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Effect of photoaging on skin test response to histamine independent of chronologic age

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ABSTRACT

Background: Skin prick-puncture test responses to histamine on the upper back and forearms in older individuals are frequently small or absent but are often present or larger when repeated on the lower back.
Objective: To determine whether photoaging or natural aging causes a smaller response to a prick-puncture skin test.
Methods: Prick-puncture skin tests to histamine were performed on sun-exposed and sun-protected areas in younger (n = 61, aged 20–50 years) and older (n = 63, aged 60–87 years) adult volunteers. The skin was scored for photoaging by physical examination, and coloration was measured by a colorimeter.
Results: Large variation of photoaging occurred within age groups. Histamine wheals and flare were not different between the 2 age groups, but those adults with the greatest photoaging had smaller histamine wheals and flare on the upper back, with a trend for smaller flares on the volar aspect of the forearms and lower back. There was marked variability in response to histamine within individual adults, depending on the locale of the tests.
Conclusion: Photoaging, but not age alone, is associated with a smaller response to histamine in sun-exposed areas. Before prick-puncture skin tests are performed, the skin should be examined for sun damage, and a sun-protected area should be selected; in vitro allergy testing may be substituted if there is no sun-protected skin area.

Introduction

Skin changes in elderly individuals are due to a combination of natural aging and photodamage, 2 biologically different processes. Natural aging occurs on all skin areas, including sun-protected areas, whereas photodamage occurs in sun-exposed areas, especially the face, the upper back, and dorsal surfaces of the hands and upper extremities.

We have observed that allergy skin test responses in some, but not all, older individuals are very small or negative. In some older patients, the response to skin testing to histamine is small or absent when performed on the upper back, but when performed on the back below the belt line, the response is frequently larger with a mean wheal diameter of more than 3 mm. It also has also been observed that some older patients with less photoaging have robust responses to histamine.

During natural aging, the epidermis of older people undergoes atrophy, resulting in fewer cell layers, a decrease in cellularity and collagen, and a marked reduction in blood vessels.[1,2] The epidermis of older individuals may have only 2 to 3 cell layers compared with approximately 20 cell layers in younger individuals. Some skin changes in elderly individuals result from the passage of time and some from sun exposure. Sun-damaged skin exhibits both hypermelanotic and hypomelanotic lesions, along with atrophy of the subcutaneous tissue, hypertrophy of the epidermis, and increased keratin. Elastosis is also present in severe photodamage, with deposition of an abnormal, yellow, altered elastin. UV light exposure suppresses prick-puncture responses after even a single exposure of a suberythematous dose.[3]

There are good methods to measure sun damage. Glogau described 4 types of photoaging: type I, little or no sun damage; type II, wrinkles in motion; type III, wrinkles at rest; and type IV, severe sun damage (Fig 1).[4] Seitz and Whitmore[5] reported on measurement of erythema and tanning responses in human skin using a colorimeter.

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Figure 1. Representative images of progressive photoaging of skin. From left to right, these hands show increasing wrinkles, pigmentation, and keratosis. Photograph courtesy of the National Institute on Aging.

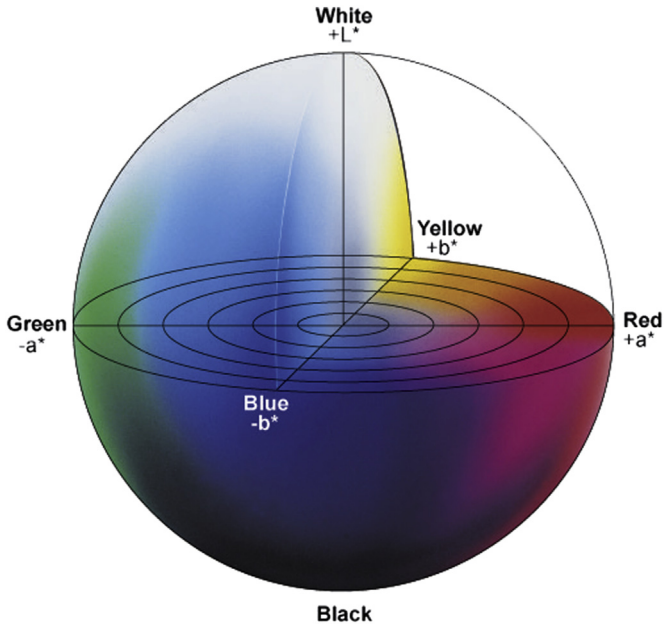

Figure 2. Color wheel Commission International l'Eclairage Lab color space values: lightness, with 100 indicating white and 0 indicating black; redness, with 0 indicating no red and 60 indicating all red; and yellowness, with 0 indicating no yellow and 60 indicating all yellow. Reprinted with permission from Konica Minolta Sensing Americas, Inc.

It is common practice to place a positive histamine and negative saline diluent control when performing skin tests. The cutoff for a minimum positive response to histamine is a mean diameter wheal of 3 mm.[6]

The objective of this study is to determine the effects of aging and photodamage on the prick-puncture test (PPT) responses to histamine and saline by comparing the PPT on sun-damaged vs sun-protected skin in younger and older adults who present with respiratory allergic symptoms.

Methods

One hundred twenty-four individuals participated in the study. Participants enrolled were (1) referred to the Allergy Clinic at the James A. Haley Veteran's Hospital, Tampa, Florida, (2) referred to clinics associated with the University of South Florida Morsani College of Medicine, (3) or recruited from the community. All had physician-diagnosed allergic rhinitis or allergic asthma. Older participants were those older than 60 years, and younger participants were aged 20 to 50 years. Individuals of all races were invited to participate, and 122 whites and 2 Asians volunteered. All participants received a full explanation of the study and signed an informed consent form before participating in the study. The institutional review boards of the University of South Florida Morsani College of Medicine and the James A. Haley Veteran's Hospital approved the study.

Exclusion criteria included the following: skin cancer or scars on the back or forearms or severe sun damage (Glogau class IV) and medications that could alter PPT results or increase the risk of a systemic allergic reaction, such as antihistamines, antidepressants, and β-blockers. Also excluded were individuals with infectious, metabolic, and connective tissue diseases; malignant tumors within the last year; pregnant or lactating women; nude sun bathing or tanning parlor exposure for more than 30 days during a lifetime or during the past year; current or cigarette smoking during the past year; and allergen immunotherapy within the past year. Long- and short-acting bronchodilators, inhaled corticosteroids, and short-acting antihistamines (diphenhydramine or chlorpheniramine) were allowed for up to 48 hours, and long-acting antihistamines (loratadine and fexofenadine) were held at least 7 days before PPT.

Table 1
Photoage scores[a]

Glogau type (photoage score range)	Wrinkles	Upper back pigmentation (tanning)	Keratosis
I (0–2)	0 (None)	0 (Same as low back)	0 (None)
II (3–5)	1 (Only in motion)	1 (Moderately darker than low back)	1 (Palpable only)
III (6–7)	2 (At rest)	2 (Much darker than low back)	2 (Visible)
IV (8–9)	3 (Only wrinkles)		

[a]The sum of individual scores for wrinkles, upper back pigmentation, and keratosis approximates the Glogau types. For example, Glogau type I indicates no wrinkles (score, 0), moderate pigmentation (score, 1), and no keratosis (score, 0) (sum, 1). Individuals with Glogau type IV photoaging were excluded from the study.

Physical Examination

A history and physical examination were performed with an emphasis on lifetime sun exposure and skin characteristics.

Table 2
Mean diameters of prick-puncture test results

Group	Histamine wheal, mm	Histamine flare, mm
Upper back (n = 122)		
All participants	4.15	14.8
Male	3.73[a]	13.31
Female	4.53[a]	16.15
Younger age group	4.17	16.2
Older age group	4.13	13.49
Lower back (n = 122)		
All participants	5.14	16.25
Male	4.80	13.65
Female	5.45	18.66
Younger age group	4.87	15.62
Older age group	5.40	16.85
Forearm (n = 63)		
All participants	4.53	9.93
Male	4.47	10.47
Female	4.60	9.35
Younger age group	4.59	11.86[b]
Older age group	4.35	8.23[b]

[a]$P < .05$ between upper back wheals in men and women.
[b]$P = .07$ between forearm measurements in the younger and older groups.

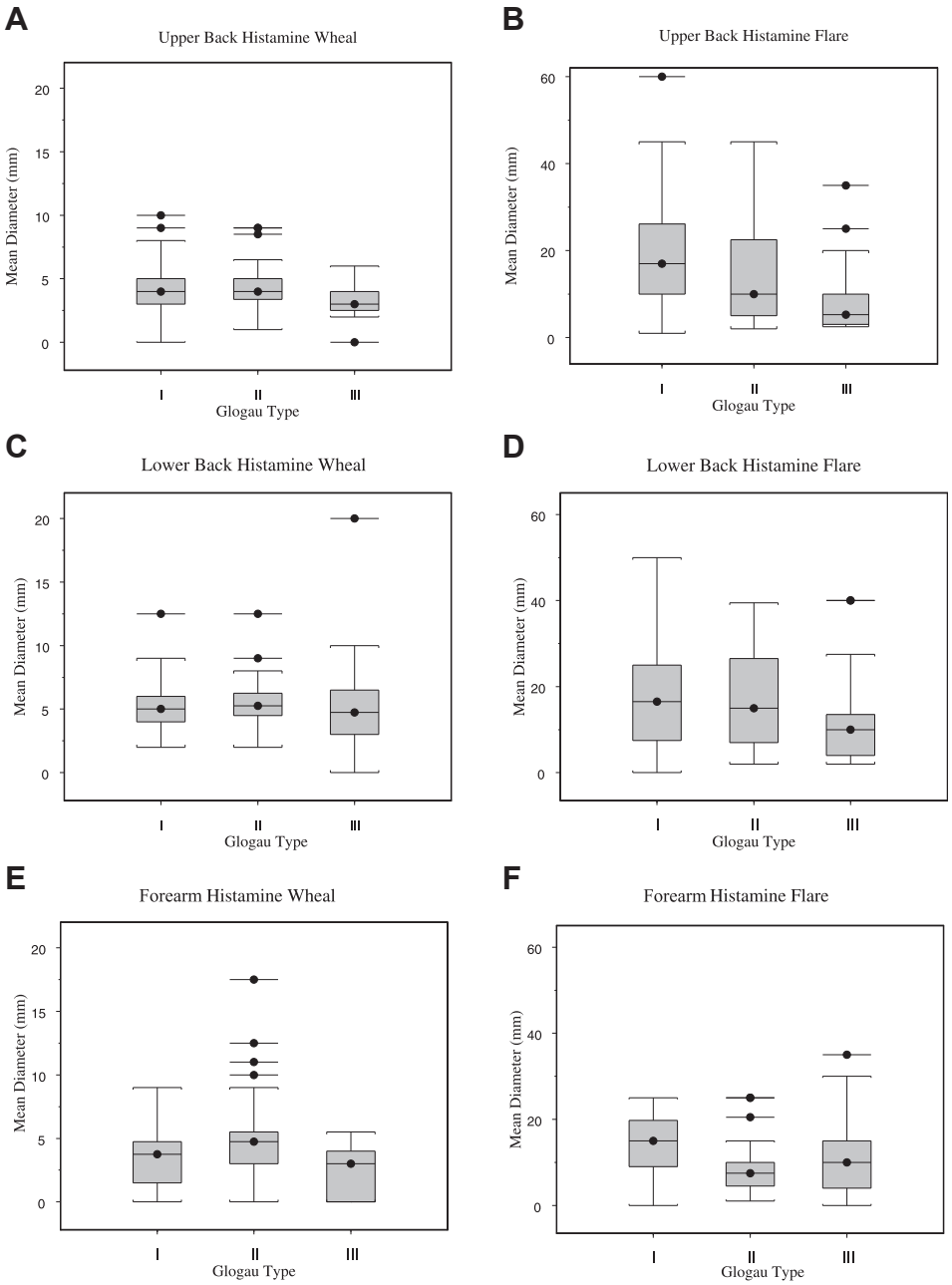

Figure 3. Histamine skin test response relative to photoage. Wheal (A, C, and E) and flare (B, D, and F) responses stratified by Glogau scores. Upper back wheal and flare (A and B) were significantly larger in those with the least photoaging (Glogau type I) vs those with the most photoaging (Glogau type III). No difference was seen in histamine response on the lower back (C and D) or arm (E and F) among varying degrees of photoaging.

A photoaging score was assigned after assessing wrinkles (range, 0–3), upper back pigmentation (range, 0–2), and keratosis (range, 0–2). A total photoaging score of 0 to 2 was equivalent to Glogau type I, 3 to 5 was Glogau type II, and 6 to 7 was Glogau type III (Table 1).

Skin Color

Skin color was measured on the sun-exposed upper back and sun-protected lower back, below the tan line on all individuals, in the first phase and on the volar surface of the forearms in the second phase using a Minolta BC-10 colorimeter (Konica Minolta Sensing Americas, Inc, Ramsey, New Jersey). Results were expressed in Commission International l'Eclairage Lab color space values (lightness, with 100 indicating white and 0 indicating black; redness, with 0 indicating no red and 60 indicating all red; yellowness, with 0 indicating no yellow and 60 indicating all yellow) (Fig 2).[5]

Prick-Puncture Tests

The PPTs were performed with a Morrow Brown needle (a 27-mm-long device with a single 1.25-mm point below a shoulder) (Alkaline Corporation, Oakhurst, New Jersey) using a glycerinated phenol-saline for the negative control and a histamine base of 1.8 mg/mL (5 mg/mL [16.3 mmol/L] of histamine phosphate) for the positive control. The PPTs were performed on all participants on the upper back, above the lower margin of the scapula, and on the lower back, below the level of the second lumbar vertebra or the individual's tan line (if lower). Sixty-three of the 124 individuals received additional PPTs on the volar surface of the forearm,

avoiding the areas near the wrists and the antecubital fossae. Skin prick test responses for the wheal and the flare were recorded as the sum of the longest diameter plus the longest perpendicular diameter and then halved to obtain the mean. A ballpoint pen was used to outline these responses, where necessary. The histamine responses were recorded as the size of the wheal and flare response in each respective area.[6] Several study coordinators performed and interpreted the skin test result; all were experienced with the Morrow Brown device.

Statistical Analysis

We performed a power calculation with $\alpha = .05$ and $\beta = 0.20$, with a suggested minimum of 20 individuals in each group. Results were analyzed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina), and R version 3.1.1 (The R Foundation for Statistical Computing). Pearson correlations were calculated for skin coloration on the forearm and upper and lower back. Paired *t* tests were used to determine whether there was a significant difference in skin coloration in the upper and lower back, the upper back and the forearm, and the lower back and the forearm. The *t* test was used for age and sex group differences. Analysis of variance was run to determine histamine differences among the photoaging types.

Results

Two cohorts volunteered. The older group included 63 individuals (32 women and 31 men) aged 60 to 87 years (mean [SD] age, 69 [6.2] years), and the younger group included 61 individuals (32 women and 29 men) aged 20 to 50 years (mean [SD] age, 33 [7.8] years). The results of skin prick tests were excluded for 2 young men who did not respond to histamine in any of the areas tested. These tests were performed again on the same day and the results remained negative. Both participants declined to return for another set of PPTs. Their results were included for coloration and photodamage but not PPT reactivity. Because of a technical problem with the colorimeter, 2 additional young men did not have coloration measured. Their results were included for photoaging and PPT but not in comparing photoaging and coloration.

Coloration for All Age Groups

Color measurements of the upper vs the lower back were consistently darker, redder, and more yellow. Regardless of their age, the color differences between the areas tested on the upper and lower back were significant (paired *t* test, $P < .001$). Lightness between the volar aspect of the forearm and upper back was not statistically significant ($P = .10$). Volar aspects of the forearms were similar to the upper back for lightness in the older age group.

Photoage and Age

Photoage scores ranged from 0 to 6 (mean [SD] 1.59 [1.24]) in the younger age group, whereas they ranged from 2 to 7 (mean [SD] 4.30 [1.36]), with a large scatter of photoaging scores, within the older group. There was a significant association between age and photoage score for all participants (Pearson $r = 0.75$, $P < .001$; *P* the Kruskal-Wallis rank sum test is <0.0001). When comparing age by Glogau type, patients with type I photoaging had a mean age of 35 years, those with type II photoaging had a mean age of 65 years, and those with type III photoaging had a mean age of 68 years. For the Pearson χ^2 test, $P = .01$, indicating a significant association between age and higher Glogau type (Table 2).

Photoage and Coloration

There was a correlation between photoage and constitutional (sun-protected lower back) skin coloration: lightness ($r = 0.31$, $P < .001$), redness ($r = -0.33$, $P < .001$), and yellowness ($r = -0.35$, $P < .001$), indicating fair skin is associated with more photoaging. The difference between the coloration of the upper and lower back correlated with the photoage score for all study participants. A difference in lightness ($r = 0.37$, $P < .001$) and the difference in redness ($r = 0.21$, $P < .05$), but not the difference in yellowness ($r = .17$, $P < .10$), were significant. The correlation between lightness and photoaging ($r = -0.48$, $P < .001$) and redness and photoaging ($r = 0.34$, $P < .01$) was stronger in males.

Age and Histamine Skin Test Response

Histamine wheal size did not differ between the age groups on the lower back ($P = .78$ for the Wilcoxon signed rank test), upper back ($P = .16$), or volar aspect of the forearm ($P = .82$). There was a decrease in flare on the upper backs of the oldest women (>70 years old) (Table 2).

Photoage and Histamine Skin Test Response

The photoaging score for all eligible study participants (N = 122; range, 0–7; mean [SD], 2.99 [1.89]) had a negative correlation ($r = -0.234$, $P < .01$) with the upper back histamine wheal size (range, 0–10 mm; mean [SD] 4.27 [1.72] mm). Men had stronger correlations, ($r = -0.36$, $P < .01$), especially older men ($r = -0.48$, $P < .01$). When compared by Glogau type, individuals with Glogau type III had smaller wheals and flares on the sun-exposed upper back ($P < .05$) and a trend for smaller flares in all areas (Fig 3).

Coloration and Histamine Skin Test Response

Only red coloration was negatively correlated with histamine wheal size on the upper backs of females ($r = -0.33$, $P < .01$).

Skin Test Location and Histamine Response

Histamine wheals were 3 mm or less in diameter on the upper back in 12 individuals ($P = .10$), on the volar aspect of the forearm in 9 individuals ($P = .10$), and on the lower back in 6 individuals ($P = .049$). Overall, male sex was associated with a small upper back histamine wheal (<3 mm) ($\chi^2 = 6.84$, $P < .01$). Ten men and 2 women had upper back histamine wheal diameters less than 3 mm. These 12 individuals also had a negative correlation with the upper histamine wheal and the difference in lightness between the upper and lower back ($r = -0.68$, $P < .05$).

Histamine and Morphine PPT Response

Sixty individuals were tested with morphine and histamine. A comparison of histamine response and morphine response was significantly associated in all 3 areas tested ($P < .001$ for the upper and lower back and $P < .05$ for the forearms).

Discussion

The purpose of this study was to determine whether natural aging or photoaging correlates with smaller responses to histamine. The results indicate that there is no correlation with histamine response and natural aging but that photoaging correlates with smaller skin test responses to histamine on the volar surface of the forearm and upper back. Photoaging scores obtained on physical examination by study physicians correlate with differences in coloration of the upper and lower back. A pale, fair, constitutional skin color and a large color difference between the lower and upper back were associated with more photoaging. Individuals with a negative histamine skin test result on the upper back were likely to have a positive histamine response on either the volar aspect of the forearm or lower back. Previous reports found smaller responses to histamine in older individuals but did not assess photoaging. Skassa-Brociek et al[7] reported a decrease in skin test reactivity to histamine after 50 years of age, which

plateaued after 60 years of age. They also reported a wheal in all individuals older than 70 years, but the flare associated with the prick-puncture was difficult to detect in some individuals. Testing was performed on the forearms (exact location not indicated) using serial dilutions of histamine. They did not comment on photoaging in their study participants. Song et al[8] reported that older individuals and women have reduced skin test reactivity to histamine on the volar aspect of the forearm but also did not address photoaging.

Although histamine reacts directly on tissue and blood vessels in response to PPTs, morphine acts on mast cells, causing the release of mediators, including histamine, that in turn act on tissue and blood vessels. Further studies of the effect of natural aging and photoaging on mast cell distribution and response to morphine are needed. The Morrow Brown PPT device was used in this study because our clinical research unit has more than 15 years experience with this device without any problems. Other devices may give larger or smaller wheals or flares.

The clinical importance of photoaging associated with small histamine responses makes it imperative that the skin test area be examined for signs of photoaging before skin testing. For clinical purposes, the presence or absence of wrinkling, keratosis, and coloration or tanning of sun-exposed vs sun-protected areas should be adequate in assessing photodamage before skin testing.

In conclusion, this is the first report, to our knowledge, of photoaging associated with decreased response to histamine PPTs. When photoaging is present, the PPTs should be performed on sun-protected areas of the skin. If there are no areas of undamaged skin, in vitro allergy testing should be performed.

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