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Contact sensitization to cosmetic series of allergens in patients with rosacea: A prospective controlled study

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Abstract

Background: Previous studies have documented the cosmetic allergic contact dermatitis due to common cosmetic allergens in standard series and various cosmetic products used in rosacea patients; however, the prevalence of contact sensitization to other cosmetic allergens other than those in standard series is largely unknown.

Aims: To assess the prevalence of contact sensitization to a European cosmetic series of allergens (Chemotechnique Diagnostics AB, Malmö, Sweden) in rosacea patients and to compare this with the prevalence observed in general population.

Methods: In this prospective monocenter study, 103 patients with rosacea and 104 control subjects were investigated for contact sensitizations via patch testing the cosmetic series including 49 allergens.

Results: At least one positive allergic reaction was observed in 62 (60.2%) rosacea patients, and in 25 (24.0%) control subjects. Compared with control subjects, rosacea patients were statistically more likely to have positive patch tests. The most common allergens giving positive results were octyl gallate (10.68%), dodecyl gallate (8.74%), tert-Butylhydroquinone (7.77%), thimerosal (6.80%), euxyl K400 (6.80%), cocamidopropyl betaine (5.83%), and 2,6-Di-tert-butyl-4-cresol (4.85%).

Conclusions: This study shows that rosacea patients show a strikingly high prevalence of contact sensitization to cosmetic allergens. We recommend the additional use of cosmetic series for patch testing, and the careful use of cosmetics in rosacea patients if cosmetic contact sensitivity is suspected.

KEYWORDS

contact allergy, cosmetic patch, cosmetics, rosacea

1 | INTRODUCTION

Rosacea is a common chronic inflammatory disorder affecting skin by causing transient or persistent central facial erythema, telangiectasia, inflammatory papules and pustules, phymatous changes, and ocular features. Although the exact pathogenesis of the disease has not been fully understood yet, current knowledge suggests that it is an inflammatory disorder that develops in genetically susceptible

individuals, and a variety of environmental stimuli elicit an augmented innate immune response and neurovascular dysregulation. It has been estimated that around 10% of the population in the world are affected by rosacea.^{1,2}

Rosacea patients often observe unexplained aggravation of erythema, scaling, and/or itching in the course of their disease which is usually associated with the "irritability of the rosaceous skin" that is more prone to be affected by the adverse reactions caused by

external formulations. This hypersensitivity in rosacea patients is at least partially explained by the damaged cutaneous barrier which allows increased penetration of irritants.^{3,4} In this manner, irritating potential of certain formulations used in rosacea patients has been extensively documented in previous reports. On the other hand, it has been well known that sensitive and inflamed skin may also be more prone to develop delayed-type hypersensitivity reactions by allowing increased penetration of allergens.⁵ In addition, the increased need for frequent application of skin care products or cosmeceuticals in these patients to improve or cover up the "unaesthetic appearance" of their skin may also result in more contact sensitization. Eventually, recent interest has focused on the predisposition to developing contact allergy in rosacea patients, and a surprisingly high frequency of contact allergic patch test reactions was found.⁶⁻⁹ Although these reports mention that the detected reactions in rosacea patients were mostly created by cosmetic allergens in standard series, the prevalence of contact sensitization to other cosmetic allergens other than those in standard series is largely unknown.

In this study, we sought to assess the prevalence of contact sensitization to cosmetic series of allergens in rosacea patients and to compare the results with general population of similar age and sex distribution.

2 | MATERIALS AND METHODS

This was a hospital-based cross-sectional study involving a series of rosacea patients of the face and age-/gender-matched controls admitted to the outpatient clinic of the Department of Dermatology of Dokuz Eylul University, between April 2014 and May 2017. The study protocol was approved by the Local Ethical Committee which follows the guidelines set by the Helsinki declaration. Inclusion criteria for the patients were age more than 18 years and clinical diagnosis of rosacea according to the National Rosacea Society criteria.¹⁰ The controls were subjects referred during the study period for various dermatological complaints other than rosacea, such as hair loss, alopecia areata, epidermal inclusion cysts, tinea pedis, onychomycosis, viral warts, nevus, actinic keratosis, and basal cell carcinoma. Exclusion criteria included (a) pregnant or lactating women, (b) medical conditions that could compromise the evaluation of skin responsiveness, (c) UV exposure in the test area within the last 6 weeks, (d) use of systemic corticosteroids or any other immunosuppressive therapy, (e) use of systemic or local antihistamines 1 week before the tests and at the time of the testing, and (f) inability to come in for follow-up visits for readings. Considering to get an objective comparison of the prevalence of contact sensitization to cosmetic allergens between rosacea patients and controls, neither patients nor controls were chosen for having suspected allergic contact dermatitis at the time of the admission. Instead, all rosacea patients attending the clinic during the study period and their age- and gender-matched controls were patch tested, irrespective of the standard indications for epidermal patch testing. After explaining the procedure in detail to the subject, informed consent

was taken, and clinical and demographic data of the subjects were registered on a case report form. All subjects were patch tested with cosmetic series (Chemotechnique Diagnostics AB, Malmö, Sweden) including 49 allergens. Test allergens were applied with IQ Chambers (Chemotechnique Diagnostics AB) to the upper back of the subjects. The strips were removed after 48 hours, and reactions were evaluated by one investigator (O.O) in all subjects on day (D) 2-3 and D4-7 after patch application. Patch test reactions were interpreted with the following scale: 1+ (weak reaction; papules with erythema), 2+ (strong reaction; papules plus edema or vesiculation), or 3+ (extreme reaction; spreading papulovesicles or bullae). Macular erythematous reactions which were detected at 48 hours and showed a decrescendo reaction pattern in the following day were assessed as "irritant" reactions.¹¹

The statistical analyses of the study were performed with the SPSS/PC software (Version 22.0 for Windows; SPSS Inc, Chicago, Ill). The numeric variables were given as mean $\pm$ standard deviation by the descriptive analysis, and the percentage frequencies of the other variables were obtained. The chi-square test, Fisher's exact test, and Student's *t* test were used to compare the demographic and clinical characteristics of the groups. $P < 0.05$ was considered significant in all analyses.

3 | RESULTS

Over a period of three years, 103 rosacea patients (35 male and 68 female), aged 20-66 years (mean age 42.3 years), and 104 controls (37 male and 67 female), aged 21-64 (mean age 42.2 years), were enrolled in the study. There were no statistically significant differences in terms of age or gender distribution between patients and controls ($P = 0.925$ and $P = 0.809$, respectively). In rosacea group, erythema-totelangiectatic rosacea was the more common clinical subtype accounting for 69.9% of cases, and the remainder had papulopustular (27.2%) and phymatous subtypes (2.9%).

In general inquiry before patch tests, 48 (46.6%) of the rosacea patients and 22 (21.2%) of the control subjects described that they had experienced erythema, burning, itching, or tingling sensation at least once during their lifetime which might be associated with the use of a cosmetic product ($P < 0.001$). A personal history of atopy was present in 18 (17.5%) of the rosacea patients, and in 15 (14.4%) of the controls ($P = 0.549$).

After epidermal patch tests, at least one positive allergic reaction was observed in 62 (60.2%) subjects in the rosacea group, and in 25 (24.0%) subjects in the control group. Compared with controls, rosacea patients were significantly more likely to have a positive allergic patch test reaction ($P < 0.001$). Among the reactive cases, 41 (39.8%) subjects in the rosacea group and 14 (13.5%) subjects in the control group showed more than one positive reaction to the allergens applied ($P < 0.001$). The reactive cases in both rosacea and control groups showed a similar age (43.5% of the reactive cases in the rosacea group, and 48.0% of the reactive cases in the control group were <40 years, $P = 0.706$), and

TABLE 1 Results of the patch test assessment with cosmetic series in rosacea patients and control subjects

Contact hypersensitivity reactions, n (%)										
Allergens, concentration (% w/w)	Patients (n = 103)					Controls (n = 104)				
	Positive reaction	Weak	Strong	Extreme	Relevant	Positive reaction	Weak	Strong	Extreme	Relevant
1. Isopropyl myristate, 20 pet	-	-	-	-	-	1 (0.96)	1 (0.96)	-	-	1 (0.96)
2. Amerchol L 101, 50 pet	1 (0.97)	1 (0.97)	-	-	1 (0.97)	1 (0.96)	1 (0.96)	-	-	1 (0.96)
3. Triethanolamine, 2 pet	2 (1.94)	1 (0.97)	1 (0.97)	-	1 (0.97)	-	-	-	-	-
4. Polyoxyethylene sorbitan monooleate, 5 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
5. Sorbitan monooleate, 5 pet	1 (0.97)	1 (0.97)	-	-	-	1 (0.96)	1 (0.96)	-	-	-
6. 2-tert-Butyl-4-methoxyphenol (BHA), 2 pet	3 (2.91)	3 (2.91)	-	-	1 (0.97)	1 (0.96)	1 (0.96)	-	-	-
7. 2,6-Di-tert-butyl-4-cresol (BHT), 2 pet	5 (4.85)	4 (3.88)	1 (0.97)	-	1 (0.97)	2 (1.92)	2 (1.92)	-	-	-
8. Octyl gallate, 0.25 pet	11 (10.68)	9 (8.74)	2 (1.94)	-	1 (0.97)	4 (3.85)	4 (3.85)	-	-	-
9. Triclosan, 2 pet	-	-	-	-	-	-	-	-	-	-
10. Sorbic Acid, 2 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
11. 4-Chloro-3-cresol, 1 pet	2 (1.94)	2 (1.94)	-	-	-	-	-	-	-	-
12. 4-Chloro-3,5-xyleneol, 0.5 pet	2 (1.94)	2 (1.94)	-	-	-	-	-	-	-	-
13. Thimerosal, 0.1 pet	7 (6.80)	5 (4.85)	2 (1.94)	1 (0.97)	3 (2.88)	3 (2.88)	1 (0.96)	2 (1.92)	-	1 (0.96)
14. Imidazolidinyl urea, 2 pet	-	-	-	-	-	-	-	-	-	-
15. Hexamethylenetetramine, 2 pet	-	-	-	-	-	-	-	-	-	-
16. Chlorhexidine digluconate, 0.5 aq	2 (1.94)	2 (1.94)	-	-	-	-	-	-	-	-
17. Paraben mix, 16 pet	2 (1.94)	1 (0.97)	1 (0.97)	-	1 (0.97)	1 (0.96)	1 (0.96)	-	-	-
18. Phenyl mercuric acetate, 0.01 aq	1 (0.97)	1 (0.97)	-	-	-	1 (0.96)	1 (0.96)	-	-	-
19. 2-Chloroacetamide, 0.2 pet	1 (0.97)	1 (0.97)	-	-	-	1 (0.96)	-	-	1 (0.96)	1 (0.96)
20. Hexahydro-1,3,5-tris-(2-hydroxyethyl) triazine, 1 aq	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
21. Clioquinol, 5 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
22. Ethylenediamine dihydrochloride, 1 pet	-	-	-	-	-	-	-	-	-	-
23. Abitol, 10 pet	2 (1.94)	2 (1.94)	-	-	1 (0.97)	1 (0.96)	1 (0.96)	-	-	1 (0.96)
24. Phenyl salicylate, 1 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
25. 2-Hydroxy-4-methoxybenzophenone, 10 pet	1 (0.97)	1 (0.97)	-	-	-	1 (0.96)	1 (0.96)	-	-	-
26. Sorbitan sesquileate, 20 pet	3 (2.91)	2 (1.94)	1 (0.97)	-	1 (0.97)	2 (1.92)	2 (1.92)	-	-	-
27. Propylene glycol, 5 pet	1 (0.97)	1 (0.97)	-	-	1 (0.97)	-	-	-	-	-

(Continues)

TABLE 1 (Continued)

Contact hypersensitivity reactions, n (%)										
Allergens, concentration (% w/w)	Patients (n = 103)					Controls (n = 104)				
	Positive reaction	Weak	Strong	Extreme	Relevant	Positive reaction	Weak	Strong	Extreme	Relevant
28. Stearyl alcohol, 30 pet	2 (1.94)	1 (0.97)	-	-	1 (0.97)	-	-	-	-	-
29. Cetyl alcohol, 5 pet	-	-	-	-	-	-	-	-	-	-
30. Benzyl salicylate, 10 pet	3 (2.91)	3 (2.91)	-	-	1 (0.97)	2 (1.92)	1 (0.96)	1 (0.96)	-	1 (0.96)
31. 2-Bromo-2-nitropropane-1,3-diol, 0.25 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
32. Sodium-2-pyridinethiol-1-oxide, 0.1 aq	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
33. Cocamidopropyl betaine, 1 aq	6 (5.83)	5 (4.85)	1 (0.97)	-	1 (0.97)	3 (2.88)	3 (2.88)	-	-	1 (0.96)
34. Benzyl alcohol, 10 pet	2 (1.94)	2 (1.94)	-	-	1 (0.97)	1 (0.96)	1 (0.96)	-	-	-
35. Methylchloroisothiazolinone, 0.02 aq	3 (2.91)	3 (2.91)	-	-	-	1 (0.96)	1 (0.96)	-	-	-
36. tert-Butylhydroquinone, 1 pet	8 (7.77)	7 (6.80)	1 (0.97)	-	2 (1.92)	3 (2.88)	2 (1.92)	1 (0.96)	-	1 (0.96)
37. 2-benzotriazol, 1 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
38. Propyl gallate 1 pet	-	-	-	-	-	-	-	-	-	-
39. Dodecyl gallate, 0.25 pet	9 (8.74)	9 (8.74)	-	-	-	4 (3.85)	4 (3.85)	-	-	-
40. Quaternium 15, 1 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
41. 2-Phenoxyethanol, 1 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
42. 2,5-Diazolidinyl urea, 2 pet	-	-	-	-	-	-	-	-	-	-
43. Euxyl K400, 1.5 pet	7 (6.80)	6 (5.83)	1 (0.97)	-	1 (0.97)	3 (2.88)	1 (0.96)	2 (1.92)	-	1 (0.96)
44. DMDM Hydantoin, 2 aq	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
45. Methylidibromo glutaronitrile (MDBGN), 0.5 pet	1 (0.97)	1 (0.97)	-	-	-	-	-	-	-	-
46. Tea tree oil, 5 pet	1 (0.97)	1 (0.97)	-	-	1 (0.97)	-	-	-	-	-
47. Iodopropynyl butylcarbamate, 0.2 pet	1 (0.97)	1 (0.97)	-	-	-	2 (1.92)	2 (1.92)	-	-	-
48. 3-(Dimethylamino) propylamine, 1 aq	2 (1.94)	2 (1.94)	-	-	-	-	-	-	-	-
49. Lauryl glycoside, 3 pet	3 (2.91)	2 (1.94)	1 (0.97)	-	2 (1.94)	1 (0.96)	1 (0.96)	-	-	1 (0.96)

Abbreviations: aq, water; Pet, petrolatum.

sex distribution (67.7% of the reactive cases in the rosacea group, and 72.0% of the reactive cases in the control group were female, $P = 0.698$). In addition, although the differences were not statistically significant, women, subjects who had experienced any disturbance at least once during their lifetime which might be associated with the use of a cosmetic product, and subjects with atopy were more prone to react the cosmetic allergens in both groups ($P > 0.05$). Among the clinical subtypes of rosacea, at least one positive allergic reaction was observed in 62.5% of the subjects in the erythematotelangiectatic subtype, in 53.6% of the subjects in the papulopustular subtype, and in 66.7% of the subjects in the phymatous subtype ($P = 0.696$).

In total, 106 positive allergic reactions were observed in the rosacea group, whereas a total of 40 positive allergic reactions were observed in the control subjects. Among the positive reactions, "1+" reactions were the most common, occurring in 87.7% of the total reactions in rosacea patients, and in 82.5% of the total reactions in control subjects. None of the patch test-positive rosacea patients experienced a flare-up of the underlying rosacea. The most common allergen in rosacea patients was octyl gallate (10.68%), followed by dodecyl gallate (8.74%), tert-Butylhydroquinone (7.77%), thimerosal (6.80%), euxyl K400 (6.80%), cocamidopropyl betaine (5.83%), and 2,6-Di-tert-butyl-4-cresol (BHT; 4.85%). The results of the patch test assessment with cosmetic series in patients and controls are presented in Table 1. Although rosacea patients showed a markedly high rates of positive patch test results to almost all allergens, when positivities for each allergen were compared one by one between the patients and controls using the chi-square test, no statistically significant difference was detected.

In a detailed analysis, the detected positive reactions were relevant in 22 (21.4%) subjects in the rosacea group, and in 10 (9.6%) subjects in the control group based on the previous exposure history (experience of erythema, burning, itching, or tingling sensation with the use of a cosmetic product containing the suspected allergen; $P = 0.019$). These patients were requested to apply their own products containing the suspected allergen twice daily for 1 week (unless a dermatitis appeared earlier) to the flexor aspect of the forearm near the cubital fossa on an area of 5×5 cm for the repeated open application test (ROAT). However, only 12 of the rosacea patients and 7 of the control subjects could agree with the instructions. Of those, the ROAT was positive in 8 rosacea patients with thimerosal (2), triethanolamine (1), tea tree oil (1), propylene glycol (1), stearyl alcohol (1), benzyl alcohol (1), and abitol (1); and in 4 control subjects with thimerosal (1), abitol (1), benzyl salicylate (1), and tert-Butylhydroquinone (1).

Of note, we also recorded the irritant reactions detected both in rosacea patients and controls. At least one positive irritant reaction was observed in 53 (51.5%) rosacea patients and in 29 (27.9%) control subjects ($P = 0.001$). Finally, a total of 86 irritant reactions and a total of 43 irritant reactions were observed in the rosacea and control groups, respectively. The most common irritant reactions in rosacea patients were found to be detected with tert butylhydroquinone (14.6%) and octyl gallate (8.7%), which were also found

to be statistically significant compared to controls ($P = 0.010$ and $P = 0.001$, respectively).

4 | DISCUSSION

Although the term "cosmetic" is usually equated with makeup by the general population, the US Food and Drug Administration (FDA) defines this term as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and articles intended for use as a component of any such articles."¹² The 13 cosmetic categories defined by the FDA include baby products, bath preparations, eye makeup, fragrances, hair preparations, hair-coloring agents, makeup, manicure products, oral hygiene products, personal cleanliness products (with the exception of soap), shaving preparations, skin care preparations, and suntan preparations (excluding sunscreens or any combination product listing a sun protection factor; sunscreens are regulated as over-the-counter drugs).¹³ These products generally remain in close contact with the skin for long periods of time, thus favoring allergic contact sensitization to the numerous chemical substances they include. Besides direct application, cosmetic allergens can also reach the skin by occasional contact with an allergen-contaminated surface, by airborne contact, by transfer by the hands to sensitive areas, and by a product used by the partner or any other person.¹⁴

As well as the general population, cosmetics are also widely used products by rosacea patients to improve or alter the appearance of the face or other parts of the body. Additionally, many cosmetics, including cleansers, moisturizers, and anti-inflammatory botanicals, can be used as adjuvant therapies in combination with traditional therapies to enhance pharmaceutical outcomes and meet patient expectations in a more satisfactory manner. However, the presence of a general intolerance to cosmetic products in rosacea patients is a well-known condition, and previous reports highlight that rosaceous skin has a lower threshold for irritation caused by topically applied creams or cosmetics.^{4,15} In addition to this, with the expansion of current interest to the predisposition of rosaceous skin to develop delayed-type hypersensitivity reactions, recent studies have demonstrated that allergic contact reactions in rosacea patients are also common, and these reactions are mostly created by cosmetic allergens in standard series.⁹ Since there is a high requirement for cosmetic products that do not provoke such reactions and are suitable for use in rosacea patients, we assessed the prevalence of contact sensitization to a large series of cosmetic allergens in rosacea patients and compared their results with general population of similar age and sex distribution. We think that our study has provided some important outcomes. Firstly, this prospective study has shown that rosacea patients are more prone to react with the cosmetic allergens than the general population. Secondly, the higher prevalence of allergic patch test reactions in rosacea patients supports the earlier arguments proposing that rosacea itself may

be an unspecific predisposing condition enhancing susceptibility to contact allergy. And lastly, these results show that some important cosmetic-related contact allergies may be missed by testing patients with the European standard series or TRUE test system only, and supplemental cosmetic series may help physicians in improving their diagnostic accuracy in rosacea patients with suspected cosmetic sensitivity.

In recent years, the predisposition of contact hypersensitivity in rosacea patients has been documented in some studies.⁶⁻⁹ In the study of Corazza et al,⁸ 29 rosacea patients were patch tested with standard series, preservatives series, emulsifiers series, perfumes series and their own cosmetics and medicaments. Positive patch test results were determined in 41.4% of these patients, and 34.5% of patients showed more than one positive reaction to the allergens applied. Although patients were all negative to their own products except for one patient who showed a strong reaction to a shampoo (Kerastase®) and one other to a cream (Nizoral®), thimerosal and amerchol L 101 were among the allergens giving positive test reactions in this study. In another retrospective study, Jappe et al⁷ reviewed the patch test results of the 361 rosacea patients who had been patch tested with standard series and constituents of cosmetics and topical medicaments. A total of 118 of these patients had also been patch tested with their own leave-on cosmetics. A positive patch test reaction was found in 38.2% of the patients in this study, including the positive reactions to thimerosal (6.9%), methyltribromo glutaronitrile (MDBGN; 3%), paraben mix (3%), and methylchloroisothiazolinone (0.7%). Although in a low number, positive patch test results were also detected with the patients' own products such as creams, emulsions, lotions, gels and oils for the skin, products for making-up, shaving products, medical cosmetics, and cosmetic cleaning products. Following this study, the authors published the results of another prospectively designed study investigating the specific contact allergy on 78 rosacea patients. The patients were patch tested with standard series, constituents of topical formulations, preservatives, fragrances, topically applied drugs and, if available, their own products. As a result, 62.8% of the patients were found to show at least one positive reaction to the commercial test substances. Among those, patients reacted to some of the cosmetic allergens also included in our study, such as MDBGN (9.3%), tert-Butylhydroquinone (3.8%), chlorhexidine digluconate (2.6%), cocamidopropyl betaine (2.6%), and amerchol L-101 (2.6%). However, no allergic but only irritant patch test reactions were detected to the patients' own products including hairdressing and hair cleaning products, and sunbathing products.⁶ In another short report of Po'nyai et al,⁹ contact hypersensitivity was found in 29 (35.4%) of the 82 rosacea patients who were patch tested with standard allergen series including some of the common cosmetics such as paraben, propylene glycol, thimerosal, quaternium 15, and MDBGN. The authors commented that the relevant contact hypersensitivity detected in their study was found to associate mostly with cosmetics (46.1%) and washing agents (38.4%), and 38.8% of women face creams and makeups, and 20% lotions and

gels were found to be in connection with the contact hypersensitivity. Very recently, Erdogan et al¹⁶ reported the results of their study evaluating the contact sensitivity to cosmetic allergens in 65 rosacea patients and 60 controls, and a positive reaction to at least 1 cosmetic allergen was found in 25 (38.5%) of the rosacea patients and in 20 (25%) of the control subjects. The most common allergens in rosacea patients were nickel sulfate, textile dye mixture, fragrance mixture 2, cobalt chloride, and lyral in the European standard series; and amerchol L 101, triethanolamine, sorbitan sesquioleate, dodecyl gallate, and lauryl glycoside in the cosmetic series. These high reactivities to cosmetic allergens in rosacea patients may be related to the previous sensitizations due to the increased penetration of allergens through the rosaceous skin, or a greater exposure to cosmetics and other personal care products in attempt to improve the disturbing appearance of the rosaceous skin may have also had an enhancing effect on the dynamics required for contact sensitization in rosacea patients.

This study has certain limitations. Although most patients tended to avoid using the cosmetics including the positive allergens, did the avoidance result in any change of the rosacea side effects in patients is a mystery due to the lack of follow-up evaluation. Additionally, the patients were not tested to the standard series; thus, we may have missed out on some of the standard cosmetic allergens. It was not also possible to definitely diagnose the positive patch test relevance in each subject since it was based on the previous exposure history, and we could not perform the ROAT in all subjects who had weak positive reactions. Nevertheless, this prospective controlled study has the largest sample size in literature assessing the prevalence of contact sensitization to cosmetic allergens, using a wide range of cosmetic series in rosacea patients. To ensure a fair comparison, we included all the consecutively admitted rosacea patients and control subjects meeting the inclusion criteria during the study period, instead of just enrolling the individuals with signs of allergic contact dermatitis related with cosmetic use. In this manner, we think that the rosacea patients in this study were representative of the rosacea population seen in general dermatology practice.

In conclusion, these results show that rosacea patients have a higher prevalence of contact sensitization to cosmetic allergens. Given that most of the allergic reactions identified in patients were weak reactions, it should also be considered whether mild forms of contact hypersensitivity may mimic or trigger the exacerbation of the underlying rosacea in patients. On the other hand, it is certain that our results do not directly indicate that all of these patients with a positive allergic patch test will develop a clinically evident contact dermatitis in daily life, since the concentrations of the allergens in the patch test are often much higher than the concentrations in retail products, which may also cause chemical irritation. However, since patch testing is still the best diagnostic modality to assess the contact sensitization, the presence of such higher predisposition to react to the cosmetic allergens in rosacea patients needs to be kept in mind. Based on the results of this study, we recommend the additional use of cosmetic series for patch testing, and the careful

use of cosmetics in rosacea patients if cosmetic contact sensitivity is suspected.

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