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# Association of MBL With Work-Related Respiratory Symptoms in Bakery Workers

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Baker's asthma is the most prevalent occupational asthma, and IgE-mediated response is known as a major pathogenesis. However, recent studies have suggested the involvement of innate immune response because wheat flour contains bacterial endotoxins or lipopolysaccharides. To further understand a role of innate immune response in the development of work-related respiratory symptoms (WRS) in bakery workers, we investigated mannose-binding lectin (MBL), one of the initiating components of the complement cascade in a single cohort of bakery workers. A total of 373 bakery workers completed a questionnaire regarding WRS. The bakery workers were divided into 2 groups according to previous history of allergic rhinitis (AR)/bronchial asthma (BA): those with history of AR/BA (group I) and those without (group II). We measured serum MBL levels by using enzyme-linked immunosorbant assay and genotyped 4 single nucleotide polymorphisms of the *MBL2* gene (226G>A in exon 1, -554G>C, -431A>C, and -225G>C in the promoter) by using TaqMan assays. Fifty-nine subjects (15.5%) were previously diagnosed with AR/BA, and 64 subjects (16.8%) complained of WRS. No significant differences were found in serum MBL levels between groups I and II. However, in group II subjects, but not in group I subjects, the serum MBL levels were significantly higher in bakery workers with WRS than in those without. In addition, the serum MBL levels were significantly different according to genetic polymorphisms of the *MBL2* gene and its haplotypes. In conclusion, serum MBL, affected by genetic polymorphisms, may be associated with WRS in bakery workers with no previous history of AR/BA.

**Key Words:** Work-related respiratory symptoms; mannose-binding lectin; baker's asthma

## INTRODUCTION

Baker's asthma is the most common occupational asthma and wheat is the representative cereal causing grain-induced asthma.[1-5] IgE-mediated sensitization is known as the major mechanism of baker's asthma.[6] Work-related respiratory symptoms (WRS), including upper and lower respiratory symptoms, are frequently found in bakery workers, with an incidence of 3%-17% for lower respiratory symptoms and an 11%-30% for upper respiratory ones.[1] The sensitization rate for wheat flour ranges from 2% to 15%,[1] and risk factors for the sensitization and development of baker's asthma are atopy, exposure intensity, and genetic susceptibility.[7-11]

Regarding the pathogenesis of baker's asthma, IgE-mediated response has been believed to be a major mechanism. However, it has been suggested that innate immune response may contribute to the development of baker's asthma, because wheat flour contains bacterial endotoxins or lipopolysaccharides (LPSs) that play an important role in the development of asthma.[12-14] Genetic polymorphisms of the Interleukin-18 (*IL-18*) gene, which plays a role in regulating LPS response, and Toll-like receptor 4 (*TLR4*) gene, modulating cell surface endotoxin receptors, are associated with wheat flour sensitization and WRS in Korean bakery workers along with IL-4 receptor α.[15-18]

Mannose-binding lectin (MBL) is a soluble pattern-recognition molecule that binds to glycoconjugates, such as mannose, fucose or N-acetylglucosamine on the surface of bacteria, viruses, and fungi, and initiates the lectin pathway.[19] Post-bronchiolitis wheezing and asthma development (after bronchiolitis or pneumonia) are associated with *MBL2* genetic polymorphisms in childhood asthma cohorts.[20-22] In addition, there have been

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some studies suggesting significant associations of MBL with the phenotype of adult asthma, atopy or atopic dermatitis,[23-28] while no associations have been reported in others.[29-31]

To further understand a role of the innate immune response which may be linked to Th2-immune responses in baker's asthma, we investigated serum MBL levels and genetic polymorphisms of the *MBL2* gene in the development of WRS in a cohort of bakery workers.

## MATERIALS AND METHODS

### Subjects

A total of 373 bakery workers at the largest Korean industrial bakery were included in the study. Clinical data, such as age, sex, smoking history, previous history of AR/BA, asthma duration, atopy, serum total IgE, and spirometry results, were collected. Atopy was defined by positive results of skin prick test (SPT) to common inhalant allergens. The bakery workers were divided into 2 groups according to previous history of AR/BA: those with history of AR/BA (group I) and those without (group II). Exposure intensity in the workplace was classified into minimal, intermediate, and high by measuring environmental dust concentrations with personal inhalable dust samplers. The geographic mean of wheat dust exposure levels were 0.01, 1.16, and 3.04 mg/m$^3$ in minimal, intermediate, and high exposure group, respectively.[9] A questionnaire on upper and lower WRS-nasal itching, runny nose, sneezing, and nasal congestion for upper respiratory symptoms as well as cough, sputum, shortness of breath, and wheezing for lower respiratory symptoms-was completed by each bakery worker. The SPT and enzyme-linked immunosorbant assay (ELISA) to wheat flour were performed as previously described.[9] The protocol used in this study was reviewed and approved by the Ajou University Institute Review Board, and written informed consent was obtained from each participant.

### Measurement of serum MBL levels

Human serum MBL levels were measured in bakery workers and healthy controls by using a DuoSet ELISA Development kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Samples were diluted at a ratio of 1:4,000 for the assay and measured in duplicate as previously reported.[23,32] A high serum MBL level was defined as one which was greater than the mean serum MBL level (675.5 ng/mL).

### Genotyping and haplotype analysis of the MBL2 gene

Genomic DNA was extracted from whole blood by using a Puregene DNA purification kit (Qiagen, Germantown, MD, USA) according to the manufacturer's instructions. We selected 4 single nucleotide polymorphisms (SNPs) that were previously investigated in asthmatic patients.[23] We genotyped 4 SNPs of the *MBL2* gene-3 SNPs in the promoter (-554G>C, rs11003125; -431A>C, rs11003124; -225G>C, rs7096206 and 1 SNP in exon 1 (226G>A, rs1800450)-by using TaqMan assays (Applied Biosystems, Foster City, CA, USA).[23] The primer information was demonstrated in the previous study.[23] Among 4 SNPs, -431A>C was newly found from SNP screening in 40 healthy Korean volunteers,[23] and the 3 other SNPs were selected from other reports.[24,25,31,33,34]

Linkage disequilibrium among all pairs of biallelic loci was examined by using Lewontin's D' (|D'|) and $r^2$ in a linkage disequilibrium (LD) block.[35] Haplotypes were estimated by using Haploview (version 4.0; Broad Institute, Cambridge, MA, USA), and 4 haplotype sets were derived from -554G>C, -431A>C, -225G>C, and 226G>A SNPs in the *MBL2* gene.

### Statistical analysis

All statistical analyses were performed with SPSS version 19 (Statistical Package for Social Scientists Inc., Chicago, IL, USA). Significant departures of the genotype frequency from Hardy-Weinberg equilibrium at the polymorphic site were tested by $\chi^2$ analysis. Differences in genotype and haplotype frequencies according to WRS were examined by using logistic regression analysis with codominant, dominant, and recessive models. The clinical parameters of the subjects were compared according to WRS by using an independent *t* test, an analysis of variance (ANOVA), an analysis of covariance (ANCOVA) and a $\chi^2$ test.

Logistic regression analysis was used to define associations of continuous and dichotomous variables with WRS. Multivariate logistic regression analysis was conducted with variables showing *P* values less than 0.1 in univariate analysis.

## RESULTS

### Study subjects and serum MBL levels

The clinical characteristics of the study subjects were compared according to previous history of AR/BA, which is presented in Table 1. There were significant differences in sex, atopy, exposure intensity, and WRS between groups I and II.

No significant differences of MBL levels were noted according to WRS in group I, while there were significant differences in MBL levels according to WRS in group II (Fig. 1). Other clinical parameters, such as sex, smoking history, atopy, exposure intensity to wheat flour, positive SPT to wheat flour, or positive serum specific IgE to wheat flour, showed no significant differences between groups I and II (data not shown). Association analyses showed that serum MBL level was not significantly correlated with exposure period to wheat flour, total IgE, FEV1 (%), or FVC (%) in groups I and II.

### Association of clinical parameters and the serum MBL level with WRS

Logistic regression analyses of various clinical parameters and serum MBL were performed to evaluate associations with WRS

**Table 1.** Clinical characteristics according to the previous histories of AR/BA (N=373)

| Variables | Group I (n=59) | Group II (n=314) | *P* value |
|---|---|---|---|
| Age (year) | 35.1±7.0 | 34.9±7.8 | 0.845 |
| Sex (male) | 22 (37.3) | 189 (60.2) | 0.001 |
| Smoking status (smoker) | 24 (42.9) | 121 (41.7) | 0.875 |
| Atopy | 35 (59.3) | 93 (30.2) | <0.001 |
| Total IgE (kU/L) | 213.7±300.2 | 230.1±445.0 | 0.786 |
| Exposure period | 3.7±3.4 | 4.0±3.5 | 0.482 |
| Exposure intensity | | | <0.001 |
| Low | 32 (54.2) | 77 (24.5) | |
| Intermediate | 18 (30.5) | 106 (33.8) | |
| High | 9 (15.3) | 131 (41.7) | |
| WRS | 19 (32.2) | 44 (14.0) | 0.001 |
| Positive SPT to wheat | 6 (10.2) | 19 (6.1) | 0.261 |
| Positive serum sIgE to wheat | 6 (10.2) | 41 (13.1) | 0.540 |
| FEV1 (% pred.) | 97.2±15.1 | 94.2±12.2 | 0.153 |
| FVC (% pred.) | 96.1±12.7 | 93.3±12.2 | 0.109 |
| High serum MBL (>675.5 ng/mL) | 29 (49.2) | 126 (40.1) | 0.197 |
| Serum MBL (ng/mL) | 688.2±368.1 | 673.1±334.2 | 0.755 |

Group I, bakery workers with previous history of AR/BA; Group II, bakery workers with no history of AR/BA.
AR, allergic rhinitis; BA, bronchial asthma; WRS, work-related respiratory symptoms; SPT, skin prick test; sIgE, specific IgE, FEV1, forced expiratory volume in 1 second; pred., predicted value; FVC, forced vital capacity; MBL, mannose-binding lectin.

in groups I and II. Smoking history, exposure intensity and positive SPT to wheat flour showed *P* value less than 0.1 in the group I subjects. In this group, exposure intensity and positive SPT remained statistically significant after multivariate analysis (Table 2). Atopy, positive SPT to wheat flour, and serum MBL showed *P* value less than 0.1 in the group II subjects. After adjustment for other significant parameters, serum MBL remained a significant factor associated with WRS in group II (Table 3).

### Comparison of clinical parameters and serum MBL levels according to MBL2 genotypes

Clinical parameters and serum MBL levels were compared according to the genotypes of 3 SNPs in the promoter (-554G>C, -431A>C, and -225G>C) and 1 SNP in exon 1 (226G>A). Minor allele frequencies (q) were 0.496, 0.104, 0.115, and 0.204 in SNPs (-554G>C, -431A>C, -225G>C, and 226G>A, respectively). There were no significant differences in clinical parameters according to SNPs except for older age in variant genotypes (AC or CC) of -431A>C (Supplemental Tables 1-3). After adjustment for age, sex, exposure period, and exposure intensity to wheat flour by using ANCOVA, the serum MBL level significantly differed according to genetic polymorphisms of the *MBL2* gene (Fig. 2).

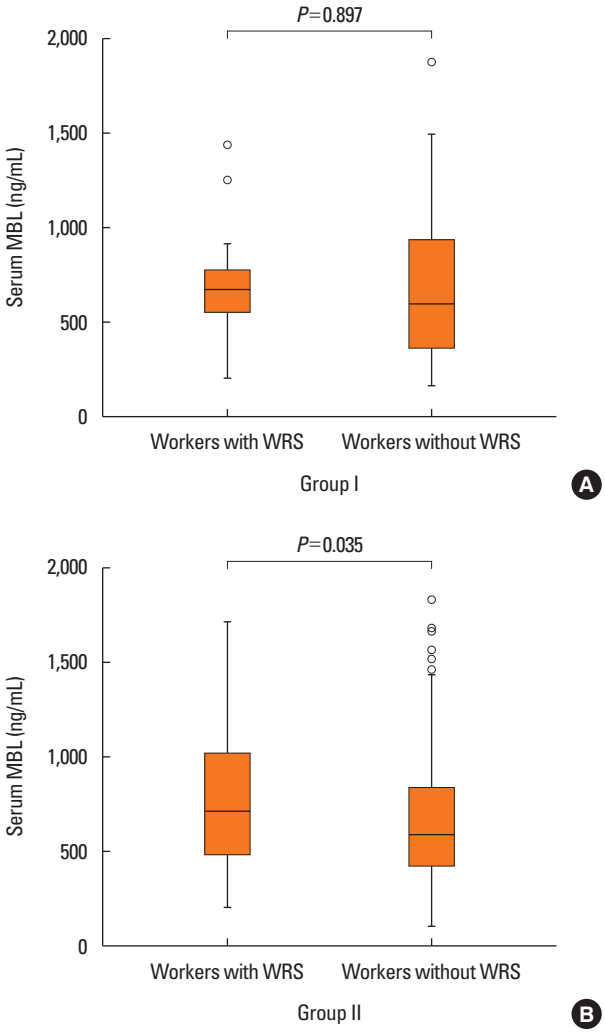


**Fig. 1.** Comparison of serum MBL levels according to WRS in group I (bakery workers with previous history of AR/BA) and group II (bakery workers with no history of AR/BA). There were no significant differences in MBL levels according to WRS in group I (workers with WRS, 679.0±300.1 ng/mL; workers without WRS, 692.5±399.9 ng/mL; *P*=0.897), while a significantly higher MBL level was noted in bakery workers with WRS in group II (workers with WRS, 790.8±399.2 ng/mL; workers without WRS, 653.9±319.1 ng/mL; *P*=0.035).

### Comparison of clinical parameters and serum MBL levels according to MBL2 haplotypes

Five haplotypes were compared in the analysis: haplotype 1 (*ht1* [GAGG], haplotype frequency 0.502), haplotype 2 (*ht2* [CAGA], 0.202), haplotype 3 (*ht3* [CACG], 0.115), haplotype 4 (*ht4* [CCGG], 0.104), and haplotype 5 (*ht5* [CAGG], 0.074). There were no significant differences in clinical parameters according to haplotypes except for older age in subjects not carrying *ht4* [CCGG] (Supplemental Tables 4-6). Serum MBL levels were significantly higher in subjects carrying *ht1* [GAGG] and significantly lower in those carrying *ht2* [CAGA] or *ht3* [CACG] after adjustment for age, sex, exposure period, and exposure intensity to wheat flour by using ANCOVA (752.9±19.0 ng/mL in *ht1*/

**Table 2.** Associations of clinical parameters with WRS in group I

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | aOR | 95% CI | *P* value |
| Age (year) | 1.003 | 0.927-1.085 | 0.944 | | | |
| Sex (male) | 1.351 | 0.441-4.134 | 0.598 | | | |
| Smoking history (smoker) | 0.338 | 0.101-1.132 | 0.079 | 0.308 | 0.077-1.234 | 0.096 |
| Atopy | 1.267 | 0.412-3.896 | 0.680 | | | |
| Total IgE (kU/L) | 1.001 | 0.999-1.003 | 0.193 | | | |
| Exposure period to wheat flour (year) | 0.865 | 0.710-1.054 | 0.150 | | | |
| Exposure intensity | | | | | | |
| Low | Ref | | | Ref | | |
| Intermediate | 3.467 | 0.959-12.536 | 0.058 | 5.056 | 1.072-23.832 | 0.041 |
| High | 5.417 | 1.109-26.466 | 0.037 | 6.401 | 1.071-38.265 | 0.042 |
| Positive SPT to wheat | 13.929 | 1.494-129.817 | 0.021 | 15.791 | 1.287-193.683 | 0.031 |
| Positive serum sIgE to wheat | 5.067 | 0.838-30.637 | 0.077 | | | |
| FEV1 (% pred.) | 0.977 | 0.941-1.013 | 0.211 | | | |
| FVC (% pred.) | 0.974 | 0.930-1.020 | 0.259 | | | |
| High serum MBL (>675.5 ng/mL) | 1.228 | 0.411-3.666 | 0.713 | | | |
| Serum MBL (ng/mL) | 1.000 | 0.998-1.001 | 0.895 | | | |

WRS, work-related respiratory symptoms; SPT, skin prick test; sIgE, specific IgE; FEV1, forced expiratory volume in 1 second; pred., predicted value; FVC, forced vital capacity; MBL, mannose-binding lectin; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

**Table 3.** Associations of clinical parameters with WRS in group II

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | aOR | 95% CI | *P* value |
| Age (year) | 1.011 | 0.971-1.053 | 0.586 | | | |
| Sex (male) | 0.764 | 0.402-1.451 | 0.410 | | | |
| Smoking history (smoker) | 1.007 | 0.522-1.941 | 0.984 | | | |
| Atopy | 2.863 | 1.484-5.521 | 0.002 | 2.603 | 1.324-5.116 | 0.006 |
| Total IgE (kU/L) | 1.000 | 0.999-1.001 | 0.796 | | | |
| Exposure period to wheat flour (year) | 1.035 | 0.948-1.131 | 0.443 | | | |
| Exposure intensity | | | | | | |
| Low | Ref | | | | | |
| Intermediate | 1.310 | 0.584-2.941 | 0.512 | | | |
| High | 0.718 | 0.308-1.672 | 0.442 | | | |
| Positive SPT to wheat | 3.989 | 1.476-10.777 | 0.006 | 3.629 | 1.287-10.231 | 0.015 |
| Positive serum sIgE to wheat | 1.912 | 0.842-4.343 | 0.121 | | | |
| FEV1 (% pred.) | 1.017 | 0.991-1.045 | 0.208 | | | |
| FVC (% pred.) | 1.009 | 0.983-1.035 | 0.507 | | | |
| High serum MBL (>675.5 ng/mL) | 1.776 | 0.936-3.369 | 0.079 | 2.101 | 1.069-4.129 | 0.031 |
| Serum MBL (ng/mL) | 1.001 | 1.000-1.002 | 0.013 | | | |

WRS, work-related respiratory symptoms; SPT, skin prick test; sIgE, specific IgE; FEV1 (% pred.), percent predicted value of forced expiratory volume in 1 second; FVC (% pred.), percent predicted value of forced vital capacity, MBL, mannose-binding lectin; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

*ht1* or *ht1*/-, 443.4±33.4 ng/mL in -/-, $P<0.001$; 422.8±24.5 ng/mL in *ht2*/*ht2* or *ht2*/-, 822.6±18.6 ng/mL in -/-, $P<0.001$; 542.3±35.7 ng/mL in *ht3*/*ht3* or *ht3*/-, 719.3±20.1 ng/mL in -/-, $P<0.001$; 730.4±41.6 ng/mL in *ht4*/*ht4* or *ht4*/-, 664.1±19.9 ng/mL in -/-, $P=0.153$; 716.9±51.6 ng/mL in *ht5*/*ht5* or *ht5*/-, 671.2±19.1 ng/mL in -/-, $P=0.407$).

## DISCUSSION

In this study, we investigated the association of MBL with

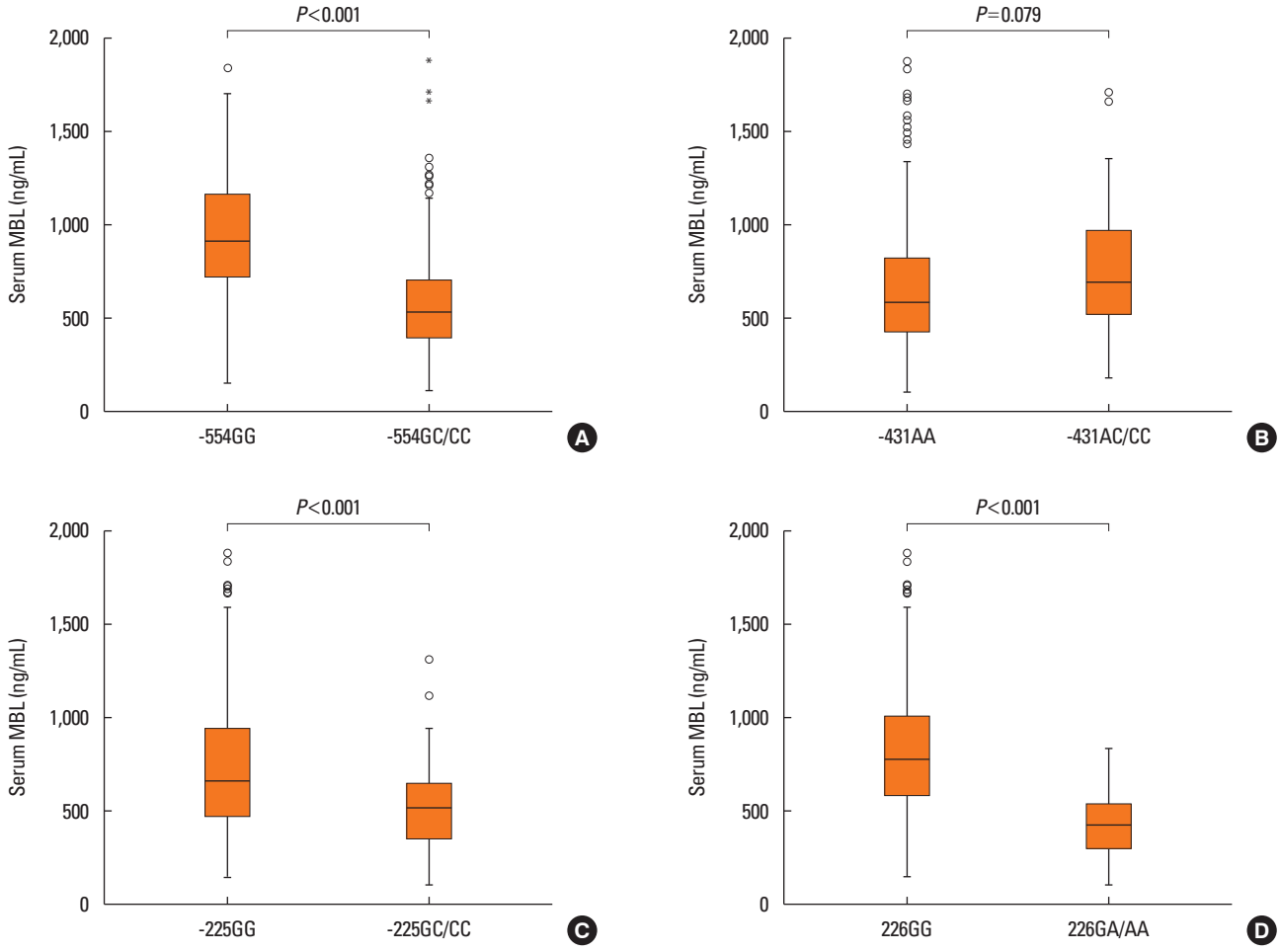


**Fig. 2.** Comparison of serum MBL levels according to *MBL2* genotypes. Serum MBL levels were significantly differed according to genetic polymorphisms of the *MBL2* gene at -554G>C (A. 955.5± 31.8 ng/mL in the GG genotype, 584.6±18.3 ng/mL in the GC or CC genotype; $P<0.001$), -225G>C (C. 719.7±19.6 ng/mL in the GG genotype, 519.3±37.2 ng/mL in the GC or CC genotype; $P<0.001$), and 226G>A (D. 821.0±18.6 ng/mL in the GG genotype, 425.5±24.5 ng/mL in the GA or AA genotype; $P<0.001$), while –431A>C genetic polymorphism showed no significant differences (660.2±20.1 ng/mL in the AA genotype, 739.3±40.1 ng/mL in the AC or CC genotype; $P=0.079$).

WRS in bakery workers to understand the role of the innate immune response in occupational asthma among bakery workers. Multivariate analysis demonstrated that exposure intensity and sensitization to wheat were positively associated with WRS in group I (workers with AR/BA). These results imply that more frequent WRS may develop in the high exposure group and that reductions in exposure intensity would help bakery workers with AR/BA prevent WRS, which is consistent with those of previous reports.[7,8] Serum MBL was not significantly associated with the presence of WRS in group I. However, in group II subjects, atopy, sensitization to wheat, and a higher serum MBL were associated with WRS. In this group, serum MBL was positively associated with WRS, and a significantly higher level was noted in subjects with WRS than in those without. These results indicated that wheat sensitization may be associated with WRS in groups I and II, while exposure intensity was a significant factor for subject with allergic diseases and the serum MBL level was a significant factor for those without allergic diseases. These results suggest that Th2-mediated immune response plays a major role in the development of WRS in bakery workers with or without previous history of AR/BA, while innate immunity may play an additional role in bakery workers with no previous history of any allergic disease. Taken these together, MBL, an initiating molecule for the innate immune response, may contribute to the development of WRS in bakery workers exposed to wheat flour with no previous history of allergic disease.

Serum MBL levels have been reported in various populations.[19] A previous study, using same methodology, reported that the mean serum MBL level is 686.7±339.2 ng/mL in adult asthmatic patients, which is significantly higher than in healthy controls (358.3±180.4 ng/mL).[23] Moreover, the MBL level of COPD patients is reported to be 918 ng/mL, which measured by the same method.[32] Elevated MBL levels are also noted in

childhood asthmatic patients with a positive correlation with peripheral blood eosinophils.[27] In the present study, the mean serum MBL level of bakery workers was 680.4±343.0 ng/mL, which is similar to that of adult asthmatics and higher than healthy controls. Significantly higher MBL levels were noted in group II subjects with WRS than in those without. These results implied that exposure to wheat flour might contribute to increasing serum MBL levels and activating the innate immune response, which may contribute to the development of WRS. We thought that MBL might play a role in the development of WRS because the complement system works as a bridge between innate and adaptive immune responses.[36]

There are some limitations in this study. First, WRSs were collected from self-reported questionnaires, but they were not confirmed by bronchoprovocation tests. However, this study is valuable because blood sampling, laboratory tests, measurement of exposure intensity of wheat flour, and questionnaires were conducted simultaneously in a relatively large population of bakers under the same condition. Second, we could not find significant associations between genetic polymorphisms and WRS. Also, we could not determine whether the elevated serum MBL level is a cause of WRS. Following prospective study is needed to clarify the role of MBL in bakery workers. However, this study found that serum MBL levels were affected by *MBL2* genetic polymorphisms, which suggests that bakery workers carrying susceptible genes associated with higher serum MBL may be a risk group to develop WRS, especially when they have no previous history of AR/BA. In addition, this study also implied that the risk factors to develop WRS may differ according to previous history of underlying allergic diseases. To the best of our knowledge, this is the first report to demonstrate a significant association of serum MBL levels with WRS in bakery workers and to analyze the bakery workers separately by dividing underlying allergic diseases.

In conclusion, serum MBL, affected by genetic polymorphisms, may be associated with WRS in bakery workers with no previous history of AR/BA.

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