

REVIEW

Isocyanate-induced occupational asthma in far-east Asia: pathogenesis to prognosis

H.-S. Park, S.-H. Cho*, C.-S. Hong† and Y.-Y. Kim*

Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, *Department of Medicine, Seoul National University, and †Yonsei University Medical College, Seoul, Korea

Introduction

Asthma is a chronic inflammatory disorder of the central and peripheral airways in which both cellular and humoral immune mechanisms are involved. Occupational asthma can be a good model for studying pathogenic mechanisms of asthma. More than 300 agents that cause asthma have been reported [1] and isocyanate, especially toluene diisocyanate (TDI), is known as the most prevalent cause of asthma in Korea as well as in other parts of the world. In particular, several immunological and non-immunologic mechanisms have been suggested in TDI-induced asthma [2]. However, in the case of high molecular weight agents, including citrus red mite, grain dust, and drugs such as protease, enzyme and herbal agents, IgE-mediated response is the main pathogenic mechanism in this country [3–6]. To further understand the pathogenic mechanisms of asthma, recent progress in cellular and humoral mechanisms of TDI-induced asthma are summarized in this paper.

Specific IgE antibody response: heterogeneity and longitudinal study

Several groups of investigators have detected IgE antibodies specific to TDI-human serum albumin (HSA) conjugate in the sera of workers showing positive bronchial challenge to TDI; the prevalence varied between 0 and 50% of workers [7–11]. Maestrelli et al. [12] revealed that there were increased numbers of IL-5 and IL-4 expressing cells in the bronchial mucosa of TDI-induced asthma patients. Our recent investigation using our conjugate showed a 13% prevalence of specific IgE in TDI-induced asthma patients by ELISA. However, when specific IgE bindings were determined with several forms of TDI-HSA conjugates, marked variation was noted depending on the preparatory conditions of the conjugate [13] and type of TDI-HSA conjugate used [14]. ELISA inhibition test using three types of TDI-HSA conjugates, that were known to be sensitive among the conjugates prepared in the same condition, revealed significant inhibitions by only one conjugate and minimal inhibitions by the other two conjugates (Fig. 1) suggesting that specific IgE bindings to a new antigenic determinant of TDI-HSA conjugate can be heterogeneous and differ from one individual to another.

These findings may be responsible for the variable results in the prevalence study of serum-specific IgE antibody to TDI-HSA conjugate in TDI-induced asthma.

Although precise antigenic determinants of each patient's specific IgE antibody to reactive chemicals remain to be further investigated, there is a possibility that TDI-HSA may have particular changes of a three-dimensional configuration, resulting in generation of new antigenic epitopes. Antibodies against new antigenic determinants of the conjugate could be produced *in vivo*. Therefore, TDI-carrier conjugates generated *in vivo* may vary among individuals sensitized to TDI. These differences *in vivo* may be one of the possible explanations for individual difference in specific IgE response patterns and variable results in the prevalence of specific IgE. A previous study [10] reported that specific IgE to isocyanate is a more specific than sensitive index of occupational asthma and that sensitivity was highest when blood was taken less than 30 days from last exposure, which is consistent with the observed half-life of approximately 6 months. However, our recent study [15] on the changes of specific IgE antibody response to TDI-HSA conjugate in asthmatic patients with high specific IgE during the initial visit showed that specific IgE continued to fall for several years. Their mean half-life ranged from 2.3 to 4.8 years, which was quite different from the study by Pirilä et al. [11].

It is certain that IgE-mediated responses as well as non-IgE-mediated mechanisms may contribute to the development of asthmatic symptoms in TDI-exposed workers. Although the results of specific IgE to methylene diisocyanate (MDI) and hexamethylene diisocyanate (HDI) may be different [16], specific IgE antibody to TDI-HSA conjugate may persist for several years after the last exposure to TDI. Specific IgE response to TDI-HSA conjugate can be heterogeneous and differ from one individual to another.

Specific IgG as a pathogenic role

The clinical significance of specific IgG response to occupational antigens seems to be complex, eliciting variable responses according to the different antigens. In a study on reactive dye asthma [17], we showed that the prevalence of specific IgG and IgG4 was significantly higher in symptomatic workers, but there was no correlation with exposure intensity or exposure duration. In contrast, some studies in other occupational settings have suggested that the presence of specific IgG may represent a response to high-dose exposure not related to the development

Correspondence: Hae-Sim Park, Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Paldalgu, Wonchodong, San-5, Suwon, Korea. E-mail: hspark@madang.ajou.ac.kr

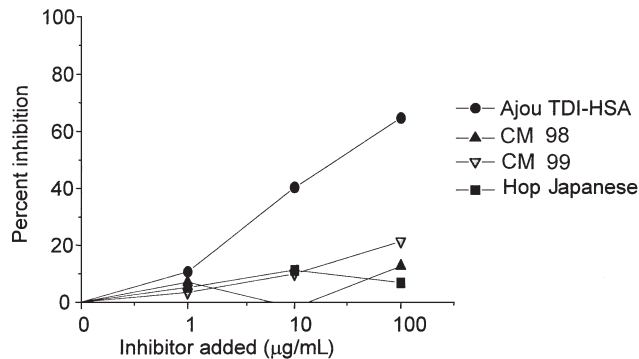


Fig. 1. Percentage inhibition of specific IgE bindings to Ajou toluene diisocyanate (TDI)-human serum albumin (HSA) conjugate by ELISA with serial additions of Hop Japanese pollen, three kinds of TDI-HSA conjugates, Ajou and two CM conjugates (98,99).

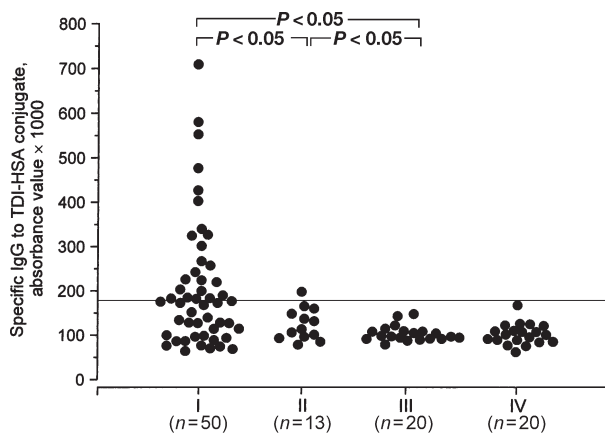


Fig. 2. Comparison of specific IgG binding to TDI-HSA conjugate determined by using ELISA in four different groups: group I, patients with TDI-induced asthma; group II, exposed subjects with asthma who had negative results on TDI-BPT; group III, unexposed subjects with allergic asthma who are sensitive to house dust mite allergen; and group IV, unexposed healthy control subjects. Significant differences were noted between groups by cross-tab analysis ($P < 0.05$).

of respiratory symptoms [18,19]. For isocyanate-induced asthma, there have been a few reports suggesting a pathogenic role of specific IgG to HDI- and MDI-HSA conjugates [20,21], as they showed greater association between specific IgG to MDI- and HDI-HSA and their bronchoprovocation results.

Although other investigators have suggested that specific IgG to MDI was only an indicator of MDI exposure [22], we have recently shown that the prevalence of serum-specific IgG antibody to TDI-HSA conjugates was higher than that of specific IgE in TDI-induced asthma [23]. Furthermore, it was significantly higher in subjects showing positive responses on TDI-bronchoprovocation test (BPT, 46%) compared with subjects with negative responses (7.7%) on TDI-BPT, allergic asthma (0%) or to unexposed healthy control subjects (0%). There was no significant difference in specific IgG level regardless of the presence of serum-specific IgE antibody to TDI-HSA conjugate or atopic status (Fig. 2). A longitudinal study [15] on serum-specific IgG response in TDI-induced asthma patients after complete avoidance and anti-asthmatic medications showed that it may persist for several years, ranging from 1.7 to 6.7 years. There were no significant differences in the prevalence of specific IgG depending upon the type of asthmatic responses

Table 1. Test characteristics of toluene diisocyanate (TDI)-human serum albumin (HSA)-specific IgE and IgG antibodies in identifying TDI-induced asthma confirmed by TDI-bronchoprovocation test among exposed workers

	Specific IgE antibody	Specific IgG antibody
Sensitivity (%)	14	46
Specificity (%)	92.3	92.3
Positive predictive value (%)	87.5	95.8
Negative predictive value (%)	21.8	30.8

during TDI-BPT. Table 1 summarizes sensitivity, specificity and positive and negative predictive values of specific IgE and IgG antibodies for identifying TDI-induced asthma in exposed subjects. The sensitivity of specific IgG in the diagnosis of TDI-induced asthma based upon TDI-BPT was higher than that of specific IgE. It was speculated that the presence of serum-specific IgG antibody to TDI-HSA conjugate was closely associated with TDI-BPT results, and that it may be used to monitor the condition before clinical diseases occur. Also, serum-specific IgG may persist for several years after the last exposure to TDI.

The cellular immune response

It is known that inflammatory mechanisms composed of eosinophils, mast cells and T lymphocytes, especially the IL-2 receptor-positive type [2,12,24,25], and increased level of cytokines produced by Th2 cells, are involved in the bronchial mucosa of TDI-induced asthma, similarly to allergic asthma. Other immune responses reported in diisocyanate asthma include lymphoproliferative responses and cytokine/chemokine production [26,27]. Our recent data applying a comparative immunohistochemical analysis of bronchial mucosa between TDI-asthma and allergic asthma, have revealed that significantly higher numbers of mast cells and neutrophils are noted in TDI-asthma [28], while there is no significant difference in T cell count. A significant correlation was also found between neutrophil and mast cell counts. With regard to T cell cytokine secretion, the production of IFN- γ was observed in both peripheral mononuclear cells and T cell lines that were collected from newly diagnosed TDI-induced asthma subjects [26]. There have been a few studies to demonstrate the role of CD8⁺ T lymphocytes in the airway mucosa of TDI-induced asthma. They succeeded in the cloning of a specific T cell line that was derived from T cells in the airway mucosa of TDI-induced asthma [29,30]. These results suggest that lymphocytes as well as other inflammatory cells such as eosinophils, mast cells and activated neutrophils may contribute to the development of TDI-induced bronchoconstriction. Further studies will be needed to document the role of CD8⁺ T cells in TDI-induced asthma.

Neutrophil activation

The bronchoalveolar lavage fluid of isocyanate-induced asthma patients shows neutrophilia, especially in those with late asthmatic response [31]. As with grain dust-induced occupational asthma [32], neutrophil counts in the bronchial mucosa of

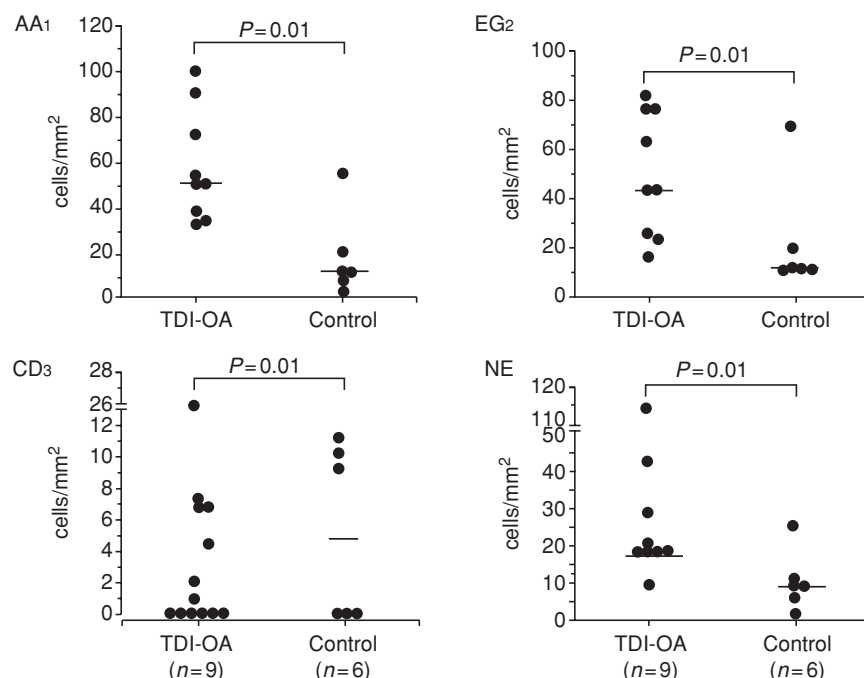


Fig. 3. Comparison of inflammatory cell numbers expressing AA1 (mast cell), EG2 (activated eosinophil), CD3 (pan T cell) and NE (neutrophil elastase) in bronchial mucosa section of subjects with TDI-induced asthma (TDI-OA) and allergic asthma (control). Significant differences were noted in AA1 and NE positive cells ($P < 0.05$, respectively).

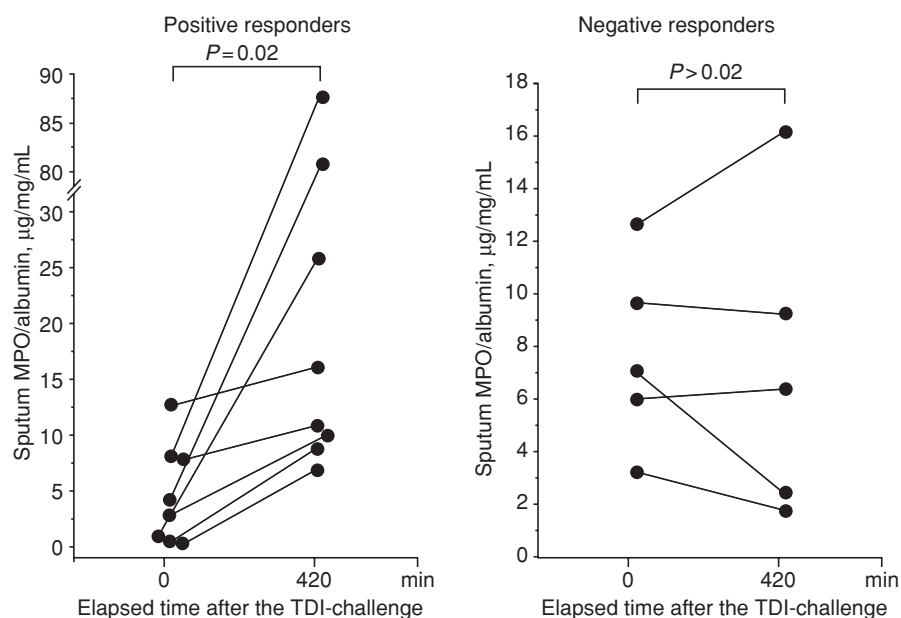


Fig. 4. Changes of myeloperoxidase (MPO) level in induced sputum before and after the TDI bronchial challenges in eight TDI-induced asthmatic subjects showing a positive result on TDI-bronchoprovocation test (a) and those with negative challenges (b). A significant increase of MPO/albumin relative to the baseline was noted after the bronchial challenge test in positive responders ($P=0.02$), while no significant changes were seen in negative responders ($P=0.47$).

TDI-asthma patients are significantly higher than those of allergic asthma [28], as shown in Fig. 3. Furthermore, serum neutrophil chemotactic activity increased significantly 10 min after TDI challenge, decreased at 60 min and then remained without significant change for up to 420 min in subjects with positive challenges, while no significant changes were noted in negative responders [33].

The origin of these activities is complete so far. However, on the basis of the time course, we speculate that neutrophil chemotactic activity found in that study may have originated from mast cells, which is comparable with the study by Saite et al. [34]. In that study, TDI-HSA conjugate itself did not have neutrophil chemotactic activity. Further studies are needed to

characterize the serum neutrophil chemotactic activity released after TDI inhalation, particularly in TDI-induced asthma. Moreover, when the level of myeloperoxidase (MPO), a neutrophil activation marker, was determined during TDI challenges, a significant increase in sputum was noted 420 min after bronchial challenge relative to baseline value in TDI-induced asthma patients, while no significant changes were found in negative responders as shown in Fig. 4 [33]. In addition, the major neutrophil-related cytokine, IL-8, was abundant in the sputum of patients with TDI-asthma and increased significantly at 420 min after TDI bronchial challenge in positive responders. A significant correlation was found between percentage increase of IL-8 and post-challenge MPO level

($r=0.89$, $P=0.02$). These results suggest that IL-8 released after exposure to TDI might have contributed to neutrophilic infiltration into airway mucosa in TDI-induced asthma. These findings suggested a potential role of neutrophil in the pathogenesis of TDI-induced asthma.

Role of bronchial epithelial cells

Mounting evidence suggest that diisocyanates bind to airway epithelial cell proteins, and are taken up by epithelial cells [35,36]. These interactions lead to airway inflammation composing of cytokine and chemokine production and cellular recruitment [2]. Studies on the toxicity of diisocyanates on airway epithelium have also been reported in the past years. MDI and HDI prepolymers were shown to induce airway epithelial barrier dysfunction that was partly associated with glutamine levels [37,38]. Specific effects of TDI on the expression of lung cytokine P450 enzymes have also been documented [39]. We also tried to culture human bronchial epithelial cell line, Beas-2B cells under exposure to TDI-HSA conjugates in order to identify the source of IL-8 that was found in the sputum of TDI-induced asthma patients [40]. IL-8 and RANTES production was significantly increased with additions of peripheral mononuclear cell culture supernatant derived from a TDI-induced asthma patient in a dose-dependent manner. Further investigations will be needed to elucidate the underlying mechanism of IL-8 and RANTES production with exposure to TDI.

Specific antibodies as prognostic factors

Long-term follow-up studies of subjects with isocyanate asthma have suggested that asthmatic symptoms may persist in some subjects for months or years after work withdrawal [41–44]. Our previous studies also demonstrated that among 35 TDI-asthma patients, 51–58% of them had persistent asthmatic symptoms after 2 years, despite complete avoidance of exposure and adequate anti-asthmatic medications. In those studies, favourable outcome was associated with a short duration of asthmatic symptoms before diagnosis, immediate cessation of exposure after diagnosis, milder degree of airway hyper-responsiveness at diagnosis, and the presence of specific IgE to TDI-HSA. Regarding the role of specific antibodies as prognostic factors of isocyanate-induced asthma patients, there has been an interesting study on the prognostic value of specific IgE to isocyanate-HSA [11]. This suggested that favourable outcome was associated with IgE-mediated responses and differences in prognosis were noted with different isocyanates, and it was confirmed that TDI had the worst prognosis.

We expanded our investigation by examining both serum-specific IgE and IgG antibodies to TDI-HSA conjugate in predicting long-term prognosis of TDI-asthma among subjects followed for more than 5 years [45]. Two groups of TDI-induced asthma patients were compared: group I, no improvement in airway hyper-responsiveness with persistent asthma during a 5-year follow-up period; group II, partial improvement in airway hyper-responsiveness with persistent symptoms. Although there were no significant differences in prevalence of specific IgE to TDI-HSA conjugate between groups ($P>0.05$), the prevalence of specific IgG tended to be higher in group I than in

the favourable prognostic group (group II, $0.05<P<0.1$). Moreover, the levels of specific IgG were significantly higher in group I than in group II, whereas levels of specific IgE were significantly higher in group II than in group I, which was comparable with another study [11]. When comparing clinical parameters according to long-term prognosis, no significant differences were noted in exposure duration, sex, age, atopic status or total IgE level. It confirmed that favourable outcome is related to a milder degree of airway hyper-responsiveness to methacholine at initial diagnosis. These results also suggested that high serum-specific IgG at initial diagnosis may be used as a poor prognostic factor in predicting persistent asthmatic symptoms.

Role of transforming growth factor- β_1 (TGF- β_1) in airway mucosa of TDI-induced asthma related to asthma symptoms

The underlying mechanism to explain the poor prognosis of TDI-induced asthma is still unknown. The expression of TGF- β_1 , which is an anti-inflammatory and fibrosing cytokine, is increased in the airway mucosa of bronchial asthma patients [46,47]. We applied immunohistochemistry with monoclonal antibodies to TGF- β_1 in bronchial mucosa from 22 subjects with TDI-induced asthma and compared the frequency and intensity of their expressions between the two groups (group I, 10 newly diagnosed patients; group II, 12 subjects with persistent asthma symptoms for more than 5 years after the diagnosis) [48]. Grade of TGF- β_1 expression in group II was significantly higher in the bronchial epithelium, vascular endothelium and smooth muscle than in those of group I (Fig. 5 and Fig. 6). When a second biopsy was performed after 5 years in the same patients in group II, TGF- β_1 expression was significantly increased. Significant correlations were noted between the duration of asthma after diagnosis and grade of TGF- β_1 expression in epithelium, vascular endothelium and smooth muscle. These findings suggest that TGF- β_1 may contribute to the development of chronic airway inflammation in TDI-induced asthma.

Conclusion

Recent investigations have added new insights into diisocyanate asthma, including: (i) the identification of diisocyanate-conjugated proteins that may act as antigens with individual differences; (ii) the pathogenic role of specific IgG as well as specific IgE, and their possible role in predicting long-term prognosis; and (iii) the potential involvement of neutrophil and epithelial cells in response to TDI exposure. As more than 50% of TDI-induced asthma patients had persistent asthmatic symptoms after complete avoidance, further studies will be needed to develop early diagnostic markers and clarify the underlying mechanism that causes persistent asthma symptoms.

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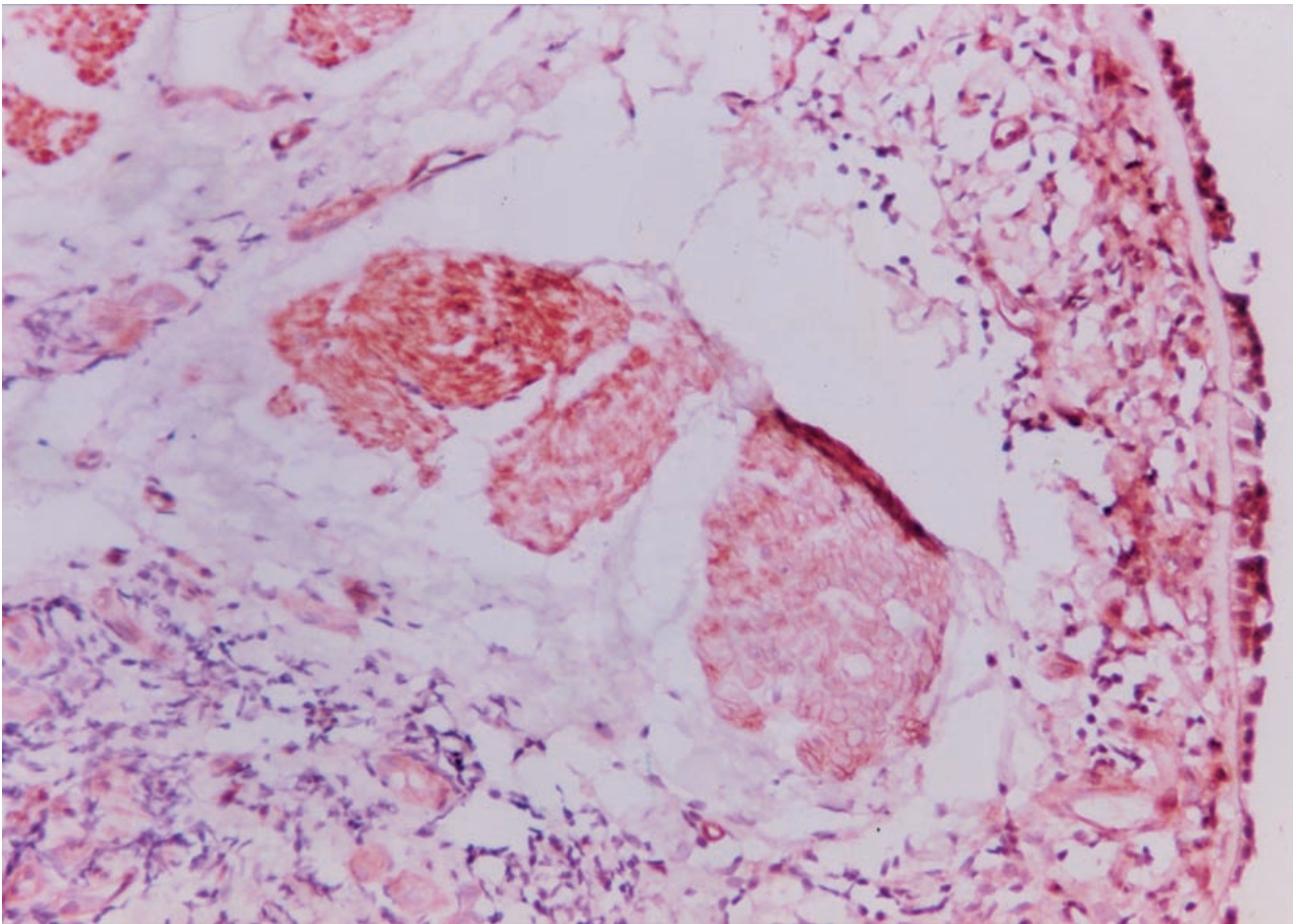


Fig. 5. Expression of TGF- β_1 in airway mucosa of a TDI-induced asthmatic subject that was collected 5 years later.

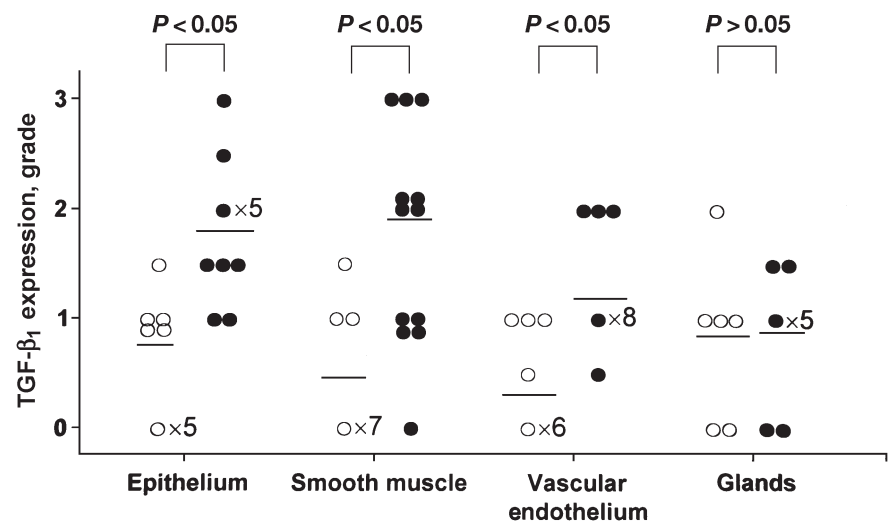


Fig. 6. Comparison of TGF- β_1 expression in airway mucosa of toluene diisocyanate (TDI)-induced asthmatic patients. Horizontal bars indicate mean values. ○=biopsy collected at initial diagnosis, ●=biopsy collected 5 years later. Statistical significances were noted in TGF- β_1 expression in epithelium, smooth muscle, vascular endothelium ($P < 0.05$, respectively).

References

- Bernstein DI, Bernstein IL. Occupational asthma. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW. Allergy: Principles and Practice, 5th edn. St Louis: Mosby, 1999: 963–80.
- Wisniewski AV, Redlich CA. Recent developments in diisocyanate asthma. *Curr Opin Allergy Clin Immunol* 2001; 1:169–75.
- Park HS, Nahm DH, Suh CH et al. Occupational asthma and IgE sensitization to grain dust. *Kor J Med Sci* 1998; 13:275–80.
- Kim HY, Park HS, Kim YG et al. Identification of IgE binding components of citrus red mite (CRM) in CRM-sensitive asthmatic patients. *J Allergy Clin Immunol* 2000; 107:344–8.
- Park HS, Kim MJ, Moon HB. Occupational asthma caused by two herb materials, *Dioscorea batatas* and *Pinellia ternate*. *Clin Exp Allergy* 1994; 24:575–81.
- Lee SK, Kim SS, Nahm DH, Park HS. Occupational asthma and rhinitis caused by multiple herbal agents in a pharmacist. *Ann Asthma Allergy Immunol* 2000; 86:469–74.
- Park HS, Nahm DH. Isocyanate-induced occupational asthma: challenge and immunologic studies. *J Korean Med Sci* 1996; 11:314–8.
- Karol MH, Loset HH, Alarie YC. Toly-specific IgE antibodies in workers with hypersensitivity to toluene diisocyanate. *Am Ind Hyg Assoc J* 1978; 39:454–8.
- Baur X, Dewier M, Fruhmman G. Detection of immunologically sensitized isocyanate workers by RAST and intracutaneous skin tests. *J Allergy Clin Immunol* 1984; 73:610–8.
- Tee RD, Cullinan P, Welch J, Buige PS, Newman-Taylor AJ. Specific IgE to isocyanates: a useful diagnostic role in occupational asthma. *J Allergy Clin Immunol* 1998; 101:709–15.
- Piirilä PL, Nordman H, Keskinen HM et al. Long-term follow-up of hexamethylene diisocyanate, diphenylmethane diisocyanate-, and toluene diisocyanate-induced asthma. *Am J Respir Crit Care Med* 2000; 162:516–22.
- Maestrelli P, Occari P, Turato G et al. Expression of interleukin (IL)-4 and IL-5 proteins in asthma induced by toluene diisocyanate (TDI). *Clin Exp Allergy* 1997; 27:1292–8.
- Son M, Lee M, Kim YT, Yoon JK, Park HS. Heterogeneity of IgE response to TDI-HSA conjugates by ELISA in toluene diisocyanate (TDI)-induced occupational asthma patients. *J Korean Med Sci* 1998; 13:147–52.
- Park HS, Kim HY, Suh JH et al. Diverse profiles of specific IgE response to toluene diisocyanate (TDI)-human serum albumin (HSA) conjugate in TDI-induced asthma patients. *J Kor Med Sci* 2000; 16:57–61.
- Park HS, Suh JH, Kim HY et al. Longitudinal study of specific antibodies to toluene diisocyanate (TDI) antibodies inpatients with TDI-induced asthma. *J Allergy Clin Immunol* 2000; 105:50S.
- Redlich CA, Stowe MH, Wisniewski AV et al. Subclinical immunologic and physiologic responses in hexamethylene diisocyanate-exposed autobody shop workers. *Am J Ind Med* 2001; 39:587–97.
- Park HS, Hong CS. The significance of specific IgG and IgG4 antibodies to a reactive dye in exposed workers. *Clin Exp Allergy* 1991; 21:357–62.
- Zock JPG, Doekes D, Heederik D, Van Zuylen M, Wielard P. Airborne dust antigen exposure and specific IgG response in the potato processing industry. *Clin Exp Allergy* 1996; 26:542–8.
- Yokata K, Yamaguchi K, Takeshita T, Morimoto K. The significance of specific IgG4 antibodies to methyltetrahydrophthalic anhydride in occupationally exposed subjects. *Clin Exp Allergy* 1998; 28:694–701.
- Cartier A, Grammer L, Malo JL et al. Specific serum antibodies against isocyanate: association with occupational asthma. *J Allergy Clin Immunol* 1989; 84:507–14.
- Aul DJ, Bhaumik A, Kennedy AL et al. Specific IgG response to monomeric and polymeric diphenylmethane diisocyanate conjugates in subjects with respiratory reactions to isocyanates. *J Allergy Clin Immunol* 1999; 107:749–55.
- Lushniak BD, Reh CM, Bernstein DI, Gallagher JS. Indirect assessment of 4,4'-diphenylmethane diisocyanate (MDI) exposure by evaluation of specific humoral immune responses to MDI conjugated to human serum albumin. *Am J Ind Med* 1998; 33:471–7.
- Park HS, Kim HY, Nahm DH, Son JW, Kim YY. Specific IgG, but not specific IgE, antibodies to toluene diisocyanate-human serum albumin conjugate are associated with toluene diisocyanate bronchoprovocation test results. *J Allergy Clin Immunol* 1999; 104:847–51.
- Bentley AM, Maestrelli P, Saetta LM et al. Activated T-lymphocytes and eosinophils in the bronchial mucosa in isocyanate-induced asthma. *J Allergy Clin Immunol* 1992; 89:821–8.
- Redlich CA, Karol MH, Graham C et al. Airway isocyanate-adducts in asthma induced by exposure to hexamethylene diisocyanate. *Scand J Work Environ Health* 1997; 23:227–31.
- Lee M, Park S, Park HS, Yoon JK. Cytokine secretion pattern of T cells responding to haptenized-human serum albumin in toluene diisocyanate-induced asthma patients. *J Korean Med Sci* 1998; 13:459–65.
- Lumms ZL, Alam R, Bernstein JA, Bernstein DI. Diisocyanate antigen-enhanced production of monocyte chemoattractant protein-1, IL-8, and tumor necrosis factor-alpha by peripheral mononuclear cells of workers with occupational asthma. *J Allergy Clin Immunol* 1998; 102:265–74.
- Park HS, Hwang SC, Nahm DH, Yim HE. Immunohistochemical characterization of cellular infiltrate in airway mucosa of toluene diisocyanate-induced asthma. *J Korean Med Sci* 1998; 13:12–6.
- Maestrelli P, Del Prete GF, De Carli M et al. CD8 T-cell clones producing interleukin-5 and interferon-gamma in bronchial mucosa of patients with asthma induced by toluene diisocyanate. *Scand J Work, Environ Health* 1994; 20:376–81.
- Del Prete GF, De Carli M, Maestrelli P et al. Allergen exposure induces the activation of allergen-specific Th2 cells in the airway mucosa of patients with allergic respiratory disorders. *Eur J Immunol* 1993; 23:1445–9.
- Fabbri LM, Boschetto P, Zocca E et al. Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. *Am Rev Respir Dis* 1987; 136:36–42.
- Park HS, Jung KS, Hwang SC, Nahm DH, Yim HE. Neutrophil infiltration and release of IL-8 in airway mucosa from subjects with grain dust-induced occupational asthma. *Clin Exp Allergy* 1998; 28:724–30.
- Park HS, Jung KS, Kim SS, Kim HY, Nahm DH. Neutrophil activation following TDI bronchial challenges to the airway secretion from subjects with TDI-induced asthma. *Clin Exp Allergy* 1999; 29:1395.
- Saite J, Banks DE, Lopez M, Barkman HW, Savagto JE. Neutrophil chemotactic activity in toluene diisocyanate (TDI)-induced asthma. *J Allergy Clin Immunol* 1990; 85:567–72.
- Wisniewski AV, Srivastava R, Herrick C et al. Identification of human lung and skin proteins conjugated with hexamethylene diisocyanate in vitro and in vivo. *Am J Respir Crit Care Med* 2000; 162:1–7.
- Lange RW, Day BW, Lemus R et al. Intracellular S-glutathionyl adducts in murine lung and human bronchoepithelial cells after exposure to diisocyanatotoluene. *Chem Res Toxicol* 1999; 12:931–6.
- Pauluhn J. Inhalation toxicity of 1,6-hexamethylene diisocyanate homopolymer (HDI-IC) aerosol: results of single inhalation exposure studies. *Toxicol Sci* 2000; 58:173–81.
- Pauluhn J. Acute inhalation toxicity of polymeric diphenyl-methane 4,4'-diisocyanate in rats: time course of changes in bronchoalveolar lavage. *Arch Toxicol* 2000; 74:257–69.

- 39 Pons F, Haag M, Corcos L et al. Inhalation of toluene diisocyanate affects cytochrome P450 2B1 expression in rat lung. *Arch Toxicol* 2000; 74:397–403.
- 40 Park HS, Suh JH, Kim HY, Nahm DH, Kwon OJ. Exposure to toluene diisocyanate (TDI) induces IL-8 and RANTES production from bronchial epithelial cells: its modulation by dexamethasone. *Allergy* 1999; 54:214.
- 41 Mapp CE, Chieura P, Marzo ND, Fabbri L. Persistent asthma due to isocyanate. *Am Rev Respir Dis* 1988; 137:1362–9.
- 42 Tarlo SM, Banks D, Liss G, Broder I. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. *Occup Environ Med* 1997; 54:756–61.
- 43 Lemiere C, Cartier A, Dolovich J et al. Outcome of specific bronchial responsiveness to occupational agents after removal from exposure. *Am J Respir Crit Care Med* 1996; 154:329–33.
- 44 Park HS, Nahm DH. Prognostic factors for toluene diisocyanate-induced occupational asthma after removal from exposure. *Clin Exp Allergy* 1997; 27:1145–50.
- 45 Park HS, Lee SK, Kim HY et al. Specific IgE and IgG antibodies to TDI-HSA conjugates: useful markers for predicting long term prognosis in toluene diisocyanate (TDI)-induced asthma. *J Allergy Clin Immunol* 2000; 105:50S.
- 46 Holgate STFRCP, Davies DE, Lackie PM et al. Epithelial–mesenchymal interactions in the pathogenesis of asthma. *J Allergy Clin Immunol* 2000; 105:193–204.
- 47 Vignola AM, Chanez P, Chiappara G et al. Transforming growth factor- β expression in mucosal biopsies in asthma and chronic bronchitis. *Am J Respir Crit Care Med* 1997; 156:591–9.