

# Does pregnancy-associated plasma protein A have a role in allergic rhinitis?

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## ABSTRACT

**Background:** Pregnancy-associated plasma protein A (PAPP-A), also known as insulin-like growth factor binding protein 4 protease, is postulated to be a new inflammatory marker in various clinical situations such as cardiovascular events, dialysis, renal transplantation, and asthma. PAPP-A also is produced in high concentrations by trophoblasts during pregnancy.

**Methods:** We evaluated PAPP-A levels in allergic rhinitis patients and compared these with levels in healthy subjects. Thirty-one newly diagnosed allergic rhinitis patients and 29 healthy controls were included in the study. Serum PAPP-A, IgE, urea, creatinine, aspartate aminotransferase, creatine kinase (CK), CK-MB isoenzyme, total cholesterol, and triglyceride levels were determined.

**Results:** The serum PAPP-A level was significantly higher ( $p = 0.013$ ) in the allergic rhinitis group ( $6.1 \pm 2.9$  mU/L) than in the control group ( $4.5 \pm 1.7$  mU/L). The PAPP-A level in patients with allergic rhinitis and asthma ( $6.1 \pm 2.3$  mU/L) was not significantly different ( $p = 0.959$ ) from that in patients with allergic rhinitis alone ( $6.1 \pm 3.3$  mU/L). The serum PAPP-A level in allergic rhinitis patients who had turbinate hypertrophy ( $6.9 \pm 2.2$  mU/L) had a tendency to be higher than that in patients who had no turbinate hypertrophy ( $5.5 \pm 3.2$  mU/L); however, this difference was not statistically significant ( $p = 0.151$ ).

**Conclusion:** Increased PAPP-A activity may be involved in the inflammation and tissue remodelling that occurs in allergic rhinitis. (Am J Rhinol 22, 219–222, 2008; doi: 10.2500/ajr.2008.22.3179)

**Key words:** Allergic rhinitis, hypervascularity, IGF, IGFBP-4, inflammation, matrix metalloproteinase, nasal mucosa, PAPP-A, pregnancy, tissue remodeling

Pregnancy-associated plasma protein A (PAPP-A) is produced in high concentrations by trophoblasts during gestation, and low serum levels of PAPP-A have been used as a predictor of some genetic fetal developmental disorders such as Down's syndrome<sup>1</sup> and Cornelia de Lange syndrome.<sup>2</sup> In addition, a high serum level of PAPP-A has been proposed as a marker in patients with cardiovascular conditions such as plaque instability and acute coronary syndrome.<sup>3</sup> Recent evidence suggests that PAPP-A also might be a novel marker of inflammation, especially in dialysis and renal transplantation patients.<sup>4–6</sup> Fialova *et al.* have shown a relationship among the levels of PAPP-A, C-reactive protein (CRP), and advanced oxidation protein products in dialysis patients.<sup>4</sup> Lauzurica *et al.* have reported a significant positive correlation between CRP and PAPP-A levels in pretransplant patients<sup>5</sup> and have proposed the pretransplant PAPP-A level as an independent risk factor for posttransplant cardiovascular disease.

PAPP-A, also known as insulin-like growth factor binding protein 4 (IGFBP-4) protease, has an important function in regulating the IGF axis, which is involved in the regulation of growth, proliferation, and differentiation of a variety of cell types.<sup>7</sup> Although several studies have established the importance of IGFs in the regulation of vascular smooth muscle

growth,<sup>8</sup> limited information is available on the pathophysiological roles of IGFs and related molecules in airway tissues, especially those of the upper respiratory tract and nasal mucosa.

Allergic rhinitis is an inflammatory response in the nasal mucosa that is characterized by the clinical symptoms of sneezing, itching, congestion, and nasal discharge and obstruction.<sup>9</sup> Matrix metalloproteinases (MMPs) play an important role in the inflammatory events of allergic rhinitis, including inflammatory cell migration and increased vascular permeability, and can lead to structural changes such as thickening of the basal membrane, fibrosis, and loss of epithelium, with areas of epithelial metaplasia.<sup>9</sup> PAPP-A is a zinc-binding metalloproteinase belonging to the metzincin superfamily of metalloproteinases.<sup>10</sup> In this study, we compared the levels and significance of PAPP-A between allergic rhinitis patients and healthy controls.

## MATERIALS AND METHODS

### Patient Population

Patient characteristics are summarized in Table 1. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all subjects. Thirty-one newly diagnosed allergic rhinitis patients (14 men and 17 women) and 29 control subjects (16 men and 13 women) were selected. The patients had complaints of watery nasal discharge, sneezing, and nasal obstruction, and all patients were symptomatic at the time of testing. The diagnosis of allergic rhinitis was made after taking a history; performing a routine ear, nose, and throat examination; administering a skin-prick test; and determining the total serum IgE level. None of the patients had received inhaled or orally adminis-

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Table 1 Characteristics of patients and control subjects of study population

| Characteristics                           | Allergic Rhinitis Group<br>( <i>n</i> = 31) | Control Group<br>( <i>n</i> = 29) | <i>p</i> -Value |
|-------------------------------------------|---------------------------------------------|-----------------------------------|-----------------|
| Age (yr; mean $\pm$ SD)                   | 25.5 $\pm$ 14.1                             | 30.6 $\pm$ 4.8                    | 0.066           |
| Male/female ratio ( <i>n</i> : <i>n</i> ) | 14:17                                       | 16:13                             | 0.438           |
| Smoking [ <i>n</i> (%)]                   | 4 (12.9)                                    | 3 (10.3)                          | 0.758           |
| Asthma [ <i>n</i> (%)]                    | 14 (45.2)                                   | 0                                 | —               |
| TH [ <i>n</i> (%)]                        | 13 (41.9)                                   | —                                 | —               |
| TH with asthma [ <i>n</i> (%)]            | 7 (22.6)                                    |                                   |                 |
| TH without asthma [ <i>n</i> (%)]         | 6 (19.4)                                    |                                   |                 |

TH = turbinate hypertrophy.

tered corticosteroids or any other anti-inflammatory drugs such as sodium cromoglycate or nedocromil sodium. Patients with an established inhalant allergen on a skin-prick test were selected. Turbinate hypertrophy was assessed clinically during anterior rhinoscopy. When the width of the turbinate was greater than three-fourths the width of the nasal passage, the turbinate was considered hypertrophic. We used the Global Initiative for Asthma (GINA) criteria to decide whether a patient had asthma.<sup>11</sup> None of the asthma patients used inhaled steroids. Exclusion criteria included major surgical treatment within 6 months, cardiovascular events, renal insufficiency, and pregnancy.

### Blood Sampling

Blood samples were drawn from the antecubital vein of 31 allergic rhinitis patients and 29 control subjects. All blood samples were centrifuged for 10 minutes at 1500  $\times$  *g*, and sera were stored at  $-20^{\circ}\text{C}$  until analysis. All samples were processed within 2 months.

### Biochemical Assay

Although PAPP-A is regarded as a plasma protein, it also is detectable in serum. Serum PAPP-A levels were determined using an ultrasensitive enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories, Webster, TX). The minimum detection limit was 0.24 mU/L, and the coefficient of variation was 4.80%. Serum IgE levels were determined by a solid-phase, chemiluminescent, immunometric assay on an automatic hormone analyzer (Immulite; DPC, Los Angeles, CA). Serum urea, creatinine, aspartate aminotransferase, creatine kinase (CK), CK-MB isoenzyme, total cholesterol, and triglyceride levels were determined by standard clinical chemistry methods using an Olympus AU 640 autoanalyzer (Olympus, Tokyo, Japan).

### Statistical Analysis

The Kolmogorov-Smirnov test was used to evaluate the normality of the data. Results are expressed as the mean  $\pm$  SD. Data were normally distributed, and an unpaired Student's *t*-test was used to evaluate the significance of differences between the allergic rhinitis patients and the controls. Significant differences in patient characteristics (gender and smoking) were analyzed by Fischer's exact  $\chi^2$ -test. A value of  $p < 0.05$  was considered statistically significant.

### RESULTS

As shown in Fig. 1, the serum PAPP-A level was significantly higher ( $p = 0.013$ ) in allergic rhinitis patients ( $6.1 \pm 2.9$  mU/L) than in the control group ( $4.5 \pm 1.7$  mU/L). There was no significant difference in the serum PAPP-A level between male and female subjects in either the control or allergic rhinitis groups. The serum PAPP-A level was higher in patients with turbinate hypertrophy ( $6.9 \pm 2.2$  mU/L) than in patients without turbinate hypertrophy ( $5.5 \pm 3.2$  mU/L); however, this difference was not statistically significant ( $p = 0.151$ ). We divided the turbinate hypertrophy group into two subgroups according to the presence of asthma and compared the PAPP-A level between these subgroups (Table 1). The difference in the PAPP-A level was not statistically significant ( $p > 0.05$ ) between the turbinate hypertrophy plus asthma ( $7.1 \pm 2.5$  mU/L) and the turbinate hypertrophy without asthma ( $6.7 \pm 1.8$  mU/L) groups. Furthermore, the PAPP-A level did not differ significantly ( $p = 0.959$ ) between patients with allergic rhinitis and asthma ( $6.1 \pm 2.3$  mU/L) and patients with allergic rhinitis only ( $6.1 \pm 3.3$  mU/L). The serum urea, creatinine, aspartate aminotransferase, CK, CK-MB, total cholesterol, and triglyceride levels were within the respec-

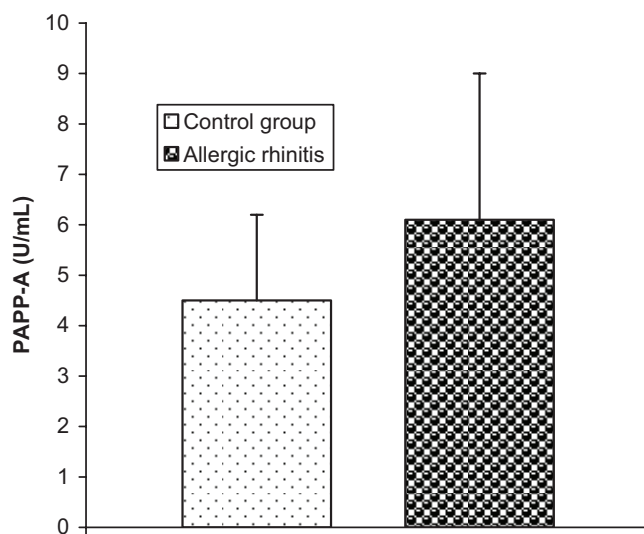


Figure 1. Serum PAPP-A levels of the control group and allergic rhinitis patients.

tive reference ranges in both the patient and the control groups (Table 2).

## DISCUSSION

To the best of our knowledge, this study is the first to investigate the PAPP-A level in allergic rhinitis. PAPP-A is a high-molecular-mass glycoprotein that is stable under normal laboratory conditions.<sup>12</sup> In pregnancy, PAPP-A is produced by trophoblasts and forms a complex, called PAPP-A–pro-MBP complex, with the proform of eosinophil major basic protein (pro-MBP) and its endogenous inhibitor.<sup>13</sup> However, in men and nonpregnant women, PAPP-A in serum exists in the free form, not bound to pro-MBP. For instance, PAPP-A released during atherosclerotic plaque disruption seems to be in an active form that is not complexed with pro-MBP.<sup>13</sup> PAPP-A belongs to the metzincin superfamily of metalloproteinases and is potentially proatherosclerotic, through its role in disrupting the integrity of the protective cap of atheroma.<sup>10,14</sup>

Metalloproteinases, especially MMPs, are produced by various cell types, including fibroblasts, macrophages, and eosinophils, and mediate the migration of inflammatory cells through the basement membrane, thereby propagating inflammation.<sup>15,16</sup> Immunohistochemical studies of nasal tissues from patients with allergic rhinitis have revealed an accumulation of eosinophils and basophils/mast cells within the lamina propria and epithelium.<sup>17</sup> The exact mechanism of inflammatory cell migration into the site of inflammation is not well understood but is thought to require the degradation of extracellular matrix (ECM) proteins,<sup>18</sup> which is accomplished in part by the secretion of MMPs.<sup>19,20</sup> In addition to classic inflammatory responses, structural changes that include epithelial disruption, mucus gland hypertrophy, enhanced mucosal collagen deposition, mucosal myofibroblast transformation, and increased matrix protein deposition have been reported within the nasal walls in allergic rhinitis patients. These cellular events, referred to as tissue remodeling, involve extensive alteration of the ECM<sup>21,22</sup> and are mediated by MMPs.<sup>22–24</sup>

We observed a significant increase in the serum PAPP-A level in allergic rhinitis patients, indicating an important role

for PAPP-A in the inflammatory response and structural changes in allergic rhinitis. Although the PAPP-A level was not significantly associated with turbinate hypertrophy in this study, we only measured PAPP-A at a single time point and did not use a precise measurement of turbinate mass. We hypothesize that a high PAPP-A level may cause turbinate hypertrophy in allergic rhinitis, at least in part, by cleaving IGFBP-4 and thus increasing the IGF concentration.

Elevated levels of PAPP-A can occur in asthma because of the continuity between the lower and upper airways. In our previous study, we showed that the serum PAPP-A level is increased in asthma patients and is positively correlated with the severity of asthma.<sup>25</sup> In our current study group, 14 allergic rhinitis patients had concomitant asthma, but the PAPP-A level was not significantly different between allergic rhinitis patients with and without asthma. We divided the turbinate hypertrophy group into two subgroups according to the presence of asthma and found no significant difference in the PAPP-A level between these two subgroups. We conclude that the significant increase in the PAPP-A level observed in our study could not only be attributed to the asthma patients in the study group.

The PAPP-A level has been shown to increase in injured cultured smooth muscle cells and injured arteries *in vivo*, where it may function in releasing IGF-I from IGFBP-4.<sup>26</sup> Hoshino *et al.* have shown the presence of IGF-I<sup>+</sup> cells in the epithelium, smooth muscle, and ECM of the lower-airway submucosa in patients with asthma.<sup>27</sup>

Noveral *et al.* have suggested that IGFs and IGFBPs are important in the regulation of smooth muscle cell growth in the airway and that the IGF axis is a potent regulator of smooth muscle cell proliferation in the airway.<sup>28</sup> In addition, Adams *et al.* have shown that the addition of IGF-I to injured nasal epithelial cells increases the rate of scratch closure and have speculated that IGF-I has a potential role in improving healing in the nasal mucosa.<sup>29</sup> Oligonucleotide microarray analysis of nasal tissues has revealed the up-regulated transcription of vascular endothelial growth factor, an angiogenic growth factor, in allergic rhinitis.<sup>30</sup> The evaluation of other features of vascular change in rhinitis has revealed disease-specific changes in mucosal blood vessels, with thinning and

**Table 2 Serum PAPP-A, urea, creatinine, AST, CK, CK-MB, total cholesterol, triglyceride, and total IgE levels of patients and control subjects**

| Parameters                | Control Group<br>(n = 29) | Allergic Rhinitis Group<br>(n = 31) | Reference<br>Range |
|---------------------------|---------------------------|-------------------------------------|--------------------|
| PAPP-A (mU/L)             | 4.5 ± 1.7                 | 6.1 ± 2.9                           | —                  |
| Urea (mg/dL)              | 25 ± 4.4                  | 26 ± 8.2                            | <50                |
| Creatinine (mg/dL)        | 1.0 ± 0.1                 | 0.8 ± 0.2                           | <1.2               |
| AST (U/L)                 | 19 ± 7.1                  | 23.9 ± 9.5                          | <33                |
| CK (U/L)                  | 114 ± 22.9                | 100 ± 53.6                          | <167               |
| CK-MB (U/L)               | 11 ± 4.8                  | 17 ± 6.5                            | <24                |
| Total cholesterol (mg/dL) | 159 ± 31.4                | 161 ± 27.1                          | 120–200            |
| Triglyceride (mg/dL)      | 102 ± 23.7                | 113 ± 46.8                          | 40–150             |
| Total IgE (IU/mL)         | 68 (23–99)                | 273 (176.5–592)                     | <87                |

AST = aspartate aminotransferase.

destructive changes in the arteriolar wall, deposition of globulins and complement in the vascular wall, and vascular dilatation.<sup>22</sup> PAPP-A also may function in these vascular changes in allergic rhinitis through an influence on IGFs.

## CONCLUSION

The serum PAPP-A level is increased in allergic rhinitis patients, indicating that PAPP-A, as an IGFBP-4-specific metalloproteinase, may have an important function in the inflammatory events and structural changes, referred to as tissue remodeling, that are characteristic of allergic rhinitis.

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