

The Usefulness of Job Relocation and Serum Eosinophil Cationic Protein in Baker's Asthma

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Key Words

Asthma · Occupational diseases · Eosinophil cationic protein

Abstract

Background: Although the most widely recommended treatment for occupational asthma is to completely avoid the causative agents, job relocation within the same company is often substituted for a complete career change. However, there is not much data on the efficacy of job relocation within the workplace and appropriate follow-up parameters. We investigated baker's asthma patients to validate the efficacy of job relocation and follow-up markers. **Methods:** Twelve bakery plant workers diagnosed with baker's asthma were enrolled in the study. Asthma-related symptoms and methacholine provocation test were followed up 6 months after a job relocation. Skin prick test and ELISA to detect wheat flour-specific IgE and eosinophil cationic protein (ECP) in sputum and serum were also followed up to evaluate the status of allergic inflammation. **Results:** After a 6-month job relocation, all 12 workers showed an improvement in symptoms, and airway hyperresponsiveness to methacholine was negatively converted in 9 of them. There

were no significant differences in skin reactivity and serum flour-specific IgE levels before and after the relocation. While sputum ECP levels did not show a significant difference ($338.3 \pm 93.0 \mu\text{g/l}$ vs. $175.0 \pm 78.9 \mu\text{g/l}$, $p = 0.118$), there was a remarkable difference in serum ECP levels before and after the relocation ($12.2 \pm 3.0 \mu\text{g/l}$ vs. $2.8 \pm 3.1 \mu\text{g/l}$, $p = 0.004$).

Conclusions: Job relocation was effective in managing baker's asthma. Serum ECP level was a useful follow-up marker of baker's asthma.

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Introduction

Baker's asthma can develop in association with the bread production process by bakery allergens, such as flour proteins and yeast [1, 2]. It is one of the most common types of occupational asthmas (OAs) and its annual incidence rate is 1–10 per 1,000 workers in the baking industry [2].

The most important treatment for OA is allergen avoidance [3]. Although a change in job is the most widely recommended solution for OA, it is not easily accepted by most workers. The existing evidence that removal

from exposure improves asthma symptoms and lung function compared to continued exposure is of very low quality [4]. Therefore, relocation within the workplace would be a more practical alternative for most patients in real practice.

However, current data are insufficient to prove the efficacy of job relocation within the workplace and to show the appropriateness of the follow-up parameters, especially for baker's asthma. We investigated 12 patients who had confirmed baker's asthma to estimate the efficacy of job relocation within the workplace and to compare various follow-up parameters, such as symptoms, lung function, hypersensitivity to methacholine, specific IgE to wheat flour and serum and sputum eosinophil cationic protein (ECP), in order to determine the most optimal and reliable follow-up measures.

Methods

The study subjects were 12 bakery-plant workers who had initially been diagnosed with baker's asthma on the basis of the wheat flour-specific bronchial provocation test [1]. They were advised to relocate to a less flour-exposed division within the same plant and were instructed to wear a dust-proof mask. Bakery sectors were classified into direct- or indirect-exposure areas by the level of exposure to flour dust as previously described [1]. In the direct-exposure sectors, workers handled flour directly including weighing, mixing, dough-making, fermenting, rolling and bread-forming while the indirect-exposure sectors consisted of panning, cooling, wrapping, inspection, mechanics and superintendence. We could not check the dust levels of individual sectors, but flour-dust-exposure level was 0.48–2.92 mg/m³ (n = 5) in the direct-exposure sectors of weighing, mixing and bread-forming. This exceeded the level of American Conference of Governmental Industrial Hygienist (ACGIH) Threshold Limit Values-Time Weighted Average of 0.5 mg/m³ in 80% [5]. Six months after relocation, we checked for symptoms, lung function, methacholine provocation test, serum-specific IgE to wheat flour and ECP levels in the serum and sputum. Symptoms were investigated initially and after 6 months with the International Study of Asthma and Allergies in Childhood (ISAAC), Korean version [6].

Nonspecific bronchial provocation test with methacholine was performed by the modified method of Chai et al. [7]. We used a nebulizer (DeVilbiss, Carlsbad, Calif., USA) to make an aerosol of saline and of methacholine. Patients inhaled saline or methacholine 5 times, and after 90 s, FEV₁ was measured with a dosimeter (Laboratory for Applied Immunology, Baltimore, Md., USA). Methacholine concentrations were 0.25, 0.625, 1, 4, 16, 25 mg/ml. Positive bronchial hyperresponsiveness (BHR) was defined as more than a 20% reduction in the FEV₁ from baseline below 25 mg/ml of methacholine.

We checked for specific IgEs to wheat flour antigens by skin prick test and ELISA to assess the change in sensitization to wheat flour antigens. For the skin prick test, we used three kinds of wheat flour antigen extracts (high-gluten flour, all-purpose flour, and

pastry flour) i.e. the same flour which is used in the bakery plant. The concentration of flour extracts was 1 mg/ml. An allergen/histamine (A/H) ratio higher than 1.0 was defined as positive. Wheat flour-specific IgEs were measured with ELISA [8]. A mixture of three wheat flour extracts was used. The cut-off value of the positive reaction was determined by the mean absorbance value of 47 control subjects who had no history of chronic respiratory symptoms or direct exposure to flour dust in the workplace.

For the measurements of serum and sputum ECP, separated serum and sputum induction and processing were used as previously described [9]. ImmunoCAP 250[®] (Phadia AB, Uppsala, Sweden) was used to measure ECP levels in the serum and sputum supernatant.

SPSS (version 19.0) was used to analyze the data. Data were expressed as the mean ± standard error. Differences between before and after the relocation in the variable tests were measured by paired t test. A p value of less than 0.05 was considered statistically significant.

In the Republic of Korea, a workplace which has a risk for the development of work-related asthma (WRA) has to be monitored by the Ministry of Employment and Labor. All the tests included in this study used for the evaluation of asthma status were performed as a part of regulatory surveillance for WRA in bakery plants but were not originally planned for research purposes. Therefore, this study did not require the formal approval of an Institutional Review Board. All the patients received information about the surveillance and the tests and gave their informed consent to participate.

Results

Twelve patients (referred to as patients A–L) were educated about allergen avoidance and it was recommended that they be relocated to an allergen-free or relatively hypoallergenic job in a different department or within the same division (table 1). Patients A–K were relocated to a relatively hypoallergenic job, and patient L had to quit, so he was no longer exposed to flour dust. Ultimately, 8 patients were relocated to different departments with less flour exposure, 3 were relocated to less dusty jobs within the same division and 1, patient L, took a leave of absence for personal reasons.

After relocation, all showed improvement in their symptoms: rhinorrhea, sneezing, cough and chest tightness. Nine of the 12 patients (75%) experienced no more symptoms and were not on medication. Three others (B, E and G) also had a remarkable improvement in their symptoms with maintenance of low-dose inhaled corticosteroid therapy only. There was no difference in the improvement with regard to the comorbid rhinitis symptoms.

In all 12 patients, there was no significant difference in the FEV₁ % predicted value between the period before and

Table 1. Changes in FEV₁ and PC₂₀ after job relocation

	Patients sex/number	Length of employment months	Initial job	Relocated job	FEV ₁ , liters		FEV ₁ , %		PC ₂₀ , mg/ml	
					initial	after relocation	initial	after relocation	initial	after relocation
A	M/28	13	mixing	bread-forming	4.06	4.08	104	105	2.26	9.82
B	M/27	65	mixing	fermenting	3.59	3.81	87	92	2.44	4.40
C	M/30	28	mixing	rolling	4.42	4.43	115	115	8.23	negative
D	M/39	25	mixing	mixing	3.74	3.68	102	101	12.4	negative
E	M/32	60	dough making	superintendence	3.83	3.7	101	98	1.06	6.49
F	F/54	237	bread forming	wrapping	2.59	2.63	120	123	9.07	negative
G	F/44	17	bread forming	wrapping	1.29	1.21	63	60	10.2	negative
H	F/28	55	bread forming	wrapping	2.92	3.04	98	102	19.4	negative
I	F/43	139	bread forming	wrapping	2.88	2.85	129	129	25.0	negative
J	F/20	17	wrapping	wrapping	3.02	3.3	93	101	4.59	negative
K	M/41	168	mechanic	mechanic	4.14	4.12	115	116	23.5	negative
L	M/23	59	management	leave of absence	4.63	4.81	106	111	negative ^a	negative

^a Patient L was diagnosed with baker's asthma by the wheat flour-specific provocation test.

that after the relocation ($102.8 \pm 5.0\%$ vs. $104.4 \pm 5.1\%$, $p = 0.117$). Among the 11 patients with initial methacholine hyperresponsiveness, 8 showed a negative conversion of methacholine hyperresponsiveness and 3 had a remarkable improvement in their PC₂₀ values (80.3–512.3%) after 6 months of having been relocated in their jobs (table 1).

The skin prick tests with wheat flour were performed on 11 patients. Patient G was on antihistamine medication and was unable to participate in the skin test. Differences between the A/H ratio before and after relocation were not statistically significant: high-gluten flour 1.34 ± 0.15 vs. 1.70 ± 0.19 ($p = 0.172$) all-purpose flour 1.33 ± 0.12 vs. 1.31 ± 0.20 ($p = 0.923$) and pastry flour 1.31 ± 0.17 vs. 1.56 ± 0.30 ($p = 0.474$) (fig. 1a–c). Serum wheat flour-specific IgE levels declined in 7 out of 12 patients and the postrelocation level did not show a significant decrease compared to the prerelocation level (0.27 ± 0.03 vs. 0.25 ± 0.03 , $p = 0.245$) (fig. 1d).

Sputum ECP levels (normal value 20–1280 µg/l [10]) were detected in a wide range from 23 to 909 µg/l, while serum ECP levels (normal value 2–20 µg/l [10]) were relatively low and were detected in a narrow range from 2.79 to 36.2 µg/l (fig. 2). Sputum ECP levels had decreased in 8 of the 12 patients 6 months after the relocation, but the difference was not statistically significant (338.3 ± 93.0 vs. 175.0 ± 78.9 µg/l, $p = 0.118$), while the serum ECP levels decreased in all of the 12 patients, with statistical significance (12.2 ± 3.0 vs. 2.8 ± 3.1 µg/l, $p = 0.004$).

Table 2. Skin sensitivity of patients

	Patients sex/number	Skin sensitivity to Dp	Skin sensitivity to Df	Skin sensitivity to flour	Specific IgE to flour
A	M/28	yes	yes	yes	no
B	M/27	yes	yes	yes	no
C	M/30	no	no	yes	no
D	M/39	yes	no	yes	yes
E	M/32	not done	not done	yes	yes
F	F/54	not done	not done	yes	yes
G	F/44	not done	not done	yes	no
H	F/28	yes	yes	yes	yes
I	F/43	yes	yes	no	yes
J	F/20	yes	yes	yes	no
K	M/41	not done	not done	yes	yes
L	M/23	yes	yes	yes	yes

Df = *Dermatophagoides farinae*; Dp = *Dermatophagoides pteronyssinus*.

Discussion

Baker's asthma is one of the most important OAs in the food industry [2]. Avoidance of the allergens that cause it constitutes the most fundamental treatment [3], but, in the real world, it is not easy for most patients to quit their job. Another choice is the relocation strategy, and this is relatively easier and is less of a burden on the workers [3].

Fig. 1. Changes in skin reactivity (mean of long axis and short axis) to three kinds of flour antigens: high-gluten flour (**a**), all-purpose flour (**b**), pastry flour (**c**) and serum-specific IgE to wheat flour (**d**) after job relocation. O.D. = Optical density.

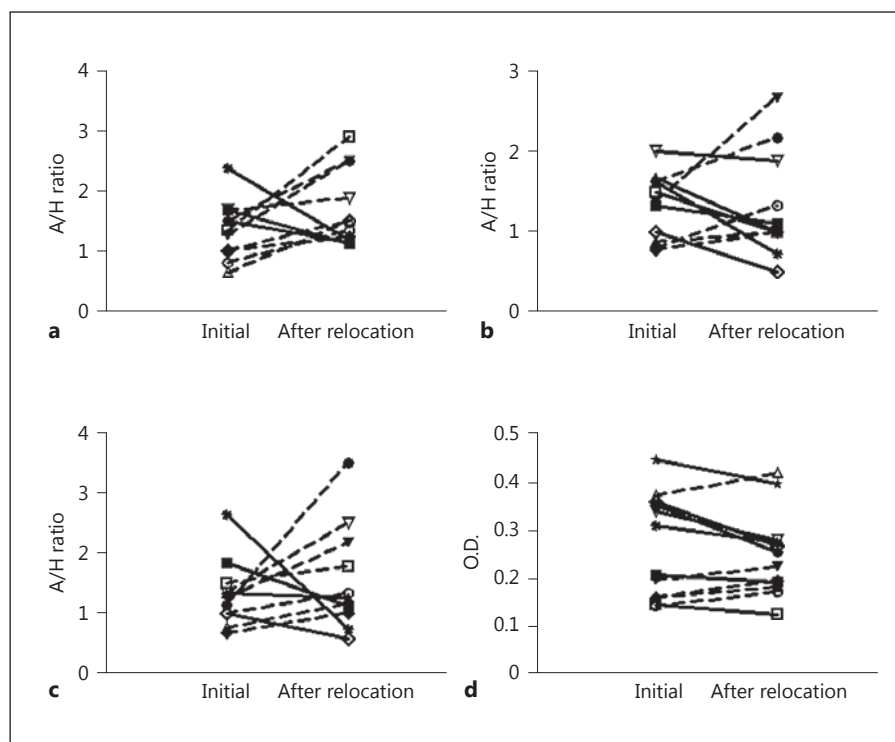
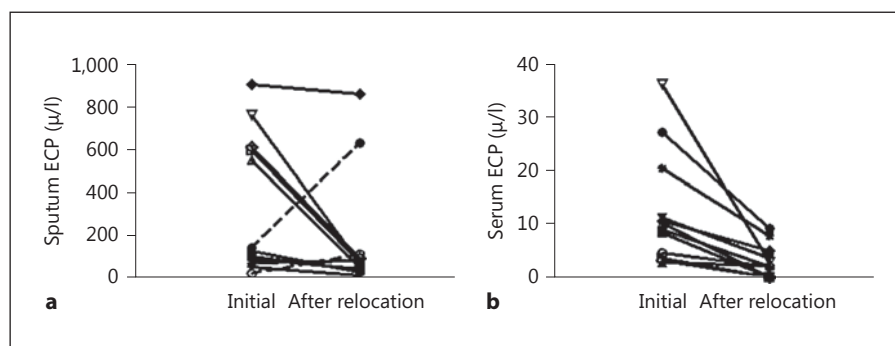


Fig. 2. Changes in ECP levels in the sputum (**a**) and serum (**b**) after job relocation.



Recent clinical practice guidelines presented that the reduction of exposure in OA could lead to an improvement in the asthma and could be considered as an alternative to complete avoidance [4, 11, 12]. However, a recent systematic review of management OA described that the likelihood of improvement and recovery of asthma symptoms was lower and risk of aggravation of symptoms was higher in the patients with exposure reduction compared to those with complete avoidance [13]. The review only compared the exposure-reduction group to the complete-avoidance group, but not to the full-exposure (or no-management) group, hence it did not fully reflect the effect of the exposure reduction method. Therefore, it is still curious that reduction of exposure would be effective for the

management of occupational asthmatics who could not completely avoid the allergens [13]. In a previous study, the wheat dust concentration was different in each sector. The wheat dust exposure level was as high as 3.04 mg/m^3 in the weighing, sieving and mixing departments, but only 1.16 mg/m^3 in the foaming, baking and decoration departments and as low as 0.01 mg/m^3 in the remaining areas other than the main production area [14]. Therefore, relocation to less dusty departments can be an effective therapeutic option without quitting the job, as seen in our study. It has also been reported that complete avoidance increases the risk of unemployment, but exposure reduction does not. We have to consider the risk of unemployment and clinical benefit of management [4].

Generally, follow-up methods of OA are restricted to mainly symptoms or lung function [13]. However, asthma symptoms or lung function are known as irrelevant markers in evaluating the inflammatory status of the airways [15]. Though PC₂₀ has also been used as a follow-up parameter comparing airway hyperresponsiveness before and after relocation [13, 16], the methacholine provocation test carries the risk of inducing asthma symptoms and the associated inconvenience for the patient. Furthermore, airway hyperresponsiveness does not always reflect airway inflammation and often persists, despite an improvement in clinical symptoms [16]. Recently, it was reported that the level of allergen sensitization measured by the skin test and ELISA was closely related to BHR and respiratory symptoms in baker's asthma [14, 17]. However, these associations were not observed in our study.

ECP is one of the inflammatory mediators, involved in the pathogenesis of asthma, which is released when eosinophils are activated [10]. ECP levels have revealed a correlation to asthma severity (symptom scoring, sputum eosinophils and FEV₁) as well as airway inflammation [10]. Some studies, however, have raised the issue that serum and sputum ECP levels in asthma patients do not reflect treatment-related changes [18].

Our study suggests that serum ECP levels have a role to play as a follow-up marker of baker's asthma. Although ECP was abundant in the sputum, its levels varied and it was less correlated with the improved BHR than with the serum ECP levels. Changes in serum ECP levels were the most compatible with improvement in symptoms or BHR among the follow-up measures used in this study.

This study has several limitations. First, the number of study subjects was limited and there were no data on serum and sputum eosinophils. Serum ECP should be validated in studies with larger number of subjects and with serum and sputum eosinophil count in the future.

Second, a direct comparison of airway hyperresponsiveness severity was unattainable because of a negative conversion of BHR to methacholine in some patients. Third, positive methacholine challenge test was defined as PC₂₀ <25 mg/ml. According to the American Thoracic Society (ATS) guidelines, PC₂₀ >16 mg/ml is defined as normal bronchial responsiveness and 4–16 mg/ml is defined as borderline BHR [19]. Although the positive standard we set in this study was higher than the recommended positive standard of PC₂₀ <8 or <16 mg/ml in the ATS guidelines, these guidelines also recommend the negative methacholine challenge result as a nonresponse to the highest concentration (PC₂₀ >8–25 mg/ml). Therefore, we used the widest and relaxed standard of positive results as PC₂₀ <25 mg/ml, because all of the patients included had asthma symptoms and the likelihood of asthma is affected by such a pretest probability. In addition, the exact wheat dust exposure level of each bakery sector was not monitored in the study. As mentioned earlier, the flour dust level exceeded the standard level in the direct sectors, and we know empirically that there was much less flour dust in the indirect sectors although this value was not measured exactly. Accurate daily monitoring of occupational dust should be implemented in a future study.

Through the findings of this study, we suggest that job relocation is clinically useful as a treatment modality of baker's asthma and that serum ECP levels have a role to play as a simple and optimal follow-up parameter of baker's asthma.

Acknowledgement

This study was supported by the Korean Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea, No. A102065.

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