

Research article

Serum folate levels after UVA exposure: a two-group parallel randomised controlled trial

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Published: 20 November 2001

Received: 20 September 2001

BMC Dermatology 2001, 1:8

Accepted: 20 November 2001

This article is available from: <http://www.biomedcentral.com/1471-5945/1/8>

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Abstract

Background: Photodegradation of certain vitamins such as riboflavins, carotinoids, tocopherol, and folate has been well-documented. Previous observations suggest that ultraviolet (UV) radiation may cause folate deficiency. This is of great importance since folate deficiency is also known to be linked with the development of neural tube defects. To investigate the influence of UVA radiation on serum folate levels in vivo, we conducted a two-group randomised controlled trial on healthy subjects.

Material and methods: Twenty-four healthy volunteers with skin type II were enrolled into the study. Eight volunteers of the study population were randomly assigned to the control group. UVA irradiation was administered with an air-conditioned sunbed. Blood samples were taken from all volunteers at baseline (T1), 30 min after the first UVA exposure (T2), and at the end of the study 24 h after the sixth UV exposure (T3). The volunteers had two UVA exposures weekly within three weeks (cumulative UVA dose: 96 J/cm²). Volunteers of the control group had no UVA exposures. Serum folate was analysed with an automated immunoassay system.

Results: At all times of blood collection the differences between serum folate levels were insignificant ($P > 0.05$), except of the non-exposed controls at T2 ($P < 0.05$). We did not observed significant differences of folate levels between UVA exposed and non-exposed volunteers ($P > 0.05$).

Conclusions: Our data suggest that both single and serial UVA exposures do not significantly influence serum folate levels of healthy subjects. Therefore, neural tube defects claimed to occur after periconceptual UVA exposure are probably not due to UVA induced folate deficiency.

Background

Folate, the conjugated form of folic acid, is an essential nutrient that is required for nucleotide respective DNA biosynthesis. Apart from macrocytic megaloblastic ane-

mia folate deficiency has also been shown to produce multiple fetal anomalies in nonhuman mammals. Moreover, it has recently been confirmed that there is a connection between defective folate metabolism, neural

tube defects (e.g., craniorachischisis, spina bifida), and impaired spermatogenesis in humans [1,2]. Folate catabolism and simultaneous folate deficiency has been observed in various conditions, such as pregnancy, alcoholism, drug use (e.g., methotrexate), and malnutrition. Photodegradation of certain vitamins such as riboflavins, carotinoids, tocopherol, and folate has been well-documented [3–5]. Photolysis of folate may be significant, especially when serum is exposed in vitro to ultraviolet (UV) radiation. In one study, published in the journal *Science*[6], it has been reported that fair-skinned patients undergoing photochemotherapy for dermatological conditions have low serum folate concentrations, suggesting that photolysis may also occur in vivo. Besides, neural tube defects (NTD) have been found associated with sunbed exposures during the first weeks of pregnancy [7]. Nevertheless, phototherapy is generally recommended by dermatologists as safe to use in pregnant women [8]. Since there is a lack of controlled studies in this field, we conducted a two-group randomised controlled trial investigating serum folate levels of healthy fair-skinned subjects undergoing a series of sunbed exposures.

Material and methods

Subjects and setting

Twenty-four healthy volunteers with skin type II [9] were subsequently recruited. Exclusion criteria included: pregnancy, abnormal diets, drug use, and UV exposure within the last two months prior to the study. All volunteers gave informed consent for participation in the study. Randomised allocation of two groups was performed by asking the volunteers to throw dice without knowing the underlying allocation criteria (nos 1–3: exposed group; nos 4–6: non-exposed group). Thus eight volunteers of the study population were randomly assigned to the control group. The study was conducted in a university dermatological department during winter.

UV source and dosimetry

An air-conditioned sunbed (JK-Products GmbH, Windhagen, Germany) was used fitted with 42 Solarium Plus R1-12-100 W fluorescence lamps (Wolff System AG, Riegel, Germany). Before the beginning of the investigation the spectral output of the lamps was measured with a calibrated MED 2000 spectroradiometer (Opsira GmbH, Weingarten, Germany). The integrated irradiance measured at skin level was 17.5 mW/cm² for UVA and 0.09 mW/cm² UVB. The emission spectrum of the fluorescence lamp is shown in Figure 1. UVA irradiance was routinely measured each exposure session with UV-METER radiometer (Waldmann, Willingen-Schwenningen, Germany). The volunteers had two UVA exposures weekly within three weeks, the controls had no exposures. The UVA dose of each exposure session was 16 J/cm², and

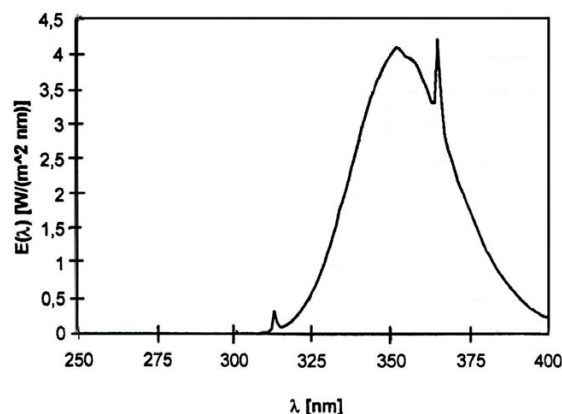


Figure 1
Spectral irradiance of the fluorescence lamp used in this study.

the cumulative UVA dose after 6 exposures was 96 J/cm².

Blood collection and determination of folate

Blood samples were taken from the volunteers in the morning at baseline (T_1), 30 min after the first UV exposure (T_2), and at the end of the study 24 h after the sixth UV exposure (T_3). Determination of serum folate was performed using the automated immunoassay system AD VIA Centaur® IS (Bayer Diagnostics, Fernwald, Germany). Normal range of serum folate is 3–20 ng/ml with the assay used.

Statistics

We used the SPSS 10.0 for Windows. Analysis of distribution was made by the Kolmogorov-Smirnov-test. For comparison of paired and independent samples by normal distribution the 2-tailed Student's t-test was used and for comparison of paired samples by non-normal distribution the Wilcoxon test. Differences were considered significant when $P < 0.05$.

Results and Discussion

A homogenous distribution of sex and age was found for the UV exposed volunteers and non-exposed controls ($P > 0.05$). Means \pm SD of serum folate levels are listed in Table 1. For all volunteers serum folate levels were within the normal range at T_1 , T_2 , and T_3 . At all times of blood collection the differences between serum folate levels were insignificant for UV exposed as well as non-exposed volunteers ($P > 0.05$), except of the non-exposed controls at T_2 ($P < 0.05$). However, this was certainly not of clinical relevance. We did not observe significant differ-

Table 1: Baseline characteristics of the 24 volunteers and means \pm SD of serum folate levels (ng/ml) before (T1) and after (T2; T3) UVA exposure

Volunteers	Sex female (f); male (m)	Mean age years	T1	T2	T3
UV exposed	11 f; 5 m	25.5 (19–39)*	10.1 \pm 3.1 (6.3–20)*	10.4 \pm 3 (6.1–17)*	10.6 \pm 3.3 (5.9–17.2)*
Non-exposed	5 f; 3 m	25.9 (18–36)*	11.6 \pm 3.5 (7.2–30)*	12.9 \pm 3.9 (8.3–32)*	11 \pm 3.1 (6.5–20.2)*

*range

ences of folate levels between UV exposed and non-exposed volunteers ($P > 0.05$).

The protective role of folate in preventing NTD is well established [9]. Jablonski and Chaplin [1] recently hypothesized that highly melanised skin protecting against UV induced photolysis of folate is of great importance for individual reproductive success, and that folate photolysis may, especially in fair-skinned women, precipitate a folate deficiency sufficient to cause a neural tube defect during the first weeks of pregnancy. Therefore it has been suggested to avoid periconceptual UV exposure [2]. It has to be stressed, however, that folate deficiency is common in pregnant women and may arise both from inadequate dietary folate and from increased utilization of the vitamin during pregnancy [4]. In fact, low prevalences of severe folate deficiency and NTD have been observed in native Africans and African Americans [11,12].

Branda and Eaton [6] found that exposure of human plasma in vitro to solar-simulated radiation causes 30–50% loss of folate within 60 min. They also conducted an in vivo trial on 10 fair-skinned Scandinavians undergoing photochemotherapy because of various skin diseases which have not been detailed in their paper. However, one may assume that it predominantly concerned psoriasis patients. They were treated with methoxalen and UVA radiation (4.5 to 9.5 J/cm²) once or twice per week. The time of blood collection was after 3 to 13.5 months after starting photochemotherapy. Baseline folate levels were not determined. The authors found that serum folate levels of the patients were significantly lower than those of 64 healthy controls. Nevertheless, the folate levels of the patients were not within the abnormal range. Possible drug interactions (e.g., methoxalen, methotrexate) and disease-associated factors (e.g., psoriasis and alcohol abuse) affecting folate metabolism were not discussed by the authors [6,13]. Because of the methodology and the restrictive description given in Branda and Eaton's report [6] definitive conclusions can hardly be drawn from their results.

Lapunzina [7] observed three patients with NTD whose mothers had sunbed exposures during the first weeks of their pregnancies. All three mothers were young and healthy. Although folate deficiency of the mothers was not proved, the author speculated that sunbed exposure may have caused teratogenesis in these three patients. Based on epidemiological data Van Rootselaar [14] also suggests that UV radiation may cause NTD in embryos of exposed mothers. Furthermore, Lapunzina [7] hypothesized that heat respective hyperthermia-related effects could possibly cause NTD. This was also postulated by Milunsky et al. [15], who found an increased risk for NTD among offspring of women exposed to heat in form of hot tub, sauna, or fever during early pregnancy.

To study photolysis of serum folate relatively independent from photoprotection due to pigmentation only volunteers with skin type II were included in our study. In comparison to Branda and Eaton [6] we used higher single UVA doses. Studies on UVB-induced alterations of serum folate levels has not been conducted. In vitro, various folate vitamers (polyglutamates) may be detected using fluorescence detection at UV excitation of different wavelength, e.g. 290 nm or 360 nm. In Figure 2 is shown that these folate vitamers can also be characterized by different absorbance spectra using high-performance liquid chromatography with a UV diode array detection system [16,17]. Apart from spectral absorbance of certain folate vitamers within the UVA range there is also considerable absorbance within the UVB and UVC range (Fig. 2). However, UVC does not form a part of solar UV radiation on earth, and because of its minor dermal penetration depth UVB radiation has probably no significant influence on serum folate levels [18]. Based on our study we cannot exclude that higher single and/or cumulative UVA doses than those used in this trial, or that UVB radiation induce folate catabolism. This should be investigated in further controlled studies. In future studies, it would be also of interest to include other parameters of folate catabolism such as red cell folate and genetic polymorphism.

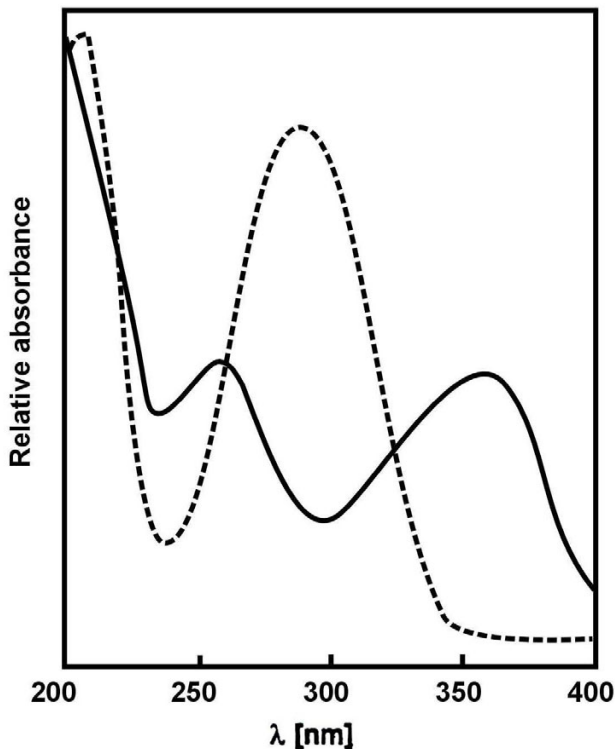


Figure 2
UV absorption spectra of tetrahydrofolate (----) and 10-formyltetrahydrofolate (—) assessed with high-performance liquid chromatography and a UV diode array detection system (17).

Conclusions

Our data suggest that both single and serial UVA exposures do not significantly influence serum folate levels in vivo. Based on these results, we conclude that NTD claimed to occur after periconceptual UVA exposure are probably not due to UVA induced folate catabolism.

List of abbreviations

UV: ultraviolet; NTD: neural tube defects

Competing interests

Have you in the past five years received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this paper? *As cited in the acknowledgement section: The sunbed used in this study was provided by the Förderverein Sonnenlicht-Systeme e. V. (FVS, Stuttgart, Germany).*

Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this paper? *No*

Do you have any other financial competing interests? *No*

Are there any non-financial competing interests you would like to declare in relation to this paper? *No*

Acknowledgment

We are very grateful to the Förderverein Sonnenlicht-Systeme e.V. (FVS, Stuttgart, Germany) who provided the sunbed for research works.

References

- Jablonski NG, Chaplin G: **The evolution of human skin coloration.** *J Hum Evol* 2000, **39**:57-106
- Jablonski NG: **A possible link between neural tube defects and ultraviolet light exposure.** *Med Hypotheses* 1999, **52**:581-582
- Roe DA: **Photodegradation of carotenoids in human subjects.** *Fed Proc* 1987, **46**:1886-1889
- Suh JR, Herbig AK, Stover PJ: **New perspectives on folate catabolism.** *Annu Rev Nutr* 2001, **21**:255-282
- Hoyumpa AM: **Mechanisms of vitamin deficiencies in alcoholism.** *Alcohol Clin Exp Res* 1986, **10**:573-581
- Branda RF, Eaton JV: **Skin color and nutrient photolysis: an evolutionary hypothesis.** *Science* 1978, **201**:625-626
- Lapunzina P: **Ultraviolet light-related neural tube defects?** *Am J Med Genet* 1996, **67**:106
- British Photodermatology Group: **An appraisal of narrowband (TL-01) UVB phototherapy.** *British Photodermatology Group Workshop Report (April 1996).* *Br J Dermatol* 1997, **137**:327-330
- Fitzpatrick TB: **The validity and practicality of sun-reactive skin types I and IV.** *Arch. Dermatol* 1988, **124**:869-887
- Minns RA: **Folic acid and neural tube defects.** *Spinal Cord* 1996, **34**:460-465
- Lawrence VA: **Demographic analysis of serum folate and folate-binding capacity in hospitalised patients.** *Acta Haematol* 1983, **69**:289-293
- Wiswell TE, Tuttle DJ, Northam RS, Simonds GR: **Major congenital neurologic malformations. A 17-year survey.** *Am J Dis Child* 1990, **144**:61-67
- Poikolainen K, Karvonen J, Pukkala E: **Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis.** *Arch Dermatol* 1999, **135**:1541-1542
- Van Rootselaar FJ: **The epidemiology of neural tube defects. A mathematical model.** *Med Hypotheses* 1993, **41**:78-82
- Milunsky A, Ulcickas M, Rothman KJ, Willet W, Jick SS, Jick H: **Maternal heat exposure and neural tube defects.** *JAMA* 1992, **268**:882-885
- Ruggeri S, Vahteristo L, Aguzzi A, Finglas P, Carnovale E: **Determination of folate vitamers in food and in Italian reference diet by high-performance liquid chromatography.** *J Chromatogr A* 1999, **855**:237-245
- Shin HC, Shimoda M, Kokue E: **Identification of 10-formyltetrahydrofolate, tetrahydrofolate and 5-methyltetrahydrofolate as major reduced folate derivatives in rat bile.** *J Chromatogr* 1993, **620**:39-46
- Hoffmann K, Kaspar K, Altmeyer P, Gambichler T: **UV transmission measurements of small skin specimens with special quartz cuvettes.** *Dermatology* 2000, **201**:307-311