cells and surrounding support cells including pericytes [9]. In contrast, Ang-2 acts as a natural antagonist of Ang-1 that competes for Tie-2 receptor and reduces vascular integrity, leading subsequently to increased vascular permeability and mucosal edema [10]. Data derived from an animal study suggest that Ang-1 protects against air way inflammation and hyperreactivity in asthma [11]. Ang-2 is increased in sputum supernatants of steroid-naive patients with asthma, is related to increased levels of vascular permeability (AVP) index [12]. Recent studies have shown that Ang-2 levels are elevated in several pathological conditions [13–15]. Parikh et al. [13] reported that Ang-2 levels were significantly elevated in patients with sepsis and impaired oxygenation. In addition, serum from these patients induces disruption of the endothelial barrier, and it has been suggested that systemic excess of Ang-2 provoked pulmonary leakage and congestion in healthy adult mice [13].

In the present study, we aimed to determine the serum levels of angiopoietin-2 and VEGF in patients with SRA as both are involved in remodeling and angiogenesis occurring in SRA leading to resistance to inhaled steroid.

Patients and methods

Patients

Patients were recruited from outpatient clinics of Cairo and Tanta chest departments from January 2013 to January 2014. All patients and control are included after taking their written consent. The diagnosis of asthma was established according to GINA guidelines [16]. The diagnosis of SRA was established according to the American Thoracic Society (ATS) criteria [1]. Fifty patients were included and divided into 25 patients with SRA and 25 patients with moderate asthma, diagnosed according to the classification of GINA 2008 [16]. All patients with asthma were never smokers. Twenty healthy, nonatopic, nonsmoking subjects served as controls. Patients with any other respiratory disease or any concomitant malignant, heart, renal, liver or collagen disease as well as subjects with a respiratory tract infection are excluded from this study.

Laboratory investigations including

Solid Phase Sandwich ELISA technique used for the measurement of angiopoietin-2 and vascular endothelial growth factor (VEGF) levels in serum as a monoclonal antibody specific for the measured marker has been precoated onto a microplate. Standards and samples are pipetted into the wells and the specific marker present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for the measured marker is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of the measured marker bound in the initial step. The color development is stopped and the intensity of the color is measured.

- Estimation of Angiopoietin-2 level in serum using R&D system Human Angiopoietin-2 Quantikine Pharm Pak (catalog no. PDANG20). The Quantikine Human Angiopoietin-2 Immunoassay is a 4.5 hour solid-phase ELISA designed to measure Human Angiopoietin-2 in serum. Serum Angiopoietin-2 levels were obtained using the standard curves of the Quantikine kit standards.
- Estimation of serum level of VEGF using R&D system Human VEGF Quantikine Pharm Pak (catalog no. PDVE00). The Quantikine Human VEGF Immunoassay is a 4.5 hour solid phase ELISA designed to measure serum VEGF. Results were obtained from the standard curves using the Quantikine Human VEGF Immunoassay standards.

Lung function

Forced expiratory volume in one-second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and reversibility were measured using the vitalograph machine according to the ATS guidelines [17].

Results

Demographic characteristics

Demographic characteristics of the study participants are summarized in [Table 1](#).

Serum level of angiopoietin 2 and vascular endothelial growth factor

[Table 2](#) shows that Ang-2 (pg/ml) levels differed significantly among patients with SRA, compared to patients with moderate asthma and healthy control. Vascular endothelial growth factor was significantly higher in patients with SRA compared with the other two groups. [Table 2](#) and [Fig. 1](#) show that in patients with SRA, Ang-2 is positively correlated with VEGF ([Table 3](#)).

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