Cumulative exposure to solar ultraviolet A & B increases apoptosis of peripheral blood cutaneous lymphocyte antigen (CLA)+ T-Lymphocytes in outdoor workers

Afif Nurul Hidayati¹, Saut Sahat Pohan¹, Widodo J. Pudjirahardjo², Isaac Effendy³

¹Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Hospital, Surabaya, Indonesia
²Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
³Department of Dermatology and Allergology, Academic Teaching Hospital Bielefeld – Klinikum Bielefeld, Germany

Email: afif_nurulhidayati@fk.unair.ac.id

Abstract

Background: Exposure to ultraviolet A & B (UVA-UVB) plays a role in the survival of human life, but it may cause negative effects, such as immunosuppression and skin cancer. The effect of solar UVA-UVB exposure on apoptosis (Bax/Bcl-2 ratio) of peripheral blood cutaneous lymphocyte antigen (CLA)+ T-lymphocyte; the immune competent cells in the skin, has not been investigated. Apoptosis of peripheral blood CLA+ T-lymphocyte affects its function; which serves as the skin's resistance and is involved in infectious diseases, skin inflammation, and malignancies. This study observed the effect of solar UVA-UVB to apoptosis (Bax/Bcl-2 ratio) of peripheral blood CLA+ T-lymphocytes.

Methods: An observational cohort study of 37 male outdoor workers (caddies on the golf course) and 33 indoor workers in Surabaya, aged 20-45 years, with skin phototype IV/V. Measurement of solar UVA-UVB doses received by the subjects was conducted for 2, 4, and 8 weeks. Examination of Bax and Bcl-2 of peripheral blood CLA+ T-lymphocyte was conducted at the beginning of the study, after 4 and 8 weeks.

Results: The average dose of solar UVA-UVB for 8 weeks received by outdoor workers was 12450.51±3948.81 (J/m²) and that by indoor workers was 1793.97±1518.46 (J/m²). Exposure to solar UVA-UVB leads to the increase of apoptosis (Bax/Bcl-2 ratio) of peripheral blood CLA+ T-lymphocytes (p=0.003).

Conclusion: Cumulative exposure to solar UVA-UVB radiation in high-dose or received within 8 weeks resulted in the increase in apoptosis of peripheral blood CLA+ T-lymphocytes.

Keywords: apoptosis, Bax, Bcl-2, CLA+ T-lymphocyte, solar UVA-UVB

Background

Ultraviolet rays reaching the earth consist of 95-98% UVA and 2-5% UVB whereas almost all UVC rays are absorbed by stratosphere ozone layer.¹,² Exposure to ultraviolet rays, in addition to having beneficial effects, also causes adverse effects to the human body, such as acute and chronic skin inflammation, cancer, premature aging, and apoptosis or cell death, as well as induction of adverse reactions of some drugs.²-⁵

It has been proven that exposure to ultraviolet rays will affect keratinocyte apoptosis.⁶-⁷ Physiologically, the balance of keratinocyte growth system is regulated by keratinocyte apoptosis and proliferation. If excessive increase of apoptosis occurs, the skin system function will decline, leading to the occurrence of several diseases. Some proteins play roles in apoptosis, namely Bax, BAD, Bak which are pro-apoptotic protein and Bcl-2, Bcl-xl, Bcl-w which are anti-apoptotic protein.¹,⁸ The increase of Bax/Bcl-2 ratio shows the increase in apoptosis.⁹

In vitro experiment studying the exposure to ultraviolet rays which induced apoptotic peripheral blood mononuclear cells (PBMCs) and was
influenced by wavelength, dosage, and time has been conducted. T-lymphocyte (CD3) is the major member of PBMCs, which accounts for 45-70% of PBMCs. Among the T-lymphocytes in peripheral blood, there are T-lymphocytes expressing cutaneous lymphocytes antigen (CLA). CLA T-lymphocyte is a memory T-lymphocyte which plays role in many skin disorders, including infection, inflammation, hypersensitivity, autoimmune, and malignancy.

The possibility of exposure to ultraviolet rays affects the increase of pro-apoptotic protein Bax, which indicates an increase in peripheral blood CLA T-lymphocyte apoptosis. Furthermore, whether the increase of post-apoptotic protein Bax will affect the function of T-lymphocytes in the pathogenesis of many skin disorders has not been investigated. The purpose of this study is to assess the effect of exposure to UVA-UVB rays on the increase of apoptosis (Bax/Bcl-2 ratio) of peripheral blood CLA T-lymphocytes.

Methods

An analytic observational cohort study was conducted for 8 weeks to evaluate the subjects receiving exposure to UVA-UVB with large doses in their daily activities. The outdoor workers working on the golf course "Ahmad Yani" Surabaya were enrolled as the observation group and indoor workers working in Surabaya were enrolled as the control group.

The number of samples for each group was 28 subjects, as calculated based on sample size determination in health studies. By taking into account the drop out cases of 10%, the number of samples for each group was 31 subjects. Thirty-seven outdoor workers and 33 indoor workers met the inclusion criteria. The control group was matched by age and skin phototypes.

Inclusion criteria for observation group were male, aged 20-45 years old, healthy, working for minimum 6 months and maximum 2 years, skin phototype IV/V according to Fitzpatrick’s classification, and wearing short-sleeved shirt while working. Inclusion criteria for the control group were the same as the observation group, except that they were wearing long-sleeved shirt or jacket when performing outdoor activities. Exclusion criteria for both groups included skin abnormalities (atopic dermatitis, inflammation, infection), chronic diseases, immunosuppression, using topical medications, sunblock, taking any medications affecting exposure to UVA and UVB rays, immunosuppression drugs, or receiving light “therapy” (as medication, cosmetics, and related to their job). The control group conducting outdoor activities within the last 6 months was also included in the exclusion criteria.

Total solar UVA and UVB doses received by subjects was measured using VioSpor® dosimeter blue line II type, which had the capacity to detect solar radiation ranging 100-5500 J/m² dose of 290-380nm wavelength (UVA-UVB), and the data were analyzed in BioSense, Laboratory for Biosensory Systems, Postfach 5161, D-53318 Bornheim, Germany. The installation of VioSpor® type of blue line II in this study was conducted for the first 2 weeks. Then; based on weather data, including temperature, wind speed, and rainfall during the study obtained from Meteorology, Climatology and Geophysics Agency (BMKG) Juanda Surabaya, that was submitted to BioSense, Laboratory for Biosensory Systems, Postfach Bornheim, Germany, the calculations of solar UVA-UVB for 4 weeks and 8 weeks were obtained.

Measurement of Bax and Bcl-2 expressing by CLA T-lymphocyte of peripheral blood was conducted at the beginning of the study, on the 4th week, and on the 8th week. CLA T-lymphocytes were obtained through examination using PE anti-human CD3 (BioLegend) and FITC anti-human Cutaneous Lymphocyte Antigen (CLA) - HECA-452 (BioLegend). The expression of Bax in CLA T-lymphocytes was examined using flow cytometry methods with Rabbit Anti-Bax Polyclonal Antibody PE-Cy5 Conjugated (Bioss). The expression of Bcl-2 in CLA T-lymphocytes was examined using flow cytometry methods with Rabbit Anti-Bcl-2/RAP46 polyclonal PE-Cy5 Conjugated Antibody (Bioss). PBMC examination was carried out in the Animal Physiology Laboratory of Faculty of Mathematics, Universitas Brawijaya, Malang, Indonesia. Flow cytometry examination was carried out in Biology Laboratory, Faculty of Mathematics and Science, Universitas Brawijaya, Malang, Indonesia.

Homogeneity test was conducted using Independent sample T test. Data distribution was conducted using Kolmogorov-Smirnov test. T test was conducted to prove the existence of dose differences in the exposure to solar UVA-UVB and the expression of Bax and Bcl-2 in both groups. The effect of exposure to solar UVA-UVB to the expression of Bax CLA T-lymphocytes in the peripheral blood was analyzed using Pearson correlation test. Significance level of p ≤ 0.05 and confidence interval of 95% were used. This study was approved by the Research Ethics Committee.
of Institute for Research and Community Service, Universitas Airlangga, Surabaya, Indonesia.

**Results**

The study involved 70 subjects consisting of 37 outdoor workers and 33 indoor workers (one person (3.03%) dropped out). F test and T test showed that the subjects of this study were from homogeneous population in terms of age (p=0.905). Kolmogorov-Smirnov Test showed normal data distribution.

The mean solar UVA-UVB dose received in 2 weeks was 3113.08±986.92 J/m² for outdoor workers and 448.48±379.68 J/m² for indoor workers (p<0.01); the dose received in 4 weeks was 6226.24±1973.95 J/m² for outdoor workers, and 897.07±759.27 J/m² for indoor workers (p<0.01); the dose received in 8 weeks was 12450.51±3948.81 J/m² for outdoor workers and 1793.97±1518.46 J/m² for indoor workers (p<0.01). There were significant differences in the average solar UVA-UVB dose received by observation group and the control group for 2 weeks, 4 weeks, and 8 weeks period of exposure.

**Expression of Bax in peripheral blood CLA⁺ T-lymphocytes after exposure to solar UVA-UVB.**

Figure 1 shows flow cytometry examination result to measure the expression of Bax protein in peripheral blood CLA⁺ T-lymphocytes. Expression of Gated-Bax protein appears in the upper right (UR) quadrant.

![Flow Cytometry Examination of Bax in Peripheral Blood CLA⁺ T-Lymphocytes](image)

**Figure 1.** Flow Cytometry Examination of Bax in Peripheral Blood CLA⁺ T-Lymphocytes. Remarks: FSC: forward scatter; UL: upper left; UR: upper right; LL: lower left; LR: lower right ID: identity code of sample; K-A: code of sample; CLA: Cutaneous Lymphocytes Antigen; BAX: protein Bax; Quad: quadrant; R3: Gated-Bax protein

| Quad | Events | % Gated | % Total |
|------|--------|---------|---------|
| UL   | 0      | 0.00    | 0.00    |
| UR   | 23     | 18.11   | 0.08    |
| LL   | 0      | 0.00    | 0.00    |
| LR   | 104    | 81.89   | 0.38    |
Figure 2 shows that there was an increase of Bax expression in the observation group among all three points of observation whereas in the control group, there was a decrease of Bax after 4 weeks, which was then increased after 8 weeks. There were significant differences in the expression of Bax in the observation group compared to the control group on week 4 (p<0.05) and week 8 (p<0.05).

Statistical analysis showed that in the observation group, Bax from the beginning of the study increased significantly after 4 (p<0.01) and 8 weeks (p=0.008). If assessed from the beginning of the study to the 8th week, the increase of Bax in the observation group (p<0.01) was still significant. However, the significance was not found on the control group’s Bax on both week 4 (p=0.420) and week 8 (p=0.434). Assessing from the beginning of the study to week 8, there was also no significant increase of Bax in the control group (p=0.976).

The result of Pearson correlation test showed that there was no significant correlation of solar UVA-UVB on Bax expression after 4 weeks (p=0.12), but there had been a significant correlation after 8 weeks (p<0.01) with a moderate relationship (0.428).

**Figure 2.** Average Expression of Bax in Peripheral Blood CLA⁺ T-Lymphocytes in the Observation Group (Caddy) and the Control Group (Indoor Workers) at the Beginning of the Study (Bax1), 4 Weeks (Bax2), and 8 Weeks (Bax3)
**Bcl-2 expression in peripheral blood CLA^+ T-lymphocytes after UVA-UVB exposure**

Figure 3 shows flowcytometry examination of the expression of Bcl-2 in CLA^+ T-lymphocytes of peripheral blood-gated appear in the upper right quadrant (UR).

**Figure 3.** Flowcytometry Examination of Bcl-2 Expression in Peripheral Blood CLA^+ T-Lymphocytes. Notes: FSC: forward scatter; UL: upper left; UR: upper right; LL: lower left; LR: lower right. ID: identity of sample; R3: Gated-Bcl-2 protein; Quad: quadrant
**Bcl-2 expression in peripheral blood CLA⁺ T-lymphocytes after UVA-UVB exposure.**

The mean protein expression of Bcl-2 CLA⁺ T-lymphocytes at baseline, after 4 weeks, and after 8 weeks are shown in figure 4. There was significant difference of Bcl-2 expression between observation and control group after week 4 (p=0.041), but the difference became insignificant after week 8 (p=0.82). The increased Bcl-2 expression in observation group from the beginning of study to week 4 was significant (p=0.0001), but not from week 4 to week 8 (p=0.157). Evaluating from the beginning of study to week 8, there was a significant difference (p=0.0001) between each period. The study showed that the increased value of BCl-2 expression in the observation group at week 4 and week 8 was not significant (p>0.05). The Pearson correlation test also showed that there was no significant effect of solar UVA-UVB on Bcl-2 expression (protein anti-apoptosis) after 4 weeks.

**Bax/Bcl-2 Ratio in peripheral blood CLA⁺ T-lymphocytes after solar UVA-UVB exposure**

Apoptosis was described by the ratio of Bax as a pro-apoptotic protein compared to Bcl-2 as an anti-apoptotic protein. Expression of apoptosis in this study was described by Bax/Bcl-2 ratio which was categorized as follows: Bax/Bcl-2 ratio ≥1 indicating increase of apoptosis while ratio <1 were decrease of apoptosis.

*Figure 4. The Mean of Bcl-2 Expression in Peripheral Blood CLA⁺ T-Lymphocytes of Observation Group (Caddy) and Control Group (Indoor Workers) at Baseline Bcl-2(1), 4 Weeks Bcl-2(2), and 8 Weeks Bcl-2(3)*
Figure 5 shows Bax/Bcl-2 ratio during this study. In the observation group, from baseline, after 4 weeks and 8 weeks it appears that Bax/Bcl-2 ratio showed an increase in apoptosis (ratio>1) whereas in the control group, the ratio of Bax/Bcl-2 was <1. The discriminant statistical analysis showed that there was significant difference of apoptosis between observation group and control group (p=0.003).

**Discussion**

This study aimed to prove the effect of cumulative exposure to solar UVA-UVB rays on increased apoptosis (Bax/Bcl-2 ratio) in peripheral blood CLA+ T-lymphocytes. CLA+ T-lymphocytes are T-lymphocytes that express cutaneous lymphocytes antigen (CLA), a subset of memory T cells homing the skin and constituting T-lymphocytes which have been activated previously. The population of CLA+ T-lymphocyte in peripheral blood is approximately 10-25% of T-lymphocytes in peripheral blood vessels, 5-20% of T-lymphocytes in tonsil and peripheral lymph nodes, and approximately 80-90% of T-lymphocytes in the skin suffering from chronic inflammatory diseases. Over 90% of T-lymphocytes involved in skin inflammatory disease is CLA+ T-lymphocytes. To assess the apoptosis of peripheral blood CLA+ T-lymphocytes resulted from the exposure of solar UVA-UVB, Bax and Bcl-2 were examined. Increased Bax indicates an increase in apoptosis process, which contradicts to increased Bcl-2, which indicates decrease of apoptosis. If the cell is stressed, for example by exposure to UV, the exposure of pro-apoptotic proteins of Bcl-2 family (e.g. Bax, Bad, and Bak) will increase. This study showed that there were significant differences in the expression of Bax in the observation group compared with the control group after 4 and 8 weeks.
weeks. It proved that Bax expression of peripheral blood CLA⁺ T-lymphocytes from individuals receiving high exposure to solar UVA-UVB (the expression of Bax was high) differed from those receiving low exposure to UVA-UVB.

The analysis of the increased expression of Bax from the initial to the end of study showed that in the observation group, there was a significant increase in the expression of Bax after 4 weeks and 8 weeks whereas in the control group, there was a decreased expression of Bax after 4 weeks which increased after 8 weeks. It proved that exposure to high solar UVA-UVB causes a significant increase in pro-apoptotic protein Bax expression of peripheral blood CLA⁺ T-lymphocytes. This finding was in accordance with the theory that exposure to the stressor will lead to the increased expression of pro-apoptotic protein in the cell.

This study showed that there was no significant effect of solar UVA-UVB dose to the increase of Bax at the 4th week. It was probably caused by the low dose of UVA-UVB received by subjects. In contrast, at the 8th week, the dose of exposure to UVA-UVB received was greater than at the 4th week; thus, providing significant effect to the increase of Bax expression. It has been known that exposure to UV causes increased Bax expression in keratinocytes. This study proved that exposure to solar UVA-UVB on the human body also increases Bax expression of peripheral blood CLA⁺ T-lymphocytes, which plays an important role in skin immunity. This study confirmed the opinion that lymphocyte may undergo apoptosis and necrosis if exposed to UV radiation since the first day of tissue culturing. Apoptosis or necrosis of T-lymphocytes can affect the quality of T-lymphocytes as immune cells which are important in the body's defense mechanism.

Mechanism for the increased Bax is resulted from the exposure to solar UVA-UVB. The possibility is through the mechanism of DNA damage caused by the exposure to the sun, triggering the expression of p53 protein. The p53 protein causes increase of Bax expression. Bax stimulates the increase of mitochondrial membrane permeability, causing cytochrome-c release into cytoplasm. Cytochrome-c activates Apaf-1, and then apoptosis is formed. Apoptosome causes caspase-9 activation which activates caspase-3, 6, and 7, and eventually triggers apoptosis. Another mechanism to identify whether UV affects the Bax expression is also evidenced by the study to Bcl-2-interacting mediator of cell death (Bim), which is the initiator of apoptosis intrinsic pathway through Bax activation. BimL is involved in Solar UV-induced apoptosis through Bcl-xL neutralization, and then followed by Bax release and activation, which ultimately triggers apoptosis.

Study on ultraviolet irradiation resistance-associated gene (UVRAG) proved that UVRAG acts as a suppressor of Bcl-2-associated X protein (Bax) in regulating apoptotic. UVRAG interaction with Bax inhibits Bax translocation from mitochondria, decreases the mitochondrial membrane potential, inhibits the release of cytochrome-c, and inhibits the activation of caspase-9 and 3. UVRAG deletions cause tumor cells more sensitive to chemotherapy and radiation that induces apoptosis.

This study also showed that there were differences in Bcl-2 expression of peripheral blood CLA⁺ T-lymphocytes in the observation group compared with the control group after 4 and 8 weeks. The results of this study indicated that in the observation group, there was an increased expression of Bcl-2 significantly after 4 weeks. However, from 4 weeks to 8 weeks there was no significant improvement. These results were in accordance with the expression of Bax; which was at 4 weeks had not demonstrated a significant increase while Bcl-2 expression was still quite high. These was likely because Bax had not been significantly suppressing Bcl-2. That phenomenon likely due to the effects of UVA-UVB rays of the sun, did not give a great influence on Bax and Bcl-2 in 4 weeks exposure. However, the Bax/Bcl-2 ratio, both at baseline and at 4 weeks, showed that the expression of Bax was greater than the Bcl-2, which means an increase in apoptosis of CLA⁺ T-lymphocytes in the peripheral blood at 4 weeks. On the other hand, at 4 weeks to 8 weeks, no significant increase was found in the expression of Bcl-2 in the observation group, in line with its expression of Bax, from 4 weeks to 8 weeks. It showed that after 8 weeks, the effects of UVA-UVB already led to a significant increase in the expression of Bax accompanied by an insignificant increase in expression of Bcl-2 due to the increase of Bax in 8 weeks suppressing Bcl-2 expression. If the expression of Bax is greater than the expression of Bcl-2 it means increase of apoptosis. In the control group, there was a decrease of Bcl-2 expression after 4 weeks, then increased after 8 weeks. However, compared to the expression of Bax at week 4 and 8, it appeared that the expression of Bax was lower than the expression of Bcl-2. It showed that in the control group, there was no increase in apoptosis. Theoretically, increase in apoptosis was shown by greater expression of Bax than the expression of Bcl-2.
These results, supported by the correlation analysis, proving that the effect of solar UVA-UVB on the increase of the expression of Bcl-2 (antiapoptotic protein) after 4 weeks and 8 weeks had no significant influence. It can be concluded that exposure to solar UVA-UVB for 8 weeks did not cause a significant increase in the expression of Bcl-2 as an antiapoptotic protein in CLA+ T-lymphocytes of peripheral blood but led to a significantly increased Bax as a proapoptotic protein of CLA+ T-lymphocytes in the peripheral blood. Based on the ratio of Bax which was greater than the Bcl-2, it can be concluded that an increase in apoptosis due to exposure to UVA-UVB in peripheral blood CLA+ T-lymphocytes happened in the observation group.

Previous research proved that UVB radiation was the originator cause of apoptosis via several pathways, even though the mechanism of the relationship of some of those lines are still unclear and needs further research. One path is through the DNA damage caused by exposure to UVA-UVB. DNA damage causes decreased expression of Bcl-2 antiapoptotic protein. Another mechanism is through the induction of p53 and E2f1. At low doses of UVB exposure, wild-type p53 resembles the "OFF state" apoptosis, whereas exposure to high doses of UVB, it switched to "ON state". The target of the movement is Bcl-2. There was decreased Bcl-2 against photoprocess response to DNA from UVB exposure in cells deficient in p53. Bcl-2 also decreased as a result of the response to DNA caused by UVB photoprocess without p53 and E2f1. It is already known that there are four lanes ending in Bcl-2, which contributed to the decrease in apoptosis after UVB radiation. Also, it shows that Bcl-2 is an integrator of multiple pathways of apoptosis.

In addition to analyzing the effect of exposure to UVA-UVB sun rays on the expression of Bax and Bcl-2, increased apoptosis is described by Bax expression ratio as compared to Bcl-2 expression. If the expression of Bax is greater than the expression of Bcl-2 then it indicates increased apoptosis. This study also proved that in the observation group after 4 and 8 weeks, it appeared that the expression of Bax in peripheral blood CLA+ T-lymphocytes was greater than the expression of Bcl-2 in peripheral blood CLA+ lymphocytes T. The ratio of Bax / Bcl-2 was >1, which indicates an increase in peripheral blood CLA+ T-lymphocyte apoptosis on both week 4 and 8 whereas in the control group, it was proven that after 4 and 8 weeks, the expression of Bax was smaller than the expression of Bcl-2 (Bax/Bcl-2 ratio was <1), which indicated that in the control group in after 4 and 8 weeks, there was no increase of peripheral blood CLA+ T-lymphocyte apoptosis; moreover, it showed a decrease of apoptosis.

Discriminant analysis on the effect of solar UVA-UVB to apoptosis (ratio of Bax/Bcl-2) of peripheral blood CLA+ T-lymphocytes on day 28 showed that the group of high UVA-UVB exposure (observation group) or a group of low UVA-UVB exposure (control group) had not yielded significant results in distinguishing apoptosis (Bax/Bcl-2 ratio) whether it was increased or decreased. After 8 weeks, high UVA-UVB exposure group (observation group) and low UVA-UVB exposure group (control) had already shown significant results in distinguishing apoptosis (Bax/Bcl-2 ratio) whether it was increased or decreased. It appeared that after week 8, peripheral blood CLA+ T-lymphocytes in the observation group had increased apoptosis, but those in the control group decreased apoptosis.

This study proved that exposure of solar UVA-UVB for 8 weeks caused increased apoptosis of peripheral blood CLA+ T-lymphocytes. Peripheral blood CLA+ T-lymphocytes apoptosis is an important process because these are immune cells with important role in various skin diseases. In cases of excessive CLA+ T-lymphocyte apoptosis, it will affect the quality of CLA+ T-lymphocytes in peripheral blood which further will play an important role in the skin defense. If apoptosis occurs continuously, it will cause the deaths of CLA+ T-lymphocytes of peripheral blood. CLA+ T-lymphocyte is an important immune component, because more than 90% of T cells involved in inflammatory skin disease are CLA+ T cells. If many T-lymphocytes undergo apoptosis, the function of peripheral blood CLA+ T-lymphocytes as the body's defense mechanism can decrease, especially in the disturbed skin.

**Conclusion**

Cumulative exposure of solar UVA-UVB for 8 weeks on individuals taking outdoor activities affects the increase of apoptosis (Bax/Bcl-2 ratio) of peripheral blood CLA+ T-lymphocytes. Caution is needed against exposure to high dose solar UVA-UVB for individuals with a lot of outdoor activities. Further study on UVA-UVB causing negative effects should be developed as the exposure to low UVA-UVB dose can give beneficial effects to human body while on the contrary will give harmful effects.
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