Prevalence of type I allergy to natural rubber latex and type IV allergy to latex and rubber additives in operating room staff with glove-related symptoms

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ABSTRACT

There is lack of data on the prevalence of latex allergy in the health care setting in Iran. This study was performed to determine the prevalence of type I latex allergy and type IV allergy to latex and rubber additives among the operating room staff with glove-related symptoms in 13 general hospitals in Tehran. Skin-prick tests with commercial latex extract, patch tests with latex and 25 rubber additive series, and total and latex-specific IgE detection were performed on the operating room staff who reported latex glove-related symptoms. Five hundred twelve self-administered questionnaires (100%) were completed by all operating room staff and latex glove-related symptoms were reported by 59 (11.5%) employees. Among all symptomatic operating room staff tested, the prevalence of type I latex allergy was 30.5% and the prevalence rates of type IV allergy to latex and rubber additives were 16.7 and 14.6%, respectively. The most positive patch test result with rubber additives was related to tetramethylthiuram monosulfide (38.5%). The risk factors for type I latex allergy were female sex (p = 0.009) and positive patch test with rubber additives (p = 0.012). Subjects who had positive patch test with latex were significantly more likely to have positive patch test with rubber additives (p < 0.0001). Our results showed a high prevalence of type I latex allergy and type IV allergy to latex and rubber additives. Based on this study, we recommend eliminating powdered latex gloves from the operating rooms of the 13 studied general hospitals and support the substitution of powder-free latex gloves.

Key words: Allergy, contact dermatitis, glove-related symptoms, natural rubber latex, operating room staff, patch test, prevalence, rubber additives, skin prick test, tetramethylthiuram monosulfide

An increased prevalence of latex-related symptoms has been observed in health care workers (HCWs), who are at high risk for latex allergy due to daily exposure to latex products. However, a marked decrease in the incidence of latex allergy in HCWs has been reported because of the decrease in the use of powdered latex gloves in the HCW’s setting. Studies have estimated that the prevalence of latex allergy in HCWs varies widely, ranging from 2.9 to 17%. Frequent exposure to rubber products and latex-containing devices could be a major risk factor for the development of latex allergy. Hand dermatitis associated with occupational exposure to irritants, such as detergents and disinfectants, is another risk factor for latex allergy. Irritant dermatitis disrupts the skin barrier and facilitates sensitization to latex allergens. Additional risk factors for latex allergy include a history of atopy, which may manifest as rhinitis; reactive airway disease or childhood dermatitis; eczema, due to increased invasion of latex proteins through disrupted skin; and allergies to foods with known cross-reactivity with latex allergens, such as avocado, banana, chestnut, and kiwi.

The most common form of reaction to latex is a nonimmunologic irritant contact dermatitis. The least common, but potentially most serious form of reaction, is type I latex allergy. This is an IgE-mediated immediate-type reaction to extractable proteins from natural rubber latex. IgE-mediated clinical manifestations range from local reactions (contact urticaria), rhinoconjunctivitis, asthma, angioedema, and pharyngeal edema to severe systemic reactions such as anaphylactic shock. Other immunologically mediated reactions such as delayed “allergic” contact dermatitis (type IV allergy) occur probably more frequently than type I reactions. The additives that are used to act as
preservatives, vulcanizing agents, and accelerators during the processing and manufacturing of rubber products served as allergens that can cause type IV allergy.13 Because the prevalence of latex-related symptoms among HCWs was reported to increase especially in operating room staff,14 we decided to determine the prevalence of type I latex allergy and type IV allergy to latex and rubber additives among 512 operating room staff.

MATERIALS AND METHODS

Study Questionnaire and Subjects

This cross-sectional study was performed on all 512 operating room staff from 25 operating rooms of 13 general hospitals affiliated with the Tehran University of Medical Sciences during 2001–2003 (the total population of 25 operating rooms was 512 employees). All operating room staff who had daily contact with surgical powdered latex gloves completed the self-administered questionnaire detailing latex glove exposure designed to elicit symptoms of suggestive type I allergy (urticarial hand rash, itch/redness, eczematous hand rash, or glove-related rhinitis or breathing difficulties that began <24 hours after contact with latex gloves) and symptoms of suggestive type IV allergy (itchy nonurticarial rash that began >24 hours after latex exposure without other symptoms). Subjects completing the questionnaire who reported any symptoms or reactions attributed to latex gloves were asked to undergo skin-prick tests, patch tests, and total and specific IgE tests. All symptomatic subjects signed an informed written consent to undergo the aforementioned tests.

Skin-Prick Test

Standardized commercial extract of natural nonammoniated latex (Allergopharma, Hamburg, Germany) was used for skin-prick testing. Histamine dihydrochloride (1 mg/mL) was used as a positive control and physiological saline was used as a negative control. Skin-prick tests were performed on the volar aspect of each participant’s forearm. A reading was done 15–20 minutes after application. The skin-prick test was considered positive if the mean diameter of the wheal was ≥3 mm and the results were scored based on the histamine wheal.15 Results of the skin tests were disregarded if a subject had a reaction to the negative control or no reaction to the positive control. Antihistamines were not taken by participants for skin-prick test in the 48 hours before the test.

Patch Tests

Patients were patch tested with latex [LAN 960C(M)—Low Nitrosamine Latex, total solid 61%, nonammoniated and antioxidant-free latex], natural rubber latex (Standard Revertex Latex, total solid 73%, nonammoniated latex), and 25 glove additives (Rubber Additives Series; Table 1). The IQ Chambers, latex extracts, and 25 Rubber Additive Series were purchased from Chemotechnique Diagnostics, Malmo, Sweden. Patch testing was performed by applying latex extracts and rubber additive series to the IQ chambers, which were supplied in units of 10 chambers on a hypoallergenic nonwoven adhesive tape.16 The test units were left on to the patients’ backs for 48 hours. Reading of the test was performed 72 hours after the test application. All reactions were scored in accordance with the scheme used for allergic contact dermatitis.17

Total and Latex-Specific IgE Tests

Three milliliters of whole blood was taken from each symptomatic patient and the serum was isolated and stored at −70°C. Serum total IgE was measured by ELISA kit (Diagnostic Automation, Calabasas, CA) and latex-specific IgE was measured by ELISA kit (Allergopharma) under standardized conditions, as recommended by the manufacturer. The levels of specific IgE were classified according to the manufacturer’s recommendations. The results were classified in classes from 0 to 4 and levels higher than 0.35 kilo units of antigen per liter (kUA/L) (class 1 and up) were considered a positive result.

Statistical Analysis

Data were analyzed using the statistical software SPSS version 10.0, Independent sample t-test were performed for quantitative variables, and chi-square test was performed for qualitative variables. All p values were two-tailed, and those <0.05 were considered statistically significant.

RESULTS

Study Questionnaire Results

Five hundred twelve questionnaires (100%) were completed for all of the operating room staff of all 25 operating rooms of 13 general hospitals affiliated with the Tehran University of Medical Sciences. The characteristics of all 512 operating room employees who had daily use of powdered latex gloves are shown in Table 2.

Fifty-nine subjects (11.5%) reported latex glove-related symptoms. The most common symptoms were hand eczema (52.6%) and itch/redness (35.6%); breathing difficulties was an uncommon symptom (1.7%) reported by symptomatic subjects (Table 3).

Results of Skin-Prick Test, Total IgE, and Latex-Specific IgE Tests

All 59 symptomatic subjects had skin-prick tests performed; 52 (88.1%) had total IgE and 49 (83%) had
latex-specific IgE blood testing performed. Eighteen (30.5%) subjects had positive skin-prick tests to natural rubber latex and 45 (91.8%) subjects had positive latex-specific IgE (Table 4). None of the participants experienced adverse reactions during skin-prick testing. The mean (±SD) titers of total IgE and latex-specific IgE antibodies were 26.75 IU/mL and 0.42 ± 0.047 kU/L, respectively.

Results of Patch Tests

Eleven (18.6%) of 59 symptomatic subjects refused to undergo the patch tests. Of 48 subjects tested, 12 (25%) and 13 (27.1%) had positive patch tests with latex and the Rubber Additive Series, respectively (Table 4). Nine (56.3%) subjects had positive patch tests with both latex and the Rubber Additive Series. The most positive patch test result with rubber additives was related to tetramethylthiuram monosulfide (38.5%; Table 1). The subjects with positive patch test to latex were significantly more likely to have a positive patch test to rubber additives ($p < 0.0001$).

Comparison between the Group with Type I Latex Allergy and the Group without Type I Latex Allergy

Among all 59 symptomatic operating room staff, 18 subjects with type I latex allergy (who had positive prick tests to natural rubber latex) were compared with 34 subjects without type I latex allergy (who had negative prick test to natural rubber latex). We found a significant association between female sex and type I latex allergy ($p = 0.009$). The most common latex glove–related symptoms in the group with type I latex allergy were hand eczema (55.1%) and itch/redness (32.7%), but no significant differences have been observed between the two groups. One of the subjects with type I latex allergy had a history of fruit allergy (kiwi) and 11 (61.1%) of them had a personal and/or family history of atopic diseases. Nine (50%) subjects with type I latex allergy were operating room technicians, eight (44.4%) subjects were operating room nurses, and 1 subject was an operating room cleaner. No significant differences in history of fruit allergy, personal and/or family history of atopic diseases, and job title have been observed between two groups. The mean duration of weekly glove usage in the group

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Table 1  List of rubber additive tested and positive patch test reactions (48 subjects tested)

<table>
<thead>
<tr>
<th>Rubber Additives</th>
<th>No. Positive Reaction</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-(Cyclohexylthio)phthalimide 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dodecyl mercaptan 0.1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dibutyl thiourea 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diethyl thiourea 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2,2,4-Trimethyl-1,2-dihydro-quinoline 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zinc dimethylthiocarbamate 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N,N-Diphenyl thiourea 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4,4-Diaminodiphenylmethane 0.5% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hexamethylene tetramine (methenamine) hexamine 2% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N-Phenyl-2-naphthylamine 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N,N-Dibeta-naphtyl-4-phenylenediamine 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zinc dibutylthiocarbamate 1% pet</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>Zinc diethylthiocarbamate 1% pet</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>N,N-Diphenylguanidine 1% pet</td>
<td>2</td>
<td>15.4</td>
</tr>
<tr>
<td>2-(4-Morpholinylmercapto) benzothiazol 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N-Cyclohexyl-2-benzothiazyl sulphanamide 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dibenzothiazyl disulfide 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-Mercaptobenzothiazole (MBT) 2% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N-Isopropyl-N-phenyl-4-phenylenediamine 0.1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N,N-Diphenyl-4-phenylenediamine 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N-Cyclohexyl-N-phenyl-4-phenylenediamine 1% pet</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dipentamethylenethiuram disulphide 1% pet</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>Tetraethylthiuram disulfide 1% pet</td>
<td>2</td>
<td>15.4</td>
</tr>
<tr>
<td>Tetramethylthiuram monosulfide 1% pet</td>
<td>5</td>
<td>38.5</td>
</tr>
<tr>
<td>Tetramethylthiuram disulfide 1% pet</td>
<td>1</td>
<td>7.7</td>
</tr>
</tbody>
</table>
with type I latex allergy was greater than that of the group without type I latex allergy (43.3 \pm 13.2 hours versus 36.1 \pm 14 hours); however, the difference was not significant. There was a significant relationship between positive patch tests with rubber additives and type I latex allergy (p = 0.012).

### Diagnosis of Type IV Allergy

Among 48 operating room staff tested, the diagnosis of type IV allergy to latex and the Rubber Additive Series, using patch tests with clinical relevance, were established in 8 (16.7%) and 7 (14.6%) subjects, respectively. Both type IV allergy to latex and the Rubber Additive Series were seen in six (12.5%) of the tested subjects.

### Latex Allergy Type I and Type IV Allergy

We found that 5 (8.5%) of 59 symptomatic subjects had both type I latex allergy and type IV allergy to rubber additives. There was a significant association between type I latex allergy and type IV allergy to rubber additives (p = 0.012).

### DISCUSSION

This study was the first epidemiological study of latex allergy in Iran, performed on operating room staff of 13 general hospitals in Tehran. Our findings showed...
the high prevalence rates of type I latex allergy and type IV allergy to latex and Rubber Additive Series among 512 operating room staff with latex glove-related symptoms in 13 general hospitals in Tehran.

Our results revealed that the prevalence of type I latex allergy based on skin-prick tests among operating room staff was 30.5%; however, in the other studies, it was 8.1 and 86% among HCWs,18,19 8.3% among laboratory workers,20 and 18.6% among operating room nurses.21 One explanation for obtaining various results in different studies could be caused by the various populations being studied.22 Another explanation is due to the variable latex reagents that were used for skin-prick tests.

In our study, the positive latex-specific IgE was shown in 45 (91.8%) of 49 symptomatic subjects tested but all of them were in low level (0.35–0.7) and the clinical significance of class 1 ELISA positive subjects to latex is questionable. The prevalence of positive latex-specific IgE was 49% in a previous similar study.23 The differences in latex-specific IgE results probably are because of the different technologies used, confounding estimation of prevalence.

We did not find an association between latex skin-prick tests and latex-specific IgE (p = 0.187). Nevertheless, Jaeger et al.23 found a good correlation between latex-specific IgE and latex skin-prick tests. In some studies, comparing skin tests with latex and the CAP system for analyzing latex-specific IgE, skin-prick tests usually were reported to be more sensitive than in vitro latex-specific IgE assays.24

In some previous studies, the prevalence of self-reported glove-related symptoms among HCWs had varied from 24 to 54%.18,25–27 Our results showed that 11.5% of operating room staff reported latex glove-related symptoms according to the self-administered questionnaire. Two other previous studies showed the prevalence rates of 13.6 and 13.7% among HCWs.28,29 The most common reported symptoms associated with latex glove use among operating room staff with type I latex allergy in this study were hand eczema and itch/redness, which is in agreement with the study by Larese et al.14 The other similar studies26,27,30–32 also revealed that the clinical symptoms of latex allergy in the majority of subjects were skin lesions with itching, but breathing difficulties were rarely seen. It is in agreement with our study in which only 1.7% of operating room staff reported breath difficulties.

Contact urticaria, conjunctivitis, rhinitis, and asthma have been reported as symptoms on exposure to latex gloves among HCWs,14,18,20,29,33,34 but these have unexpectedly not been reported by any of the participants in this study. In our study, there was no significant association between type I latex allergy and any of the glove-related symptoms, but significant association was found between type I latex allergy and itching, erythema, and contact urticaria in a previous study.22

History of food allergy has been considered as a risk factor for latex allergy,25 although we could not find the association between history of food allergy and latex allergy in this study. In various studies, it was reported that there was a relationship between allergy to a variety of fruits and latex allergy,27,36 which is

<table>
<thead>
<tr>
<th>Test</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of SPT done</td>
<td>59 (100)</td>
</tr>
<tr>
<td>Total no. of total IgE test done</td>
<td>52 (88.1)</td>
</tr>
<tr>
<td>Total no. of specific IgE test done</td>
<td>49 (83)</td>
</tr>
<tr>
<td>Total no. of patch test done</td>
<td>48 (81.4)</td>
</tr>
<tr>
<td>Total no. of sensitized to latex (either SPT or specific IgE test positive)</td>
<td>49 (83)</td>
</tr>
</tbody>
</table>

SPT with latex

Positive (total) | 18 (30.5)
+1 (25%) | 9 (15.3)
+2 (50%) | 2 (3.4)
+3 (100%) | 5 (8.5)
+4 (200%) | 2 (3.4)
Negative | 41 (69.5)

Total IgE test (IU/mL)

≤99 | 37 (71.2)
100–199 | 7 (13.5)
200–499 | 4 (7.7)
≥500 | 4 (7.7)

Latex-specific IgE test (kU/\text{L})

Positive (total) | 45 (91.8)
1 (≥0.35 < 0.7) | 45 (91.8)
2 (≥0.7 < 3.5) | 0
3 (≥3.5 < 17.5) | 0
4 (≥17.5) | 0
Negative (<0.35) | 4 (8.2)

Patch test with latex

Positive (total) | 12 (25)
+1 | 9 (18.7)
+2 | 3 (6.3)
+3 | 0
IR | 0
Negative and doubtful reactions | 36 (75)

Patch test with Rubber Additive Series

Positive (total) | 13 (27.1)
+1 | 10 (20.9)
+2 | 2 (4.2)
+3 | 1 (2.1)
IR | 0
Negative and doubtful reactions | 35 (72.9)

IR = irritant reaction; SPT = skin-prick test.
related to clinical and immunochemical cross-reactivity between latex and fruit or vegetable allergens. However, in our study we did not find a significant relationship between reported history of allergy to fruits and latex allergy.

Female sex was reported as a risk factor for latex allergy; we found significant correlations between female sex and type I latex allergy in our study as well. Atopy has been considered a risk factor for latex allergy in some studies, but we did not find any significant correlation between history of atopic diseases and latex allergy in this study.

In some studies there was a significant relationship between duration of latex glove exposure and latex allergy. Nevertheless, we did not find any significant correlation between total hours of latex exposure at work per week with latex allergy, similar to a previous study.

The prevalence of type IV allergy to latex was 16.7% in our study; however, it was reported as 2.4% in a previous study. The prevalence of type IV allergy to Rubber Additive Series was 14.6% in our study; however, it was reported at 10.5, 7.2, and 6.6% in previous studies. In our study, the most positives in patch testing with Rubber Additive Series were related to tetramethylthiuram monosulfide, which is in agreement with a previous study; however, in another study, the most common sensitizers were thiuram mix and carba mix.

Prior hand eczema has been identified previously as a risk factor for type IV allergy to rubber additives, maybe because of easier penetration of allergens through the damaged skin, although we did not find any significant correlation in this study (p = 0.145). The prevalence of positive patch test with rubber additives in the subjects with type I latex allergy in our study was 50%, whereas it was 14.8 and 13% in previous similar studies. We found a significant relationship between type I allergy to natural rubber latex and type IV allergy to rubber additives; however, Nettis et al. and De Groot et al. found no coexistence of them.

One of the limitations of this study was the fact that the glove provocation test was not performed for the symptomatic subjects who had negative skin-prick tests with latex and negative serum latex-specific IgE. However, the glove provocation test has significant limitations; it is not standardized and it has to be performed with caution in patients with active hand dermatitis, because it increases the challenge dose of adsorption and probably induces an anaphylactic reaction. Nevertheless, it should be performed for definite diagnosis of type I latex allergy.

In conclusion, our results revealed the high prevalence of type I latex allergy and type IV allergy to Rubber Additive Series among the operating room staff of 13 general hospitals in Tehran. Finding the coexistence of type I latex allergy and type IV allergy to rubber additives suggests that evaluation for both immediate allergy to latex and delayed type of allergy to latex and rubber additives should be considered in high-risk groups for exposure to latex and rubber products (i.e., HCWs). Finally, we recommended eliminating powdered latex gloves and also support the replacement of powder-free latex gloves for all operating room staff of the 13 general hospitals that we studied.

ACKNOWLEDGMENTS

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REFERENCES


