

Vitamin E in Vitiligo: Toward Solving the Mystery

Igor V Korobko^{1*} and Konstantin M Lomonosov²¹VR Foundation, New York, NY, USA²Department of Skin and Venereal Diseases, Therapeutic Faculty, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Abstract

Vitiligo is accompanied by oxidative stress which is likely causative for disease onset. Numerous efforts were undertaken to reveal abnormalities in antioxidant system in vitiligo. Vitamin E is one of the major non-enzymatic components of antioxidant system, and several studies addressed a question of vitamin E deficiency in vitiligo, with controversial conclusions on its presence. Aiming to solve this discrepancy, we analyzed plasma vitamin E level in a cohort of non-segmental vitiligo patients. Although we failed to reveal gross plasma vitamin E level abnormalities, our data suggest that there is subgroup of vitiligo patients with low, close to lower reference value, level of plasma vitamin E, while plasma vitamin E level in remaining patients follows that in general population. While this stratification of vitiligo patients needs to be confirmed in large-scale studies, existence of a subgroup of vitiligo patients with "low vitamin E" status might reason inconsistency in previous reports on plasma vitamin E concentration in vitiligo patients. Observed lack of acute vitamin E deficiency in vitiligo patients is in line with reported moderate, if any, effect of oral vitamin E supplementation in complex therapy of vitiligo on extent of repigmentation. At the same time, adjuvant to phototherapy oral vitamin E has beneficial effect in terms of faster response, shorter treatment course and less frequently encountered erythema, likely due to coping with photo-oxidative stress elicited by ultraviolet. Finally, patients from "low vitamin E" group might benefit from vitamin E supplementation through maintaining proper antioxidant system balance thus precluding from oxidative stress-triggered disease recurrence due to lowered vitamin E level.

Keywords: Vitiligo; Oxidative stress; Vitamin E**Abbreviations:** NB-UVB: Narrow-Band Ultraviolet B; PUVA: Psoralen Plus Ultraviolet A

Introduction

Autoimmune reaction-driven loss of melanocytes in vitiligo gains the highest level of experimental evidences. However recent findings indicate that oxidative stress frequently documented in vitiligo patients at systemic level and locally in the skin, can well serve as a trigger for autoimmune response which then further drives melanocyte destruction [1,2]. Based on this intimate link, imbalance in antioxidant system and resulting oxidative stress might produce permanent threat in remitting vitiligo patients endangering disease recurrence. Vitamin E is one of the major components of non-enzymatic antioxidant system, and this drew an attention to vitamin E in respect with vitiligo, both in therapeutic area and in studying its potential deregulation in vitiligo patients.

Several studies addressed an issue of vitamin E status in vitiligo. Dell'Anna and coauthors observed decreased vitamin E level in peripheral blood mononuclear cells (but not in erythrocytes) which was more pronounced in patients with active disease [3]. At the same time, study of Maresca et al. revealed increased level of vitamin E in cultured melanocytes derived from vitiligo patient skin that was proposed to be a mechanism to compensate catalase deficiency found in these melanocytes [4]. Contrary to this report, Passi and coauthors found decreased vitamin E level in the skin of patients with active vitiligo [5]. Notably, in both studies, authors observed decrease in ubiquinol which is involved in vitamin E regeneration. Impaired ubiquinol level might explain why melanocytes with increased vitamin E are paradoxically more vulnerable to oxidative stress [4].

Even more controversial remains a question of plasma vitamin E deficiency in vitiligo patients. Picardo et al. found no difference in plasma vitamin E level between active vitiligo patients (N=62) and age-matched controls (N=60) [6]. Similarly, no difference in plasma vitamin E level was documented in the study of Tunisian patients after analysis of blood parameters of 36 vitiligo patients and 40 healthy controls, even after stratification by disease activity or age [7]. Similar results were

obtained for Indian vitiligo patient cohort (N=63) after comparison with healthy controls (N=60), with no dependence in vitamin E level from disease activity [8]. At the same time, in two studies decreased plasma vitamin E level was revealed in vitiligo patients. Indian vitiligo patients (N=30) showed significantly lower (average ~0.5 mg/dl, range 0.2-0.6 mg/dl) level of vitamin E when referenced to healthy controls (average ~1.45 mg/dl, range 1.1-1.8 mg/dl; N=30) [9]. Jain et al. [10] also found that Indian vitiligo patients (N=40) have lower plasma vitamin E (0.70 ± 0.43 mg/dl) compared to healthy controls (1.13 ± 0.57 mg/dl; N=40). Therefore decreased plasma vitamin E level and vitamin E deficiency in vitiligo patients remains a controversial issue precluding from validation of vitamin E use in management of oxidative stress in vitiligo.

Materials and Methods

Patients: Thirty-one consecutive naïve adult non-segmental vitiligo patients were seen in Department of Skin and Venereal Disease, I.M. Sechenov First Moscow State Medical University. Patient's characteristics are summarized in Table 1. The study was conducted in accordance with the principles of Declaration of Helsinki.

Plasma vitamin E level: Plasma vitamin E level was determined in clinical laboratory "Chromolab", Moscow, Russia, with certified *in vitro* diagnostics procedure.

Statistical analysis: Statistical analysis has been done with Data analysis package of the Microsoft Excel software. Differences were considered significant if two-tailed *P*-value was less than 0.05.

*Corresponding author: Igor V Korobko, 1, Penn Plaza, Suite 6205, New York, NY 10119, USA, Tel: 1-212-786-7589; E-mail: i.korobko@vrfoundation.org

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Gender	Male: $n = 11$ (35.5%)	Female: $n = 20$ (64.5%)
Age	Average: 33.9 ± 8.4	Range: 21-51 years
Disease duration	Average: 11.5 ± 9.9	Range 1-30 years
Vitiligo form	Localized: $n = 7$ (22.6%)	Generalized: $n = 24$ (77.4%)
Vitiligo activity	Stable: $n = 19$ (61.3%)	Active: $n = 12$ (38.7%)
Percentage of depigmented skin	Average: $13.1 \pm 5.3\%$	Range: 5-25%

Table 1: Characteristics of patients enrolled in the study.

Results

Aiming to resolve the controversial issue of vitamin E deficiency in vitiligo patients, we have carried out evaluation of plasma vitamin E level in 31 consecutive adult non-segmental vitiligo patients who were not on any treatment for vitiligo.

Plasma vitamin E level in vitiligo patients ranged from 5 $\mu\text{g/ml}$ to 18 $\mu\text{g/ml}$, with average value of 9.3 $\mu\text{g/ml}$. While average vitamin E level and its range can vary depending on local geosocial conditions [11] and data on population average vitamin E level for Moscow region are not available, current reference values for age group older than 20 years for normal vitamin E level are from 5 $\mu\text{g/ml}$ to 18 $\mu\text{g/ml}$. Therefore, neither of vitiligo patients has vitamin E deficiency.

Statistical analysis also failed to reveal any association of vitamin E level with gender, disease duration, vitiligo activity, vitiligo type or degree of body surface area involved.

However, despite falling into reference range with apparently normal average value for the studied cohort (9.3 $\mu\text{g/ml}$ compared to 10.5 $\mu\text{g/ml}$ derived from the US population [12]), around half of vitiligo patient had plasma vitamin E level close to lower reference threshold value (out of 31 patients, 16 patients had plasma vitamin E level from 5 $\mu\text{g/ml}$ to 7 $\mu\text{g/ml}$). At the same time, all previous studies in general population reported close to Gaussian distribution of plasma vitamin E concentrations [11,12]. In our vitiligo patient cohort, distribution is clearly different from Gaussian one (Figure 1A), which is also witnessed by the difference between median (7.0 $\mu\text{g/ml}$) and expectation (9.3 $\mu\text{g/ml}$) as well as by clearly non-linear graph of the observed values for vitamin E concentration plotted against quantiles of normal distribution (Figure 1B). Unlike Gaussian distribution in general population, there is a pronounced distortion with the peak close to low normal range value in the studies cohort (Figure 1A) that might be interpreted as a presence of two groups of vitiligo patients, one with vitamin E level following usual pattern (*i.e.* normal distribution) seen in general population, and another with low, close to deficiency limit, level of plasma vitamin E. Indeed, exclusion of 12 patients with the most abundant value of plasma vitamin E level of 6 $\mu\text{g/ml}$ from the analysis resulted in the distribution close to the normal one (equal median and average values of 13 $\mu\text{g/ml}$ and close to linear dependence of vitamin E concentration values from quantiles of normal distribution; see Figure 1C).

Discussion

In our study, like in several previous reports [6-8], we failed to reveal vitamin E deficiency in vitiligo. However, our experimental data strongly suggest that vitiligo patients are not homogeneous in terms of plasma vitamin E level, with apparent presence of patient subgroup with plasma vitamin E concentration close to lower reference value. Unfortunately, patient-by-patient data on plasma vitamin E levels are not available for previous studies thus precluding from making conclusion on presence (or absence) of similar distribution pattern of plasma vitamin E levels. However, higher standard deviation has been

noted in vitiligo patient cohort compared to healthy controls in the study of Picardo et al. [6] which might indirectly indicate deviation from Gaussian distribution. Akin, while values for vitamin E level for healthy controls had symmetrical distribution by quartiles, that was not the case for vitiligo patient cohort in the study of Khan et al. [9], with 25% percentile spanning significantly larger range of vitamin E concentration compared to data points falling out of 75% percentile. Together, these facts indirectly suggest that plasma vitamin E level in vitiligo patients might not follow Gaussian distribution, with distortion lying at the low range of vitamin E concentrations, and indirectly support our hypothesis on the presence of subgroup of vitiligo patients with "low vitamin E" status.

Presence of two groups among vitiligo patients based on plasma vitamin E level – one with apparently normal distribution following that in general population, and another with vitamin E concentrations being close to the lower reference value, might explain apparent contradictions in results of previous studies of plasma vitamin E level in vitiligo patients. Indeed, interpretation of results might be severely affected by unrecognized presence of two groups of vitiligo patients based on vitamin E level and failure to separate them. Moreover, number of enrolled patients was usually low, which can lead to incidental uneven sampling of two groups and result in eventually distorted datasets and misleading conclusions on generally lower level of plasma vitamin E in vitiligo patients.

Lack of acute vitamin E deficiency in vitiligo patients observed in our study and supported by previous reports [6-8] suggests that vitamin E supplementation in vitiligo therapy would likely to have no effect on repigmentation which is further corroborated by a vision of oxidative stress as a trigger of melanocyte destruction executed by the immune system cells rather than a driver of this process [1,2]. Indeed, use of vitamin E as a monotherapy failed to show any substantial effect on repigmentation in two studies which included vitamin E monotherapy as control arms [13,14]. Yet, owing to well-documented capacity of vitamin E to scavenge reactive oxygen species generated during photo-oxidative stress [15], an attention has been paid to use of vitamin E as a supplement to phototherapy, aiming to control oxidative damage concurrent with ultraviolet irradiation. Indeed, several studies revealed beneficial effect of vitamin E supplementation in these settings. Koshevenko reported that vitamin E supplementation reduced skin erythema and allowed to increase single UV dose with concomitant reduction of treatment duration and faster repigmentation [16]. Akin, Elgoweini and coauthors reported faster repigmentation, lower number of sessions required to achieve 50% repigmentation, and decreased rate of mild erythema experienced by patients when NB-UVB phototherapy was combined with oral vitamin E. Besides that, authors noticed better repigmentation if phototherapy was combined with vitamin E (72.7% versus 55.6% for moderate to excellent repigmentation), however number of enrolled patients (20 patients in total) was too low to draw any firm conclusion on beneficial effect of vitamin E on repigmentation [17]. Along with clinical effects, signs of oxidative stress correction have been documented when phototherapy was combined with oral vitamin E, which is in line with biological activity of vitamin E. In particular, when combined with NB-UVB, significant reduction of plasma malonaldehyde has been noted in patients receiving vitamin E [17]. Similarly, while not found any additional clinical improvement in terms of repigmentation, Akylol et al. reported decrease in lipoperoxides in patients receiving PUVA therapy when it was combined with oral vitamin E, while no such effect was seen in control group receiving PUVA therapy alone [18].

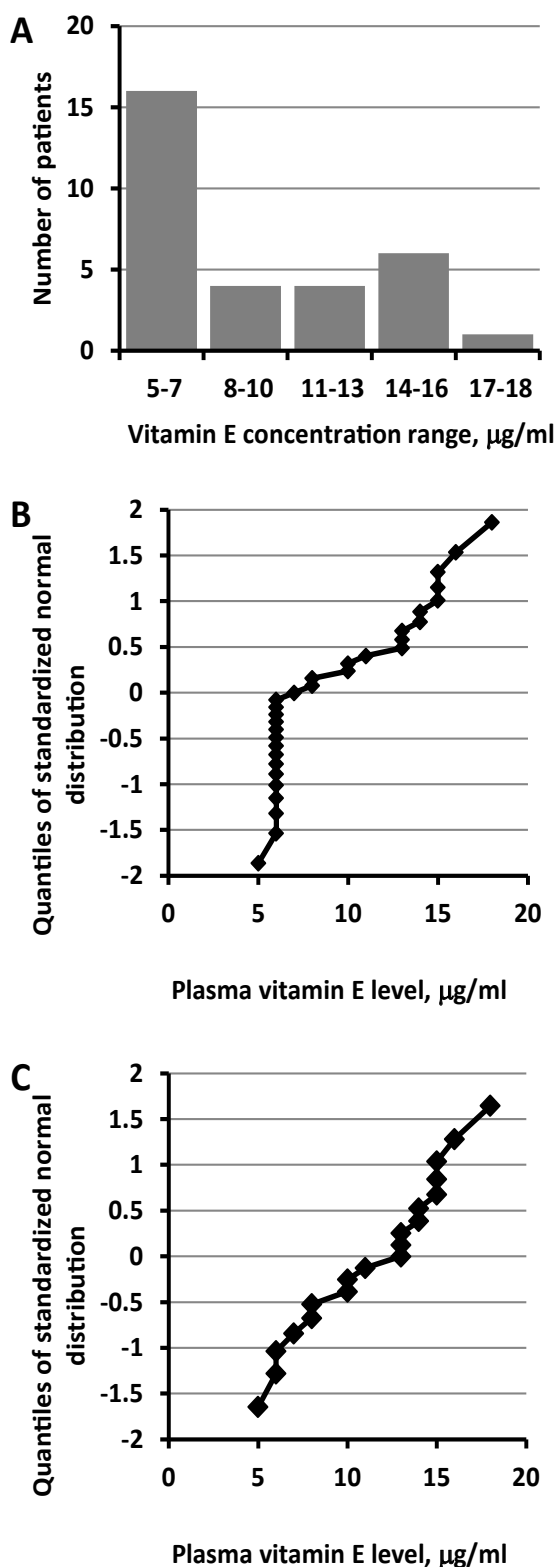


Figure 1: Graphical summary of distribution of plasma vitamin E levels in non-segmental vitiligo patients. (A) Histogram showing number of patients with plasma vitamin E values falling into specified ranges. (B,C) Plots of measured plasma vitamin E values in 31 vitiligo patients (B) or in the same cohort after exclusion of 12 patients with plasma vitamin E level equal to 6 µg/ml (C), against quantiles of standardized normal distribution.

In conclusion, described above findings clearly indicate that adjuvant oral vitamin E dosed from 400 IU to 900 IU daily is beneficial in vitiligo treatment when combined with phototherapy owing to control of photo-oxidative stress. While effect of supplemental vitamin E on repigmentation remains elusive, it might be accepted that in combination with phototherapy, vitamin E supplementation might result in faster repigmentation, lower treatment duration and better patient compliance due to decreased rate of erythema occurrence.

Although seemingly lacking benefits in repigmentation, supplementation of vitamin E can be still beneficial for vitiligo patients besides combination with phototherapy. According to our finding, a subgroup of patients with “low vitamin E” status might exist which can be interpreted as diminished antioxidant capacity. As oxidative stress emerges as a trigger of autoimmune response [1], such patients can be at risk for oxidative stress-induced vitiligo recurrence, and likely to benefit from vitamin E supplementation at remission through maintaining proper antioxidant system balance. Certainly, this hypothesis as well as presence of “low vitamin E” group among vitiligo patients requires further experimental confirmation in large-scale studies, and if confirmed, opens new advantages in vitiligo management and its personalization.

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