Association of the Köbner Phenomenon With Disease Activity and Therapeutic Responsiveness in Vitiligo Vulgaris

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Objective: To investigate the association between the experimentally induced Köbner phenomenon (KP-e) and the Köbner phenomenon by history (KP-h), disease activity, and therapeutic responsiveness in vitiligo vulgaris.

Design: Cohort study.

Setting: An outpatient clinic.

Patients: Sixty-one consecutive patients with vitiligo vulgaris.

Intervention: Three months after a standardized epidermodermal injury was induced, the KP-e was evaluated. For 1 year, UV-B (311 nm) therapy or topical fluticasone propionate plus UV-A therapy was given, depending on the severity of depigmentation.

Main Outcome Measures: The presence or absence of the KP-e and the KP-h disease activity as scored on a 6-point scale from −1 to +4 (vitiligo disease activity [VIDA] score) and therapy-induced repigmentation grade.

Results: Nineteen (31%) of the patients had a positive KP-h, whereas 37 (61%) showed a positive KP-e ($P < .001$). The VIDA score did not always predict a positive KP-e, although patients with a positive KP-e had a higher mean VIDA score (VIDA score of 1.6) than did patients with a negative KP-e (VIDA score of 0.5) ($P < .001$). The responsiveness to UV-B (311 nm) therapy among KP-e–positive or KP-e–negative patients was not significantly different ($P = .66$). However, KP-e–positive patients who were treated with fluticasone propionate plus UV-A showed a better response than did KP-e–negative patients ($P = .01$). Among patients responding to both therapies, VIDA scores were significantly decreased ($P < .001$) compared with VIDA scores before therapy.

Conclusion: The KP-e may function well as a clinical factor to assess present disease activity and may also predict the responsiveness to fluticasone propionate plus UV-A therapy but not to UV-B (311 nm) therapy.

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VITILIGO IS an acquired pigmentary skin disorder affecting approximately 1% of the world population. There are several clinical types of vitiligo.1 The most common type is vitiligo vulgaris, which is clinically characterized by symmetrically distributed depigmented macules that usually expand in size and number during the natural course of the disease. Treatment of vitiligo is aimed at stopping the disease progress and restoring the loss of melanocytes in the lesions. Although a variety of therapeutic modalities has been applied, there is still no universally effective and safe therapy available. The most practiced therapies at this time are phototherapy, corticosteroid use, and transplantation of autologous melanocytes.

To make a reasonable choice of therapy with the highest probability of success for an individual patient it is important to identify disease characteristics that help predict the outcome of therapy. Besides age, duration of disease, localization, and extent of depigmentation,2 current disease activity should also be taken into consideration during clinical decision making. This is especially essential for patients with vitiligo vulgaris because, in this type, disease activity may fluctuate at a given time. Although medical therapies may be equally effective in active and stable disease,3,4 surgical methods are suitable only for those with stabilized disease.5,6

At present, disease activity is mainly assessed by the medical history. Information on disease activity can also be obtained by physical examination. Usually, the size together with the number of lesions and the grade of repigmentation during follow-up visits are recorded using photographic material. In contrast...
PATIENTS AND METHODS

PATIENTS

In total, 61 consecutive patients with vitiligo vulgaris were selected. Included were male and female patients between 12 and 65 years old who had not received any topical or systemic medication for treatment of vitiligo in the previous 6 months.

A routine history was taken, with special attention to the presence of the KP-h, duration of disease, and the patient’s opinion of the present disease activity. The latter was scored on the 6-point VIDA scale (Table 1).

By physical examination, the type of vitiligo was noted, and the percentage of depigmentation in relation to the total body surface was estimated using the “handpalm rule,” ie, a lesion the size of the patient’s handpalm equals 1% of the total body surface.

Informed consent was obtained from all the patients; the study was approved by the Medical Ethical Committee of the Academic Medical Centre, Amsterdam, the Netherlands.

THE KP-e

Four 2-mm punch epidermal grafts using biopsy punches (Stiefel, Maidenhead, UK) were removed from a normally pigmented area, mostly the hip or the buttocks, with no vitiligo lesions present within a radius of 15 cm. The grafts were cut horizontally from the base using ophthalmologic scissors and tweezers. One of us (M.D.N.) consistently punched the skin with a constant pressure to a standard depth (2 mm) to induce an experimental epidermodermal injury.

After 3 months, the outcome of the KP-e was evaluated by 2 independent observers (M.D.N. and W.W.). When there was disagreement, a third observer was consulted (P.K.D.). The KP-e was scored negative when the wound healed without depigmentation and positive when depigmentation of the biopsy scar or even depigmentation beyond the biopsy margins occurred. In doubtful cases a dermatoscope (Heine Delta 10; Heine Optotechnik, Herrsching, Germany) was used. Subsequently, photographs were taken of the biopsy sites.

THERAPY

The following therapeutic regimens were applied according to the severity of depigmentation: (1) narrowband UV-B (311 nm) therapy twice weekly for patients with more than 5% depigmentation15 and (2) fluticasone propionate cream applied once daily combined with UV-A (10 J/cm²) therapy twice weekly for patients with 5% or less depigmentation.16

Follow-up took place every 3 months. After 1 year, the relationship between the response to each therapy and the presence or absence of the KP-e was studied, and the VIDA score was determined again for each patient.

For all patients, the degree of repigmentation was scored visually against the photographs obtained at the first visit for enrollment in the study and after 12 months of therapy. For patients in the group receiving (total-body) UV-B therapy, the overall repigmentation grade was noted; for patients in the group receiving fluticasone propionate plus UV-A therapy, the repigmentation grade of only the treated lesions was calculated. Patients were considered “good responders” when the therapy resulted in 50% or more repigmentation of the lesions and “poor responders” when less than 50% repigmentation was achieved.15,16

Response to therapy and VIDA scores were evaluated independently in a masked manner by 2 observers (M.D.N. and W.W.). When there was disagreement, a third observer was consulted (P.K.D.).

STATISTICAL ANALYSIS

Statistical analysis was performed using the 2-tailed Student t test, Wilcoxon matched pairs rank sum test, χ² test, and Pearson correlation test. The significance level was set at P<.05.

To date, the role of certain “vitiligo-associated skin manifestations”1 in the onset or progression of vitiligo is not well documented. One of these skin manifestations is the Köbner phenomenon (KP), which is defined as “the development of vitiligo at sites of aspecifically traumatized skin.”6,7,8 Results of several independent epidemiological studies show that the KP occurs in most patients with vitiligo.10,11 Its clinical relevance is not yet established, although it has been frequently postulated that the KP may indicate active disease.5,13,14 However, no further data have been obtained to support this hypothesis. Moreover, it is unclear whether patients with a positive KP have a different prognosis than patients with a negative KP.

In this study, we induced an experimental KP (KP-e) by performing an epidermodermal injury to the clinically uninvolved skin. Subsequently, we investigated the association between the KP-e and the KP by history (KP-h), disease activity by history (vitiligo disease activity [VIDA] score), and responsiveness to therapy in 61 patients with vitiligo vulgaris.
RESULTS

PATIENTS

Table 2 presents patient characteristics according to VIDA scores. In most patients (48%), disease activity was scored as +1. There was no significant correlation between the VIDA score and sex, age, percentage of depigmentation, or duration of disease ($\chi^2$ test $2 \times 6$ table [$P = .55$] and Pearson correlation coefficients of 0.10 [$P = .42$], 0.07 [$P = .60$], and −0.06 [$P = .58$], respectively). There were no significant differences between patients with active disease (VIDA scores of +4 to +1) and those with stable disease (VIDA scores of 0 to −1) regarding sex ($\chi^2$ test, $P = .90$), age (t test, $P = .09$), percentage of depigmentation (t test, $P = .27$), and duration of disease (t test, $P = .14$). The 2 patients with the highest VIDA score, +4, showed a significantly shorter duration of disease (t test, $P<.001$) and a lesser percentage of depigmentation than did the remaining 59 patients (with VIDA scores of +3 to −1), whereas sex and age were not significantly different between these 2 groups ($\chi^2$ test, $P = .19$, and t test, $P = .28$, respectively).

RELATION BETWEEN THE KP-h AND THE KP-e

By history, 19 patients (31%) recalled the experience of a KP-h occurring after burns, wounds, or scratches. They all also showed 1 or more lesions. The remaining 42 patients could not recall the occurrence of such events that had resulted in a vitiligo lesion.

In 24 patients, the injured skin healed with repigmentation (negative KP-e) (Figure 1, left). In the remaining 37 patients (61%), a positive KP-e was observed (Figure 1, right). In 2 patients (with VIDA scores of +4), depigmentation beyond the biopsy margins was noted.

The relation between the KP-h and the KP-e is shown in Table 3. The positive predictive value of the KP-h was 89% (17/19). The negative predictive value of the KP-h was 52% (22/42). Two (11%) of 19 KP-h–positive cases were false-positive, whereas 20 (48%) of 42 were false-negative. The differences as shown in Table 3 were statistically significant ($P<.001$) after performing the $\chi^2$ test.

RELATION BETWEEN THE KP-e AND THE VIDA SCORE

Figure 2 shows the distribution of KP-e-positive and KP-e-negative patients as a function of their VIDA scores. Patients with VIDA scores of +1 and +2 did not necessarily show a positive KP-e. However, all patients with VIDA scores of +3 and +4 showed a positive KP-e. There were also 2 patients with ”stabilized disease” (VIDA score of 0) who scored a positive KP-e. The 2 patients with stabilized disease and spontaneous repigmentations (VIDA score of −1) showed a negative KP-e.

Table 4 shows that sex, age, percentage of depigmentation, and duration of disease were not significantly different for those who were KP-e positive than for those who were KP-e negative. However, the 37 KP-
e–positive patients had a significantly higher mean ± SD VIDA score (1.6 ± 1.0) than did the 24 KP-e–negative patients (0.5 ± 0.8) (t test, *P* < .001).

**Table 4. The Relation Between the KP-e and Sex, Age, Percentage of Depigmentation, Duration of Vitiligo, and VIDA Score**

<table>
<thead>
<tr>
<th>KP-e</th>
<th>Sex, No.</th>
<th>+</th>
<th>−</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>10</td>
<td></td>
<td>.74†</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>14</td>
<td></td>
<td>.74†</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>37.3 ± 12.0</td>
<td>33.0 ± 12.7</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>Depigmentation, mean ± SD, %</td>
<td>9.2 ± 11.5</td>
<td>7.2 ± 6.3</td>
<td>.39</td>
<td></td>
</tr>
<tr>
<td>Duration of vitiligo, mean ± SD, y</td>
<td>13.2 ± 9.0</td>
<td>10.8 ± 7.4</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>VIDA score, mean ± SD</td>
<td>1.6 ± 1.0</td>
<td>0.5 ± 0.6</td>
<td>&lt; .001‡</td>
<td></td>
</tr>
</tbody>
</table>

KP-e indicates experimentally induced Köbner phenomenon; VIDA, vitiligo disease activity. Statistical analysis was done by 2-tailed Student’s t test except where noted.

†Good responders had ≥50% repigmentation; poor responders, <50% repigmentation.

‡Significant.

**Table 5. The Relation Between the KP-e and the Response to Treatment After 1 Year of UV-B (311 nm) Therapy (n = 27) or Topical FP + Local UV-A Therapy (n = 32)***

<table>
<thead>
<tr>
<th>Therapy</th>
<th>KP-e</th>
<th>Responders, No.†</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV-B (311 nm)</td>
<td>+</td>
<td>10‡</td>
</tr>
<tr>
<td>FP + UV-A</td>
<td>+</td>
<td>13§</td>
</tr>
</tbody>
</table>

‡x² Test for 2 × 2 table, *P* = .66.
§x² Test for 2 × 2 table, *P* = .01.

*KP-e indicates experimentally induced Köbner phenomenon; FP, fluticasone propionate.
†Good responders had ≥50% repigmentation; poor responders, <50% repigmentation.

**Table 6. Factors Affecting Response to Therapy**

<table>
<thead>
<tr>
<th>Factors, Mean ± SD</th>
<th>Response†</th>
<th>Good Responders (n = 17)</th>
<th>Poor Responders (n = 18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV-B (311 nm)</td>
<td>Age, y</td>
<td>34.2 ± 11.0</td>
<td>39.2 ± 11.5</td>
<td>.27</td>
</tr>
<tr>
<td></td>
<td>Depigmentation, %</td>
<td>14.3 ± 1.6</td>
<td>17.4 ± 1.9</td>
<td>.56</td>
</tr>
<tr>
<td></td>
<td>Duration of vitiligo, y</td>
<td>14.6 ± 8.8</td>
<td>18.3 ± 9.2</td>
<td>.31</td>
</tr>
<tr>
<td>FP + UV-A</td>
<td>Age, y</td>
<td>39.4 ± 14.7</td>
<td>33.1 ± 12.9</td>
<td>.22</td>
</tr>
<tr>
<td></td>
<td>Depigmentation, %</td>
<td>2.8 ± 1.4</td>
<td>3.6 ± 1.4</td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td>Duration, y</td>
<td>5.8 ± 5.6</td>
<td>12.9 ± 7.1</td>
<td>.003‡</td>
</tr>
</tbody>
</table>

FP indicates fluticasone propionate.
†Good responders had ≥50% repigmentation; poor responders, <50% repigmentation.
‡Significant by Student’s t test (2-tailed).

**RELATION BETWEEN THE KP-e AND THE RESPONSE TO THERAPY**

Two patients dropped out of the study because of lack of motivation to continue therapy. Further data analysis was done with the remaining 59 patients with vitiligo vulgaris who received either UV-B (311 nm) therapy (n = 27) or fluticasone propionate plus UV-A therapy (n = 32).

The data presented in Table 5 show that among KP-e–positive patients treated with UV-B (311 nm), 67% (10/15) showed good response and 33% (5/15) showed poor response. Of the KP-e–negative patients, 58% (7/12) were good responders and 42% (5/12) were poor responders. These differences in responsiveness between KP-e–positive and KP-e–negative patients were not statistically different (*P* = .66). Of the KP-e–positive patients treated with fluticasone propionate plus UV-A, 59% (13/22) showed good response and 41% (9/22) showed poor response. Only 1 (10%) of 10 KP-e–negative patients responded well to therapy, whereas, in 9 of the 10 patients, no signs of repigmentation were observed. These differences in responsiveness between KP-e–positive and KP-e–negative patients to fluticasone propionate plus UV-A therapy were statistically significant (*P* = .01).

In the UV-B (311 nm)–treated patients, age, percentage of depigmentation, and duration of disease were not significantly different between good responders (n = 17) and poor responders (n = 10) (data not shown). In the fluticasone propionate plus UV-A group, age and percentage of depigmentation were also not significantly different between good responders and poor responders (data not shown). However, patients with a good response to fluticasone propionate plus UV-A therapy (n = 14) had a significantly shorter mean ± SD duration of disease (5.8 ± 5.4 years) than did the poor-responding patients (n = 18) (2-tailed Student’s t test, *P* = .003) (Table 6).

**Figure 3** shows that a good response to either UV-B (311 nm) therapy or fluticasone propionate plus UV-A therapy...
was significantly associated with lower VIDA scores after therapy compared with VIDA scores before therapy (Wilcoxon test, \( P<.001 \) for both groups).

In poor responders treated with either UV-B (311 nm) or fluticasone propionate plus UV-A, VIDA scores were not significantly different after 1 year of therapy (Wilcoxon test, \( P>.05 \) for both groups) (results not shown).

### COMMENT

There seems to be no consensus regarding the clinical evaluation of disease activity in vitiligo. The definitions for either active or stable vitiligo seem to be different for different clinicians. According to Moellmann et al,\(^{17}\) active vitiligo is the clinical stage “when lesions are enlarging in the 6 weeks” before examination, whereas, according to Cui et al,\(^{18}\) active vitiligo is “the development of new lesions or extension of old lesions in the 3 months before the first consultation.” Other clinicians, such as Uda et al,\(^{19}\) define active vitiligo when the lesions are reported to “spread without regression within the last half year.” On the other hand, stable vitiligo is defined by Falabella et al\(^{20}\) as “a condition that has not been progressing for at least 2 years,” whereas Kumar et al\(^{21}\) consider the disease to be stable when “no progression is observed for at least one year before admission of the patient.” Boersma et al\(^{22}\) define stable vitiligo when “neither spread of existing lesions nor development of new lesions have appeared in the previous 6 months.” Using such different “cutoff points,” the disease activity of some patients will be either underestimated or overestimated. Furthermore, from a clinical standpoint, there can be only 2 possible outcomes, whether the disease is active or stable. Therefore, it is essential to establish a better and rational approach to determine clinical disease activity. In this study, disease activity was scored by history taking on a 6-point scale, the VIDA score (Table 1). The VIDA score is a simple scoring system for classifying ongoing disease activity in relation to time, as assessed by the patient. In addition, the changes in the VIDA score, as assessed in this study before and after 1 year of follow-up, also correlated well with the response to the given therapy (Figure 3). However, because disease activity tends to be unpredictable and capricious in vitiligo, it is possible that patients not receiving treatment have different VIDA scores at different times of evaluation. It would be interesting to investigate this aspect prospectively in future studies. The VIDA score does not provide us with information regarding the exact rate of pigment loss. Therefore, photographic documentation of the lesions remains important to monitor changes in the extent of depigmentation and grade of repigmentation. Perhaps in the future, computer-aided designs may reflect these changes more accurately.\(^{22}\)

Our results suggest that the presence or absence of the KP-h should be confirmed by inducing the KP-e because the KP-e seems to occur more frequently than the KP-h. We assume that the KP-h may not always be accurate. The recollection for occurrence of a KP-h may be false-negative or false-positive. Table 3 shows that a high percentage of the cases (48% [20/42]) were false-negative. It is possible that some patients did not recognize or notice the appearance of a white lesion after a skin injury. It is also possible that some patients never had skin trauma at all. In addition, it has been previously postulated that the KP only appears when a certain “threshold value” is exceeded or a certain depth of trauma is induced to the skin. Gopinathan\(^{23}\) observed depigmentation of healthy-looking skin in 69% (9/13) of the patients with vitiligo studied after performing “scarification” procedures. In contrast, “tape stripping” did not produce depigmentation in any of these patients. He concluded that the KP only occurs after epidermal trauma and not after (superficial) epidermal trauma of the skin.\(^{23}\) However, the KP has been reported to occur after all sorts of “trauma” to the skin. It has also been hypothesized that even superficial but constant “friction or pressure” to the skin may lead to depigmentation in susceptible individuals.\(^{1,13,24}\) In the cases reported, no direct evidence supports this hypothesis; therefore, any relationship between superficial trauma and the development of vitiligo should be regarded as highly speculative.

On the other hand, there were only 2 false-positive cases (11%). These 2 patients referred the KP-h to a surgical scar that had existed for many years. At the time of...
The performance of the KP-e, they both stated that the disease had stabilized (VIDA score of 0).

The observation that patients with a positive KP-e had a significantly higher mean VIDA score (VIDA score of 1.6) than did patients with a negative KP-e (VIDA score of 0.5) (Table 4) indicated that a positive KP-e is associated with active disease and a negative KP-e is associated with stabilized disease. On the other hand, Figure 2 shows that VIDA scores between 0 and +2 did not always predict a positive KP-e. Twelve of 61 patients with VIDA scores of +1 and +2 claimed that their disease was active while KP-e was negative. Two patients who claimed that their disease had stabilized (VIDA score of 0) showed a positive KP-e. The patients' impression of the disease activity might not always be accurate. In particular, fair-skinned patients report that during the summer more white patches appeared. However, this phenomenon could also be caused by an increased contrast between healthy and lesional skin caused by sun exposure. As a result, the white patches became more obvious. These patients report that the disease is active, but it could have stabilized. It is also conceivable that minor expansions of old lesions or the appearance of new but small lesions are not always noticed by the patient, especially when these are located on sites that are less conspicuous to the patient (eg, axillae or back). In addition, patients with extensive vitiligo involving more than 30% of total body surface area also find it difficult to assess disease activity. All patients with a VIDA score of +3 and higher had a positive KP-e and all patients with a VIDA score of -1 had a negative KP-e.

We also performed the KP-e in patients with vitiligo segmentalis. In this less common type of vitiligo, the lesions tend to spread rapidly at onset and to show a more stable course thereafter.1 In our experiments, KP-e was not observed in any of these patients (M.D.N., P.K.D., J.D.B., W.W.). All these patients stated that their disease had stabilized at the time the KP-e was performed. These findings confirmed the results found by Koga and Tango25 in 1988, who also did not observe the KP in the segmental form of vitiligo.

The baseline variables of sex, age, percentage of depigmentation, and duration of vitiligo were not significantly different for patients with a positive KP-e or for patients with a negative KP-e. If we assume that KP-e indicates active disease, patients with a positive KP-e do not necessarily have a more severe disease, in terms of extent of depigmentation, than do those with a negative KP-e. This finding is in contrast to patients with psoriasis, in whom a positive KP-e was positively correlated with the extent of psoriatic lesions.26 This allowed us to conclude that in vitiligo, the KP-e does not have a predictive value to the extent of depigmentation.

Most patients responded well to UV-B (311 nm) therapy, which was in concordance with the results of an earlier study12 performed using this radiation therapy. The response to UV-B (311 nm) therapy was not significantly different among KP-e-positive (67% responders) or KP-e-negative (58% responders) patients, indicating that the KP-e did not predict the outcome of UV-B (311 nm) therapy. This also suggests that patients in active and stable stages of the disease may respond equally well to UV-B (311 nm) therapy. More research is needed to elucidate the mechanisms by which UV-B (311 nm) therapy leads to stabilization and repigmentation in vitiligo.

In contrast, patients with a positive KP-e responded significantly better to topical fluticasone propionate combined with UV-A therapy than did those with a negative KP-e, suggesting that this therapy is most effective when applied during the active stage of disease. It has been proposed frequently that, in vitiligo, corticosteroids act by suppressing abnormal immune responses present in actively spreading lesions; however, substantial evidence to support this theory has not yet been provided.27 The combination with UV-A therapy might have further promoted the repigmentation process in these lesions, but this also remains to be proven. Patients with a good response to fluticasone propionate plus UV-A therapy also seem to have a significantly shorter duration of disease than do those with a poor response, a finding that may also explain the difference in responsiveness to this therapy among the KP-e-positive and the KP-e-negative patients. Long-standing lesions have been shown previously to be relatively resistant to local corticosteroid treatment, probably because of the depletion of melanocyte reserves in the hair follicles.28

From the results of the present study we may conclude that the KP-e may function as a valuable clinical factor to assess disease activity. The KP-e may also predict responsiveness to local corticosteroid therapy but not to UV-B (311 nm) therapy. Although the data indicate that the VIDA score is appealing for clinical use, this new scoring system needs to be validated in other institutions with other patient groups.

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REFERENCES


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