



Contents lists available at ScienceDirect



Diagnosis and frequency of work-exacerbated asthma among bakers

Marta Wiszniewska, MD, PhD; and Jolanta Walusiak-Skorupa, MD, PhD

Department of Occupational Diseases, Nofer Institute of Occupational Medicine, Lodz, Poland

ARTICLE INFO

Article history:

Received for publication May 29, 2013.

Received in revised form August 2, 2013.

Accepted for publication August 12, 2013.

ABSTRACT

Background: Work-exacerbated asthma (WEA) is asthma worsened by workplace exposures, although the asthma is not caused by sensitizers in the work environment.

Objectives: To evaluate the frequency of WEA in bakers reporting work-related respiratory symptoms and the usefulness of diagnostic tests in differentiating WEA from occupational asthma (OA).

Methods: The study group included 393 bakers reporting respiratory symptoms at the workplace. In all patients, questionnaire, spirometry, skin prick tests (SPTs), and evaluation of serum total and specific IgE levels were performed. Recognition of OA was based on a specific inhalation challenge test.

Results: Occupational asthma was found in 44.5% of patients, whereas WEA was recognized in 16%. The latency period was 11.2 ± 8.2 years in patients with OA vs 13.3 ± 9.7 years in those with WEA. Sixty percent of patients with OA and 50.8% of those with WEA had positive SPT reactions to common allergens; occupational SPT results were positive in 74.9% and 34.9%, respectively. Specific IgE to flours were found in 61.7% of patients with OA and 28.6% of those with WEA. In addition, OA frequently coexisted with occupational rhinitis (53.7% of patients), whereas WEA and rhinitis were found in 31.7% of patients.

Conclusion: Work-exacerbated asthma was diagnosed in 16% of bakers who reported allergic respiratory symptoms. The specific challenge test for occupational allergens should be performed in bakers with suspected work-related asthma, because an assessment of sensitization (SPT to occupational allergens, evaluation of specific IgE) is not specific enough to differentiate OA from WEA.

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Exposure to flour and additive allergens can result in work-related respiratory symptoms in bakers. Conversely, irritants are the most frequently reported workplace exposures for those with history of work-exacerbated asthma (WEA). Different exposures at work can exacerbate asthma, although there are sparse data concerning bakers' environments and WEA.

Work-exacerbated asthma and occupational asthma (OA) represent important clinical problems. In addition, it is sometimes difficult to distinguish OA from WEA. OA and WEA are not mutually exclusive and may coexist in the same patient.

No generally accepted clinical and research definition and diagnostic criteria for WEA have been established. In the American College of Chest Physician consensus concerning work-related asthma (WRA), WEA was defined as asthma triggered by various work-related factors (eg, aeroallergens, irritants, or exercise) in workers who are known to have pre-existing or concurrent asthma

(ie, asthma that is occurring at the same time but is not caused by workplace exposures).¹ Other investigators have used the term WEA to describe the worsening of pre-existing or coincident (adult new-onset) asthma because of workplace environmental exposure.^{2,3} Similarly for Henneberger,⁴ WEA is the worsening of asthma attributable to workplace conditions, which occurs in people with asthma whose onset occurred before starting the suspected job (ie, pre-existing asthma) or while on the suspected job, but with onset not attributable to workplace conditions (ie, coincident or concurrent asthma). The working definitions for WEA and OA adopted in the present study were as follows. WEA was confirmed by documented baseline airflow obstruction and reversibility in forced vital capacity or forced expiratory volume in 1 second (FEV₁) greater than 12% or 0.2 L or bronchial hyper-reactivity to a histamine challenge with a provocation concentration that caused a decrease in FEV₁ of 20% lower than 8 mg/mL and a 20% decrease in FEV₁ or a 3-fold increase in nonspecific bronchial hyper-reactivity accompanied by at least 3% of sputum eosinophils that could not be found with work-associated allergen exposure performed as described in the "Methods" section. OA was confirmed by documented baseline airflow obstruction and reversibility in forced vital capacity or FEV₁ greater than 12% or 0.2 L or bronchial hyper-reactivity to a histamine challenge with a provocation concentration that caused a decrease in FEV₁ of 20%

Reprints: Marta Wiszniewska, MD, PhD, Department of Occupational Diseases, Nofer Institute of Occupational Medicine, 8 Teresy St., 91-348 Lodz, Poland; E-mail: martaz@imp.lodz.pl.

Disclosures: Diagnostic costs were covered by the Marshal's Office of the Poland Region (legal regulation).

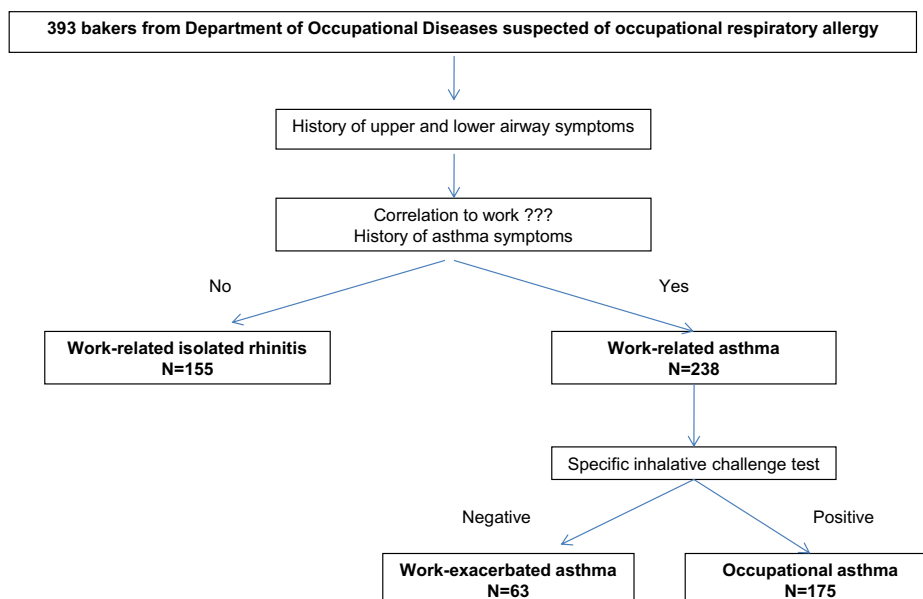


Figure 1. Study scheme.

lower than 8 mg/mL and a 20% decrease in FEV₁ or a 3-fold increase in nonspecific bronchial hyper-reactivity accompanied by at least 3% of sputum eosinophils that could be found with work-associated allergen exposure.

Because symptoms at work can be found in OA and in WEA, the essential point in WEA is that the disease has not been caused by sensitizers present in the workplace. To the authors' knowledge, detailed characteristics and assessments of sensitization to occupational allergens in bakers with WEA have never been performed.

The aim of the study was to evaluate the frequency of WEA in bakers reporting work-related respiratory symptoms and the usefulness of diagnostic tests in differentiating WEA from OA.

Methods

Patients

The study group included 393 bakers with suspected OA and/or allergic rhinitis caused by flours and additives who were diagnosed at the Department of Occupational Diseases, Nofer Institute of Occupational Medicine (Lodz, Poland) from 1997 through 2009. Of this group, 238 patients with a history of asthma (reporting work-related lower airway symptoms) were selected and underwent a histamine challenge test and a specific inhalation challenge test (SICT). After these procedures, OA was recognized in 175 cases and WEA was diagnosed in 63 bakers with asthmatic symptoms but with negative SICT result. One hundred fifty-five patients who did not exhibit asthma symptoms were not considered in the analysis of the data. The study scheme is presented in Figure 1.

The regional bioethical committee approved the study protocol. All participants gave their informed written consent before the study.

Questionnaire

The patients were administered a questionnaire that was an adaptation of the instrument developed by the International Union against Tuberculosis and Lung Disease.⁵ Among other items, it included a history of respiratory symptoms (ie, cough, wheezing, shortness of breath, chest tightness), skin symptoms, personal and family histories of atopy, exposure to pet allergens at home, medication use, and smoking habits.

Skin Prick Tests

Skin prick tests (SPTs) were performed on the volar part of the forearm using a standard battery of common allergens and bakery series, including tree and grass pollens, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, molds, weeds, oatmeal, wheat, corn, barley, and rye flour (Allergopharma, Reinbek, Germany). The negative control was an allergen diluent and the positive control was 1 mg/mL of a histamine dihydrochloride solution. The largest wheal diameter was assessed after 15 minutes. A wheal diameter of at least 3 mm and at least half that formed by histamine was defined as a positive result indicating sensitization.

Total and Specific IgE

Total serum IgE was evaluated using ImmunoCap (Phadia AB, Uppsala, Sweden). A total IgE level higher than 100 kU/L was considered elevated. Specific IgE (sIgE) reactions against flours were measured using ImmunoCap (fx20 or f4; Phadia AB). Specific IgE levels of at least 0.35 kU/L were regarded as a positive result.

Specific Inhalation Challenge Tests

The SICT with flours (eg, oatmeal, corn, barley, and rye flour) and improvers (eg, containing α -amylase or xylanolytic enzymes, which are used to improve the quality of baking products and economize the technologic process) was performed in a workplace simulation setting (room space 6 m² with temperature 22–25°C) with the patient's own samples. The patient sifted approximately 500 g of flours and improvers for 30 minutes or until the asthmatic reaction symptoms appeared. Potato flour was used as placebo and the test was performed on the previous day before the specific challenge.

Bakers who did not exhibit a significant ($\geq 20\%$) decrease in FEV₁ during the challenge test underwent a repeated challenge test for 2 hours the next day. In patients with changes in FEV₁ ranging from 10% to 20% after that challenge, the exposure was prolonged to 3 hours.

The study participants did not receive any systemic or local medication. Inhaled short-acting β_2 -agonists were stopped at least 8 hours before the study, inhaled long-acting β_2 -agonists 48 hours before the study, inhaled steroids 5 days before the study, systemic steroids 14 days before the study, and antihistamine medications 7

Table 1

Characteristics of patients with OA (n = 175) and WEA (n = 63) in study

	OA (n = 175)	WEA (n = 63)	P value
Men, n (%)	154 (88)	41 (65.1)	.0001
Age (y), mean $\pm$ SD (min; max)	37.76 $\pm$ 11.64 (18; 68)	40.6 $\pm$ 11.87 (20; 70)	NS
Family history of atopy, n (%)	44 (25.1)	11 (17.5)	NS
Smoking status, n (%)			
Active smokers	31 (17.7)	14 (22.2)	NS
Ex-smokers	60 (34.3)	18 (28.6)	NS
Total pack-years of smoking, mean $\pm$ SD (min; max)	13.4 $\pm$ 9.4 (2; 30)	13.8 $\pm$ 9.2 (3; 30)	NS
Pets at home, n (%)	42 (24)	12 (19)	NS
Age at clinical asthma symptom onset (y), mean $\pm$ SD (min; max)	30.8 $\pm$ 9.6 (16; 54)	32.3 $\pm$ 10.5 (5; 59)	NS
Baseline FVC (% predicted), mean $\pm$ SD (min; max)	92.7 $\pm$ 17.1 (31; 136)	93.9 $\pm$ 15.9 (42; 122)	NS
Baseline FEV ₁ (% predicted), mean $\pm$ SD (min; max)	86.9 $\pm$ 18.2 (23; 136)	87.9 $\pm$ 19.9 (26; 121)	NS
Baseline histamine PC ₂₀ (mg/mL), mean $\pm$ SD (min; max)	3.5 $\pm$ 4.4 (0.08; 16)	4.4 $\pm$ 3.4 (0.15; 8)	NS
Baseline change in FEV ₁ after albuterol (%), mean $\pm$ SD (min; max)	16.8 $\pm$ 6.8 (9; 38)	18.7 $\pm$ 8.1 (12; 37)	NS

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; max, maximum; min, minimum; NS, not statistically significant; OA, occupational asthma; PC₂₀, provocation concentration that causes a decrease in forced expiratory volume in 1 second of 20%; SD, standard deviation; WEA, work-exacerbated asthma.

to 42 days before the challenge test depending on the duration of action. The patient's oral statement determined compliance with such recommendations.

Pulmonary Function

Resting spirometry (Vicat 2A, Mijnhardt, The Netherlands) was performed in all patients. Bronchial response was measured by serial monitoring of FEV₁ and peak expiratory flow rate before and 5 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, and 24 hours after the provocation.

Histamine challenge was performed according to the method of Cockcroft.⁶ Bronchial response was measured by FEV₁ monitoring. Nonspecific bronchial hyper-reactivity was evaluated the day before the specific challenge test and 24 hours after the test.

Symptom Score

The number of sneezes and the degree of mucosal edema, rhinorrhea, and itching were evaluated. Total symptom score ranged from 0 to 8 and represented the sum of scores for sneezing (0 sneeze, 0 point; 1–4 sneezes, 1 point; >4 sneezes, 2 points), rhinorrhea (none, 0 point; mild, 1 point; abundant, 2 points), mucosal edema (none, 0 point; mild, 1 point; nasal block, 2 points), and itching (none, 0 point; itching of nose or throat, 1 point; itching of nose and throat, 2 points).

Nasal Lavage and Challenge Procedure

All procedures were performed according to the "nasal pool" method.⁷ Nasal washings were collected immediately before the

provocation and 30 minutes, 4 hours, and 24 hours afterward. The washing process has been described in detail elsewhere.⁸

Diagnostic Criteria

Occupational allergic rhinitis was recognized in patients reporting work-related nasal symptoms with a positive nasal response to provocation testing, namely a total score higher than 3 points and significant increases in the total count and proportion of eosinophils (2-fold increase and eosinophilia $\geq 5\%$ after the challenge) in nasal lavage fluid.

Recognition of OA was based on the SICT result with an evaluation of bronchial response ($\geq 20\%$ decrease in FEV₁) or a 3-fold increase in nonspecific bronchial hyper-reactivity accompanied by increased sputum eosinophilia ($\geq 3\%$ of eosinophils after the SICT).

Work-exacerbated asthma was recognized in patients reporting work-related chest symptoms for whom the SICT did not induce a significant bronchial response ($\geq 20\%$ decrease in FEV₁), namely early or dual asthmatic reaction or a 3-fold increase in nonspecific bronchial hyper-reactivity accompanied by increased sputum eosinophilia.

Statistical Analysis

Analyses were performed using STATISTICA 8 (StatSoft, Krakow, Poland). The χ^2 test (or Fisher exact test) and Wilcoxon rank-sum were used to compare patients with OA vs WEA. A *P* value lower than .05 was considered significant.

Results

The group under study consisted of 195 men and 43 women. Baseline characteristics are presented in Table 1. Rates of reported symptoms are presented in Table 2. In patients with OA, the latency period (duration of exposure before the occurrence of symptoms) was 11.21 $\pm$ 8.16 years and the duration of those symptoms was 6.94 $\pm$ 6.63 years; in patients with WEA, these mean periods were longer.

The SPT results to common and occupational allergens are presented in Table 3. In bakers with OA, the most frequent allergens yielding positive results were *D pteronyssinus*, *D farinae*, and grass pollens, whereas those in the WEA group were dust mite allergens. Sensitization to grass and tree pollens was more frequent in patients with OA (22.9%, 18.3%, and 17.1% respectively) than in those in WEA (9.5%, *P* = .005; 3.2%, *P* = .003; and 6.4%, *P* = .037, respectively). Obviously, sensitization to the tested flours was more frequently associated with OA (74.9%) than with WEA (34.9%, *P* < .0001); however, more than 30% of patients without recognized OA were sensitized to allergens present in the workplace. SPT results for occupational allergens in the 2 groups showed the most

Table 2

Prevalence and duration of reported symptoms in the study population

Reported symptoms	OA (n = 175)	WEA (n = 63)	P value
≥ 1 allergic symptom, n (%)	175 (100)	63 (100)	—
Cough	134 (76.6)	46 (73)	NS
Dyspnea	173 (98.9)	59 (93.7)	.044
Rhinitis	149 (85.1)	45 (71.4)	.027
Skin symptoms, n (%)	24 (13.7)	11 (17.5)	NS
Duration of symptoms (y), mean $\pm$ SD (min; max)	6.94 $\pm$ 6.63 (0.5; 38)	8.25 $\pm$ 7.4 (1; 36)	NS
Latency period (duration of exposure before occurrence of symptoms) (y), mean $\pm$ SD (min; max)	11.21 $\pm$ 8.16 (0.1; 36)	13.31 $\pm$ 9.7 (0.1; 37)	NS

Abbreviations: max, maximum; min, minimum; NS, not statistically significant; OA, occupational asthma; SD, standard deviation; WEA, work-exacerbated asthma.

Table 3

SPT results for common and occupational allergens and evaluation of total and specific IgE levels in study population

Positive SPT results	OA (n = 175)	WEA (n = 63)	P value
≥1 common allergen, n (%)	105 (60)	32 (50.8)	NS
Grass pollen	40 (22.9)	6 (9.5)	.035
Tree pollen I ^a	32 (18.3)	2 (3.2)	.006
Tree pollen II ^b	30 (17.1)	4 (6.4)	.036
Mold I ^c	9 (5.1)	2 (3.2)	NS
Mold II ^d	1 (0.6)	1 (1.6)	NS
<i>Dermatophagoides pteronyssinus</i>	48 (27.4)	18 (28.6)	NS
<i>Dermatophagoides farinae</i>	42 (24)	15 (23.8)	NS
Weeds	23 (13.1)	6 (9.5)	NS
≥1 occupational allergen, n (%)	131 (74.9)	22 (34.9)	<.0001
Wheat flour	76 (43.4)	10 (15.9)	.0001
Rye flour	82 (46.9)	7 (11.1)	<.0001
Corn flour	37 (21.1)	5 (1.9)	.030
Oatmeal flour	40 (22.9)	1 (1.6)	<.0001
Barley flour	59 (33.7)	5 (7.9)	<.0001
Total IgE level (kU/L), mean ± SD (min; max)	331.84 ± 469.8 (28; 4,000)	209.54 ± 133.9 (47; 1,000)	.004
Total IgE >100 kU/L, n (%)	91 (52)	26 (41.3)	NS
Specific IgE to flours, n (%)	108 (61.7)	18 (28.6)	<.0001

Abbreviations: max, maximum; min, minimum; NS, not statistically significant; OA, occupational asthma; SD, standard deviation; SPT, skin prick test; WEA, work-exacerbated asthma.

^aAlder, hazel, poplar, elm, and willow.

^bBirch, beech, oak, and plane.

^c*Alternaria tenuis*, *Botrytis cinerea*, *Cladosporium herbarum*, *Culvularia lunata*, *Helminthosporium* species, and *Fusarium moniliforme*.

^d*Aspergillus fumigatus*, *Mucor mucedo*, *Penicillium notatum*, *Pullularia pullulans*, *Rhizopus nigricans*, and *Serpula lacrimans*.

frequent positive results were for wheat and rye flour. Average total IgE level was elevated in the 2 groups and a significant percentage of patients with IgE levels higher than 100 kU/L was found. Specific IgE to flours were found in 61.7% of patients with OA and in 28.6% of those with WEA ($P < .0001$).

Almost 54% patients with OA had accompanying occupational rhinitis; however, of patients with WEA, rhinitis was recognized in 31.7% cases.

Discussion

Recent published reviews of literature on WRA have emphasized the need for further research on different topics related to WEA, including diagnostic techniques. Distinguishing OA from WEA with symptoms from irritant substances is essential during the diagnostic process because the final diagnostic result for a patient has important health and socioeconomic consequences (eg, removal from a job, need for retraining, financial compensation). For legal purposes, in some countries, including Poland, it is essential to confirm whether the asthma is caused by workplace agents, because diagnosis of an occupational respiratory allergy results in significant compensation for an employee. Objective testing is useful, especially in patients claiming compensation. Few studies have compared WEA with OA in different work settings, and there is a lack of clinical data concerning WEA in bakers.

It has been emphasized that WEA is highly prevalent and underdiagnosed.⁹ The diagnosis of WEA usually is based on changes in symptoms, medication use, and/or lung function temporally related to work.¹ In most epidemiologic studies on WEA, the diagnosis was mainly based on questionnaire and medical records and less frequently on clinical tests conducted by researchers.^{10–13} Because the diagnosis of WRA requires confirmation of asthma and the establishment of a relation to work,¹ the bakers in the present study were examined by physicians using questionnaire and pulmonary function testing, and then SICT was performed to distinguish OA from WEA. Similarly, in some other clinical studies, the most reliable diagnosis of WEA was established from SICT results.^{14–16}

It has been estimated that about 20% of adults with asthma exhibit worsening of their symptoms at work⁴; however, about

a half of them show no objective evidence of asthma worsening during a challenge test.¹⁷ The true prevalence of WEA is not established and the proportion of patients with WEA ranges from about 10% to 50% of cases of WRA in working adults.^{1,18,19} In the present study, WEA was recognized in 26.5% of bakers with WRA after applying diagnostic procedures, including SICT. Moreover, Moscato et al²⁰ concluded that a definite WEA diagnosis should be based on “objective indicators” of worsening of asthma and of deterioration of pulmonary function related to the work environment. In addition, if there is documented exposure to sensitizing agents, the SICT should be performed. For example in a study by Santos et al,²¹ objective tests in the diagnosis of WRA were more common in patients with OA than in those with WEA. The most common tests performed in patients with OA were serial peak expiratory flow recordings at work and off work (58%), repeat methacholine challenges during work and off-work periods (49%), and skin tests using a work agent (29%), and only 2 patients underwent an SICT.

Work-exacerbated asthma refers most often to coincidental or concurrent asthma aggravated or exacerbated at work.²¹ In contrast, some investigators have restricted the term to a previously diagnosed asthma that has worsened, but was not caused, by agents found in the workplace.²² In the present study, all included patients reported the onset of asthma symptoms after starting their exposure to baker's allergens; however, it is difficult to establish whether they might have had asthma as a child or in the distant past and might have declared the later symptoms after starting to work, because of legal regulations in recognizing OA in Poland. In the present study, in patients with WEA, symptoms began while they were working as bakers; however, owing to the SICT results, they were not diagnosed as having OA even when specific sensitization to occupational allergens was found.

Comparison of baseline characteristics of patients with OA and WEA showed no statistically significant differences except for male sex. Similarly to Santos et al,²¹ OA was recognized more frequently in men. This finding was not observed in the study by Chiry et al,¹⁶ although they examined a smaller study group exposed to heterogeneous occupational agents.

Work-related respiratory symptoms in bakery workers ranges from 4.9% to 14.3%, although a positive SPT result to flour allergens

has been found in 5% to 28% of patients.^{23–25} In the present study, all included bakers reported work-related symptoms; nevertheless, dyspnea and rhinitis were found more frequently in patients with OA. In a study by Meijer et al²⁶ in bakers with OA or WEA, work-related rhinitis and/or conjunctivitis were reported in most cases (85%). Nasal symptoms usually precede or coexist with asthma, especially in cases of OA induced by high-molecular-weight allergens.²⁷ Aggravation of asthma in the workplace can manifest as an increase in frequency or severity of asthma symptoms and/or increase in medication required to control symptoms on working days in patients with OA and those with WEA.² It has been established that patients who experience exacerbation of asthma symptoms at work do not present significant objective evidence of worsening asthma when they are exposed to a suspected work-sensitizing agent at nonirritating levels and monitored in the workplace or laboratory.^{2,28}

In the present study, a positive SPT reaction to at least 1 common allergen and a family history of atopy were similar in frequency in the study groups, although sensitization to grass and tree pollens was more frequent in patients with OA, in contrast to the report by Lemiere et al¹⁴ in which atopy was more common in OA (87%) than in WEA (74%) cases.

It is widely acknowledged that in bakers with suspected OA, IgE antibodies to occupational allergens can be detected by analyzing circulating IgE levels and SPT. In general, in immunologic tests, high-molecular-weight substances display a high sensitivity. However, the diagnostic sensitivity and specificity of SPT extracts to wheat and rye flours range from 40% to 67% and 86% to 100%, respectively, for a diagnosis of baker's asthma.²⁹ High serum levels of flour-specific IgE and confirmed positive SPT results for flour extract have been shown to be good predictors of a positive challenge test result in 107 bakers.³⁰ Based on this observation, the authors suggest that challenge tests may not always be necessary in cases displaying a clear SPT result and a serologically sIgE response. Similarly, Malo et al³¹ found a significant correlation between SPT results and sIgE antibodies to wheat flour with the presence of OA. Positive SPT results to flours were found in 50% of atopic bakers with asthma, 21% of atopic bakers, and 13% of nonatopic bakers.²⁵ In a study by Jacobs et al,³² 46% of bakery workers with asthma were IgE sensitized to wheat allergens, emphasizing the importance of occupational exposure in bakery workers with asthma. In the present study, sensitization to flours was certainly associated with OA; however, 34.9% of patients with WEA were sensitized to occupational allergens. Nevertheless, demonstrating skin sensitization to workplace agents supports the possibility of airway sensitization, but, according to the present results, a significant proportion of patients with positive SPT results to bakery occupational allergens most likely developed a concomitant sensitivity to these workplace agents. Another explanation for the high prevalence of specific sensitization in bakers with WEA is cross-reactivity with other allergens (eg, pollens). This finding indicates practical limitations for identifying OA in patients with a positive SPT response to occupational bakery allergens and a history of asthma without using other objective diagnostic methods.

For OA caused by high-molecular-weight agents, evidence of specific sensitization (positive SPT result and/or presence of sIgE) associated with a suggestive history is not enough for a diagnosis of allergic OA to the given agent. The diagnosis requires objective confirmation of asthma and work-related functional changes, a suggestive history, and exposure to an agent known to cause OA.³³ In general, the SICT has been proposed as the "gold standard" or reference test in the diagnosis of OA related to specific sensitization.³³ SICT has not been recommended for routine use because of the high cost, limited availability, potential risk of inducing severe asthmatic reactions, and possible false-positive and false-negative results.³⁴ One crucial issue in the present study was the possibility

of false-negative SICT results, especially because all bakers apparently developed asthma after starting work. In OA, false-negative test results can occur as a result of using the wrong agent or too low a dose.³⁴ In the present study, the employers were asked to provide samples of the same flours used by the patient; however, in single cases, the supplied samples may have differed from those originally used at the workplace. Although wheat flour is the most common sensitizing agent in Polish bakers, during SICT, all types of flours used by the patients were tested (eg, oatmeal, corn, barley, and rye flour). In addition, if some bakers used other powdered foods, such as powdered eggs or milk, then they were tested before deciding that challenge results were negative. Unfortunately, dust concentrations were not measured during the challenges in all cases; however, because the patients re-created their workplace conditions, the authors concluded that the concentrations were high enough. Moreover, concentrations of other chemical or allergen exposures (eg, cleaning agents, degreasers used for machinery, allergens from nuts used for baking, etc) were not measured.

The authors also identified (by self-report) patients who did not stop bronchodilator or steroid treatment, so some may have used these medications before the challenges, which may have been related to false-negative results. However, in the authors' opinion, the patients likely were honest in declaring their medicine use because they had no motive to try to obtain a negative challenge result after claiming compensation. Moreover, some patients had normalization of their nonspecific bronchial reactivity after removal from the workplace exposure. In the present study, repeated and prolonged challenge tests were performed the next day to re-expose patients to the occupational agent and determine significant decreases in FEV₁ or increases in nonspecific bronchial hyper-reactivity in sensitized patients. In contrast, Lemiere et al³⁵ concluded that specific bronchial reactivity to high-molecular-weight agents persists in most cases despite normalization of nonspecific bronchial reactivity, and that is associated with the persistence of specific immunization. In patients with negative SICT results in the laboratory, a return to the normal workplace to maximally extend the diagnostic testing was impossible because Polish legal regulations preclude employees from returning to work before establishing or excluding a final diagnosis of OA. In addition, Moscato et al³³ emphasized that the prevalence of false-negative test results has not been assessed prospectively by returning the worker to the workplace and examining changes in functional status.

It has been pointed out that SICTs are not useful in diagnosing WEA.¹ In this study, the SICT was monitored by histamine airway responsiveness and sputum differential eosinophil counts. Beach et al³⁶ compared available procedures in the diagnosis of OA and found that none of the tests used alone yields a sufficiently high combination of sensitivity and specificity that would allow it to replace SICT. Nevertheless, a combination of the presence of nonspecific bronchial hyper-responsiveness and positive results of immunologic tests has been shown to increase the likelihood of OA.³⁴ Therefore, the diagnosis should be made carefully considering the present study results. There is no consensus as to which method should be used to distinguish patients with occupational airway allergy from those with WEA. Tarlo and Liss³⁷ included negative responses to challenges with specific sensitizing agents from the workplace and negative responses to workplace sensitizers in immunologic tests among the features used to classify patients as having aggravation of pre-existing or coincidental asthma. Previous clinical studies also have indicated that the visual interpretation of peak expiratory flow graphs do not allow an accurate differentiation between OA and WEA.¹⁶ It might be claimed that patients with WEA, especially those sensitized to occupational allergens, may have been misclassified and actually had OA. Although possible, the diagnostic procedures performed

during this study were extensive and, in the authors' opinion, the misclassification is unlikely.

Vandenplas et al.³⁸ showed that sputum eosinophilia is an early marker of bronchial response to occupational agents, whereas patients with WEA show neutrophilic airway inflammation when exposed to a specific agent at the workplace.³⁹ In the present study, increased sputum eosinophilia was one of the essential criteria to recognize OA; unfortunately, changes in neutrophils were not assessed.

There are only few data concerning the potential role of food allergy as the mechanism of sensitization in bakers. In the present study, no patient reported intolerance after ingestion of food products containing baker's occupational allergens. However, wheat α -amylase inhibitor has been reported to be a relevant sensitizing allergen after ingestion and inhalation.⁴⁰ In a study by Baur and Posch,⁴¹ patients with baker's asthma and rhinitis usually were able to consume wheat without symptoms, although they showed reactions to wheat proteins. Tatham and Shewry⁴² suggested there is little doubt if the most important components responsible for baker's asthma (α -amylase) appear to be less important in food allergy, whereas wheat proteins, despite contributing to respiratory and food allergies, appear to be minor contributors and their clinical relevance requires further study.

In conclusion, WEA was recognized in 16% of bakers reporting allergic respiratory symptoms and in 26.6% reporting work-related lower airway symptoms. The study has practical implications and clinical relevance. These findings suggest the need for performing SICTs when OA is suspected in bakery workers, because assessment of sensitization (SPTs to occupational bakery allergens, evaluation of serum sIgE) is not specific enough to differentiate OA from WEA.

Acknowledgments

The authors thank Susan M. Tarlo for reviewing the manuscript.

References

- [1] Tarlo SM, Balmes J, Balkissoon R, et al. Diagnosis and management of work-related asthma: American College Of Chest Physicians consensus statement. *Chest*. 2008;134:1–41 (erratum *Chest*. 2008;134:892).
- [2] Bernstein L, Bernstein DI, Chan-Yeung M, Malo JL. Definition and classification of asthma in the workplace. In: Bernstein D, Chan-Yeung M, Malo JL, Bernstein IL, eds. *Asthma in Workplace*. New York: Marcel Dekker; 2006:1–8.
- [3] Vandenplas O, Malo JL. Definitions and types of work-related asthma: a nosological approach. *Eur Respir J*. 2003;21:706–712.
- [4] Henneberger PK. Work-exacerbated asthma. *Curr Opin Allergy Clin Immunol*. 2007;7:146–151.
- [5] Burney PG, Laitinen LA, Perdrizet S, et al. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. *Eur Respir J*. 1989;2:940–945.
- [6] Cockcroft DW. Bronchial reactivity to histamine: a method and clinical survey. *Clin Allergy*. 1977;7:503–512.
- [7] Greiff L, Pipkorn U, Alkner U, Persson CG. The 'nasal pool' device applies controlled concentrations of solution on human nasal airway mucosa and samples its surface exudations and secretions. *Clin Exp Allergy*. 1990;20:253–259.
- [8] Pałczyński C, Walusiak J, Ruta U, Górski P. Nasal provocation test in the diagnosis of natural rubber latex allergy. *Allergy*. 2000;55:34–41.
- [9] Smith AM, Bernstein DI. Management of work-related asthma. *J Allergy Clin Immunol*. 2009;123:551–557.
- [10] Henneberger PK, Derk SJ, Sama SR, et al. The frequency of workplace exacerbation among health maintenance organisation members with asthma. *Occup Environ Med*. 2006;63:551–557.
- [11] Henneberger PK, Deprez RD, Asdigian N, Oliver LC, Derk S, Goe SK. Workplace exacerbation of asthma symptoms: findings from a population-based study in Maine. *Arch Environ Health*. 2003;58:781–788.
- [12] Curwick CC, Bonauto DK, Adams DA. Use of objective testing in the diagnosis of work-related asthma by physician specialty. *Ann Allergy Asthma Immunol*. 2006;97:546–550.
- [13] Caldeira RD, Bettiol H, Barbieri MA, Terra-Filho J, Garcia CA, Vianna EO. Prevalence and risk factors for work related asthma in young adults. *Occup Environ Med*. 2006;63:694–699.
- [14] Lemiere C, Arbour K, Teolis L, Chaboillez S. Occupational asthma and work-aggravated asthma: similarities and differences. *Proc Am Thorac Soc*. 2006;3:A251.
- [15] Lemiere C, Forget A, Dufour MH, Boulet LP, Blais L. Characteristics and medical resource use of asthmatic subjects with and without work-related asthma. *J Allergy Clin Immunol*. 2007;120:1354–1359.
- [16] Chiry S, Cartier A, Malo JL, Tarlo SM, Lemièrre C. Comparison of peak expiratory flow variability between workers with work-exacerbated asthma and occupational asthma. *Chest*. 2007;132:483–488.
- [17] Vandenplas O, Ghezzi H, Munoz X, et al. What are the questionnaire items most useful in identifying subjects with occupational asthma? *Eur Respir J*. 2005;26:1056–1063.
- [18] Tarlo SM, Liss G, Corey P, Broder I. A workers' compensation claim population for occupational asthma: comparison of subgroups. *Chest*. 1995;107:634–641.
- [19] Henneberger P, Redlich C. Work-exacerbated asthma. In: Sigsgaard T, Heederik D, eds. *Occupational Asthma*. Basel: Birkhauser/Springer AG; 2010:89–100.
- [20] Moscato G, Pala G, Barnig C, et al. European Academy of Allergy and Clinical Immunology. EAACI consensus statement for investigation of work-related asthma in non-specialized centres. *Allergy*. 2012;67:491–501.
- [21] Santos MS, Jung H, Peyrovi J, Lou W, Liss GM, Tarlo SM. Occupational asthma and work-exacerbated asthma: factors associated with time to diagnostic steps. *Chest*. 2007;131:1768–1775.
- [22] Kenyon N, Morrissey B, Schivo M, Albertson T. Occupational asthma. In: Gershwin ME, Albertson T, eds. *Bronchial Asthma. A Guide for Practical Understanding and Treatment*. New York: Springer/Dordrecht: Heidelberg; 2011:285–302.
- [23] De Zotti R, Larese F, Bovenzi M, Negro C, Molinari S. Allergic airway disease in Italian bakers and pastry makers. *Occup Environ Med*. 1994;51:548–552.
- [24] Cullinan P, Lowson D, Nieuwenhuijsen MJ, et al. Work related symptoms, sensitisation, and estimated exposure in workers not previously exposed to flour. *Occup Environ Med*. 1994;51:579–583.
- [25] Houba R, Doekes G, Heederick D. Occupational respiratory allergy in bakery workers: a review of the literature. *Am J Ind Med*. 1998;34:529–546.
- [26] Meijer E, Suarthaana E, Rooijackers J, et al. Application of a prediction model for work-related sensitisation in bakery workers. *Eur Respir J*. 2010;36:735–742.
- [27] Malo JL, Lemièrre C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J*. 1997;10:1513–1515.
- [28] Tarlo SM, Leung K, Broder I, Silverman F, Holness DL. Asthmatic subjects symptomatically worse at work: prevalence and characterization among a general asthma clinic population. *Chest*. 2000;118:1309–1314.
- [29] Sander I, Merget R, Degens PO, Goldscheid N, Brüning T, Raulf-Heimsoth M. Comparison of wheat and rye flour skin prick test solutions for diagnosis of baker's asthma. *Allergy*. 2004;59:95–98.
- [30] Van Kampen V, Rabstein S, Sander I, et al. Prediction of challenge test results by flour-specific IgE and skin prick test in symptomatic bakers. *Allergy*. 2008;63:897–902.
- [31] Malo JL, Cardinal S, Ghezzi H, L'Archevêque J, Castellanos L, Maghni K. Association of bronchial reactivity to occupational agents with methacholine reactivity, sputum cells and immunoglobulin E-mediated reactivity. *Clin Exp Allergy*. 2011;41:497–504.
- [32] Jacobs JH, Meijster T, Meijer E, Suarthaana E, Heederik D. Wheat allergen exposure and the prevalence of work-related sensitization and allergy in bakery workers. *Allergy*. 2008;63:1597–1604.
- [33] Moscato G, Malo JL, Bernstein D. Diagnosing occupational asthma: how, how much, how far? *Eur Resp J*. 2003;21:879–885.
- [34] Vandenplas O. Asthma and rhinitis in the workplace. *Curr Allergy Asthma Rep*. 2010;10:373–380.
- [35] Lemiere C, Cartier A, Malo JL, Lehrer SB. Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity. *Am J Respir Crit Care Med*. 2000;162:976–980.
- [36] Beach J, Russell K, Blitz S, et al. A systematic review of the diagnosis of occupational asthma. *Chest*. 2007;131:569–578.
- [37] Tarlo SM, Liss GM. Occupational asthma: an approach to diagnosis and management. *CMAJ*. 2003;168:867–871.
- [38] Vandenplas O, D'Alpaos V, Heymans J, et al. Sputum eosinophilia: an early marker of bronchial response to occupational agents. *Allergy*. 2009;64:754–761.
- [39] Girard F, Chaboillez S, Cartier A, et al. An effective strategy for diagnosing occupational asthma. Induced sputum. *Am J Respir Crit Care Med*. 2004;170:845–848.
- [40] James JM, Sixbey JP, Helm RM, Bannon GA, Burks AW. Wheat alpha-amylase inhibitor: a second route of allergic sensitization. *J Allergy Clin Immunol*. 1997;99:239–244.
- [41] Baur X, Posch A. Characterized allergens causing bakers' asthma. *Allergy*. 1998;53:562–566.
- [42] Tatham AS, Shewry PR. Allergens to wheat and related cereals. *Clin Exp Allergy*. 2008;38:1712–1726.