Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

Antioxidant defense of children and adolescents with atopic dermatitis: Association with disease severity

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Received 9 June 2023; Accepted 10 October 2023
Available online 1 January 2024

KEYWORDS
Adolescent;
Antioxidant Defense;
Atopic Dermatitis;
Child;
Oxidative Stress

Abstract
Background: Atopic dermatitis (AD) is a relapsing, chronic cutaneous inflammatory disease with onset, in general, in early childhood. Chronic skin inflammation is associated with overproduction of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide. Oxidative stress, an imbalance between the production of free radicals and antioxidant defense, results in tissue inflammation due to the upregulation of genes that encode inflammatory cytokines. This condition plays an important role in the pathogenesis of AD.
Objective: To compare the antioxidant defense in children and adolescents with AD with that of healthy individuals and to verify the association of antioxidant defense with disease severity and nutritional status.
Methods: Cross-sectional study that evaluated 48 children and adolescents with AD and 25 controls for nutritional assessment (body mass index z score [BMIZ] and height for age z score [HAZ]) and levels of vitamins A, C, E, and D, zinc (Zn), copper (Cu), antioxidant enzymes (superoxide dismutase [SOD], catalase [CAT], glutathione peroxidase [GPx]), high-sensitivity C-reactive protein (CRP) and interleukin 33 (IL-33).
Results: There was no significant difference in the comparison between AD and control groups for serum levels of vitamins (A, D, C, and E), copper, and antioxidant enzymes. Serum zinc levels were higher in the AD group (β = 24.20; 95% CI 13.95-34.91; P < 0.001) even after adjusting the BMIZ, HAZ, gender, IL-33, and CRP. Children and adolescents with moderate or severe AD compared to mild AD (SCORAD - 36.7±17.4 vs 11.8 ± 3.9; P < 0.001) had lower values of the vitamin E/total lipid ratio (3.68 [0.29;12.63] vs 5.92 [3.27;17.37]; P = 0.013).
Conclusion: Children and adolescents with AD had higher concentrations OF elevated levels of zinc compared to controls, a fact not observed for other biomarkers of antioxidant defense. AD in moderate or severe forms presented lower concentrations of vitamin E, a potent antioxidant fat soluble.

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https://doi.org/10.15586/aei.v52i1.933

Introduction

Atopic dermatitis (AD) or atopic eczema is a chronic or chronically recurrent inflammatory skin disease, the prevalence of which is increasing significantly. It is clinically manifested by pruritus, erythema, papules, and occasionally vesicles in babies, xeroderma, and sometimes with thickening and depigmentation of the skin. The distribution is typically flexural, although it may vary depending on the age. It affects about 20% of children and 10% of adults in high-income countries.[1]

The increase in knowledge of the immunopathogenesis of AD, despite some gaps, has already allowed a great evolution in the treatment with the use of new highly efficient and well-tolerated pharmaceuticals. These can be broken down into biologicals, including monoclonal antibodies selectively targeting pro-inflammatory cytokines and small molecules that inhibit cell signaling aimed at reducing the expression of a wider array of pro-inflammatory factors.[2]

In AD, dominant Th2 inflammation is characterized by CD4+ T cells and infiltration of eosinophils into the dermis, with deposition of eosinophils and increased expression of Th2 cytokines in the skin. Activated Th2 cells release interleukins 4 and 13 promoting B-cell IgE class switching and producing antigen-specific IgE *via* signal transducer and activator of transcription (STAT) pathway.[3] Chronic skin inflammation is associated with overproduction of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide. Over time, the accumulation of ROS eventually exceeds the defense capacity of the antioxidant system. This condition, defined as oxidative stress, plays an important role in the pathogenesis of AD.[4]

Components of antioxidant defense include enzymes such as superoxide dismutase (SOD), catalase (CAT), and thioredoxin (TRX), as well as exogenous and endogenous nonenzymatic molecules such as vitamins A, C, and E, uric acid, coenzyme Q10, and the whole glutathione system, which comprises glutathione (GSH) and the enzymes glutathione reductase and glutathione peroxidases (GPX). The trace elements such as zinc, copper, selenium, and manganese act as cofactors of antioxidant enzymes.[5-7]

ROS are continuously being produced in the skin either due to cellular respiration or environmental factors. Nevertheless, it has a well-established antioxidant defense system to cope with physiological level of oxidation. Existing evidence points out that in certain skin disorders, such as atopic dermatitis, there is an imbalance in cellular redox status and an association between this delicate balance and inflammation.[8]

Recently, the role of oxidative stress in AD has been widely studied. In large quantities, ROS cause cellular damage to epidermal keratinocytes through lipid peroxidation. Evidence also suggests the contribution of oxidative stress to tissue inflammation through upregulation of genes responsible for pro-inflammatory cytokines via the nuclear factor κB pathway.[9]

A review on oxidative stress and AD showed that in the period from 1992 to 2019, only 33 articles were published, with 20 of them in the last 10 years.[4] The authors drew attention to small sample sizes, which are not adequate representation of all ethnicities and geographical areas, and to the heterogeneity of the methods used to assess oxidative stress in the different studies.[4]

Given the above, the objective of this study was to compare the antioxidant defense in children and adolescents with AD with that of healthy individuals. The study also verified the association between antioxidant defense, disease severity, and nutritional status.

Materials and Methods

A cross-sectional study was conducted at the Allergy Outpatient Clinic of the Department of Pediatrics of the Universidade Federal de São Paulo (UNIFESP/EPM), in 2016 and 2017, involving 48 children and adolescents who were diagnosed with AD according to the diagnostic criteria of Hanifin and Rajka (1980)[10] (AD group) and 25 healthy controls (control group). For the classification of AD severity, the parameters of the index *Scoring Atopic Dermatitis* (SCORAD)[11] were applied.

The exclusion criteria for AD group were as follows: (a) presence of acute or chronic infection; (b) presence of associated chronic diseases, except for other allergic diseases and excess weight; (c) use of supplements, containing vitamins A, C, D, and E, as well as zinc (Zn) and copper (Cu), in 6 months prior to blood collection. For the control group, 25 healthy individuals were selected and matched to the AD group by sex and age. Figure 1 shows the flowchart for enrolling patients in the study.

Anthropometric assessment

The following data were measured: weight, height, skinfolds (triceps, subscapular, bicipital, and suprailiac), and circumferences (waist and arms). To classify nutritional status, the WHO Anthro Plus®[12] software was used to calculate the body mass index-for-age Z-score (BMIZ) and height-for-age z-score (HAZ), using the World Health Organization[13]

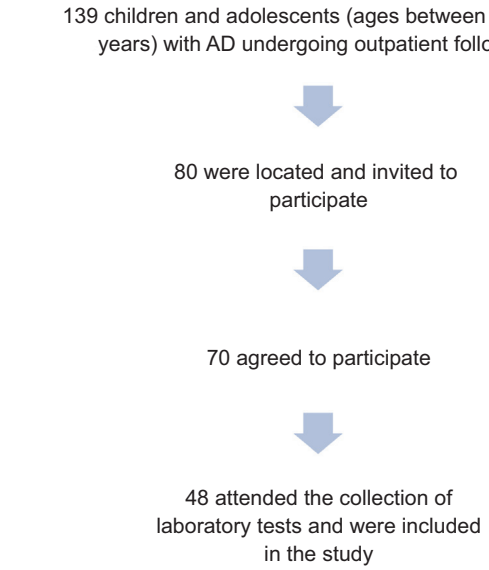

Figure 1 Flowchart for AD sample composition.

as a reference. Short stature was considered when HAZ < −2 standard deviations. The following cutoff points were considered for diagnosis based on HAZ < −2: short stature and Z score ≥ −2 normal HAZ.[13] Waist circumference (WC) was measured at the midpoint between the iliac crest and the last rib at the time of expiration, with the aid of an inelastic measuring tape and classified as altered when the WC/height ratio ≥ 0.5.[14-16] The stage of pubertal development was obtained by self-assessment and classified according to what was proposed by Marshall and Tanner.[17]

Laboratory tests

An aliquot of 15 mL blood was collected by venipuncture by a nursing professional, in the morning, respecting the 12-h fast. Centrifugation was performed at 3000 rpm for 10 min to separate the serum and stored at –80°C.

(1) Inflammation biomarkers: High-sensitivity C-reactive protein (hs-CRP) (Roche/Hitachi 902 kit, Basel, Switzerland) immunoturbidimetric assay with intensification of particle reaction and interleukin (IL)33 ELISA method (Fine test® -Wuhan, China).
(2) Biomarkers related to antioxidant defense: Glutathione peroxidase: ELISA assay – (Fine test®, Wuhan, China); Catalase: ELISA assay – (Fine test®, Wuhan, China); Superoxide dismutase: ELISA assay – (Fine test®, Wuhan, China); Serum vitamin A: ELISA assay – (Elabscience®, Wuhan, China); Serum vitamin C: ELISA assay – (Elabscience®, Wuhan, China); Serum vitamin E: ELISA assay – (Elabscience®, Wuhan, China); Serum zinc: Atomic absorption spectrophotometry ("Perkin Elmer" model 5.100) under the conditions specified by the manufacturer[18,19]; (Serum copper: Atomic absorption spectrophotometry ("PerkinElmer" model 5.100) under the conditions specified by the manufacturer.[18,19] We used ELISA automatic workstation Eti Max 3000 - Marca DiaSorin.
(3) Other biomarkers: 25 hydroxyvitamin D [25(OH)D] chemiluminescence and lipid profile: triglycerides (TG), total cholesterol (TC) and its fractions (HDL-c, LDL-c): enzymatic-colorimetric method.

Statistical analysis

For statistical analysis, the SPSS 25.0 (IBM®) Software was used. Qualitative variables were presented in absolute values and percentages, compared through the chi-square test. Continuous variables were analyzed for its normality using the Shapiro-Wilk test. Those with parametric distribution were presented in the form of mean and standard deviation and were compared using the Student's t-test. The nonparametric values were presented as median (maximum and minimum value) and compared using the Mann-Whitney test. Linear regression was used to evaluate the effect of variables (IL-33, HAZ, BMIZ, CRP, sex, and group) on zinc serum levels. Significance level adopted of 5%.

Results

A total of 73 children and adolescents, 48 (65.8%) with AD and 25 (34.2%) healthy controls participated in the study. The two groups were homogeneous in relation to gender and age (Table 1). In the AD group, severe, moderate, and mild forms were observed in 14 (29.2%), 24 (50.0%), and 10 (20.8%) cases, respectively. Six individuals (12.5%) used oral corticosteroids in the last year. Other allergic diseases, such as asthma, rhinitis, and food allergy, were associated with AD in 21 (43.8%), 30 (62.5%), and 7 (14.6%) patients, respectively. The average duration of the AD was 4.6 ± 3.6 years.

In the AD group (n = 48), the mean age was 10.3 ± 3.8; 24 (50%) were males, and 28 (58.3%) were prepubescent. The assessment of nutritional status showed a higher frequency of overweight and obesity in the AD group compared to the control group (27 [56.2%] vs 5 [20%]; P = 0.017) (Table 1).

There was no significant difference between the AD and control groups for vitamins and antioxidant enzymes and for copper (Table 2). Zinc levels (98.3 ± 21.4 mcg/dL vs 76.9 ± 16.1 mcg/dL; P < 0.001) were significantly higher and IL-33 concentrations were lower (19.0 [0.18;929.6] pg/mL vs 2.8 [0.18;702.4] pg/mL; P = 0.040) in the AD group. Zinc levels were higher in the AD group (β = 24.20; 95% CI

Table 1 General characteristics and nutritional status of the groups with atopic dermatitis (AD) and controls.

Variables	Description	AD (n = 48)	Controls (n = 25)	P
Characteristics				
Sex	Male	24 (50.0%)	13 (52.0%)	0.534
Pubertal stage	Prepubescent	28 (58.3%)	14 (56.0%)	0.918
	Thinness	1 (2.1%)	0 (0.0%)	0.017
BMI z score	Normal	20 (41.7%)	20 (80.0%)	
(classification)	Overweight	16 (33.3%)	2 (8.0%)	
	Obesity	11 (22.9%)	3 (9.0%)	
HAZ z score	Normal	46 (95.8%)	25 (100%)	0.543
(classification)	Short stature	2 (4.2%)	0 (0.0%)	
Waist-to-height ratio	≥ 0.5	21 (43.8%)	4 (16.0%)	0.021

P = Significance level of chi-square test.

Table 2 Serum levels of vitamins (A, D, E, and C), zinc, copper, antioxidant enzymes and inflammatory markers from children and adolescents with atopic dermatitis (AD) and controls.

Variables	units	AD (n = 48)	Controls (n = 25)	P
Vitamin A	ng/mL	17.7 (7.7; 67.9)	18.7 (8.3; 71.6)	0.858*
Vitamin D	ng/mL	26.8 ± 8.4	25.9 ± 6.4	0.614**
Vitamin E	µmol/L	9.2 (0.7; 32.3)	5.9 (0.7; 43.1)	0.395*
Vitamin C	µmol/L	4.7 ± 1.6	4.5 ± 1.0	0.511**
Zinc	mcg/dL	98.3 ± 21.4	76.9 ± 16.1	< 0.001**
Copper	mcg/dL	120.3 ± 40.0	103.7 ± 28.5	0.075**
Vitamin E/cholesterol		6.7 (0.4; 23.7)	3.8 (0.3; 33.3)	0.385*
Vitamin E/triglycerides		12.4 (0.8; 65.4)	10.4 (0.7; 80.8)	0.204*
Vitamin E/total lipids		3.9 (0.3; 17.4)	2.9 (0.2; 23.6)	0.285*
IL-33	pg/mL	19.0 (0.18; 929.6)	2.8 (0,18; 702.4)	0.040*
GPx	ng/mL	35.0 ± 12.6	33.4 ± 12.8	0.616**
CAT	pg/mL	177.5 (33.6; 5490.0)	195.2 (20.8; 4541.4)	0.774*
SOD	ng/mL	50.0 (2.4; 657.4)	33.3 (19.3; 354,5)	0.083*

P = Significance level of the Mann–Whitney* or Student's t-test**. IL-33, interleukin 33; GPx, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase.

Table 3 Linear regression of variables associated with zinc concentrations in the studied population.

Variable	β	95% CI		P
Atopic dermatitis	24.207	13.495	34.919	0.001
CRP	5.934	−3.299	15.167	0.204
HAZ	4.211	−0.208	8.631	0.061
IL-33	1.801	−3.057	6.658	0.462
BAZ	−1.052	−5.485	3.381	0.637
Sex	−1.327	−10.825	8.171	0.781

Dependent variable: serum zinc levels

13.95–34.91; P < 0.001) even after adjusting CRP, HAZ, IL-33, BMIZ, and gender (Table 3).

Children and adolescents with moderate or severe AD compared to those with mild AD (SCORAD – 36.7 ± 17.4 vs 11.8 ± 3.9; P < 0.001) had lower values of the ratios: vitamin E/cholesterol (5.0 [0.4;11.9] vs 9.3 [4.1;23.7]; P = 0.018), vitamin E/triglycerides (10.7 [0.8;36.7] vs 18.8 [6.9;65.4]; P = 0.010) and vitamin E/total lipids (3.68 [0.29;12.63] vs 5.92 [3.27;17.37]; P = 0.013). There was no significant difference in terms of severity in patients with AD (moderate or severe vs mild) for vitamins A, C, and D, and antioxidant enzymes, zinc, and copper (Table 4).

Table 4 Comparison of laboratory variables studied in children and adolescents with atopic dermatitis (AD) according to disease severity.

Variable	AD moderate/severe (n = 38)	Mild AD (n = 10)	P
Vitamin A (ng/mL)	17.4 (7.7; 67.6)	23.3 (7.5; 12.6)	0.475*
Vitamin D (ng/mL)	25.9 ± 8.4	30.6±7.6	0.122**
Vitamin E (µmol/L)	7.2 (0.7; 31.4)	10.9 (5.9; 32.3)	0.052*
Vitamin C (µmol/L)	4.6 ± 1.7	5.0 ± 1.2	0.489**
Zinc (mcg/dL)	99.8 ± 21.8	92.3 ± 19.9	0.325**
Copper (mcg/dL)	125.1 ± 41.9	102.1 ± 25.9	0.106**
CRP (mg/L)	0.77 (0.3; 24.9)	0.46 (0.30; 9.80)	0.601*
Vitamin E/cholesterol	5.0 (0.4; 11.9)	9.3 (4.1; 23.7)	0.018*
Vitamin E/triglycerides	10.7 (0.8; 36.7)	18.8 (6.9; 65.4)	0.010*
Vitamin E/total lipids	3.68 (0.29; 12.63)	5.92 (3.27; 17.37)	0.013*
GPx (ng/mL)	35.8 ± 12.9	32.0 ± 11.5	0.445**
CAT (pg/mL)	177.5 (33.5; 5490.0)	153.6 (37.9; 2828.7)	0.276*
SOD (ng/mL)	52.3 (18.5; 657.4)	42.1 (2.4; 234.1)	0.371*
IL-33 (pg/mL)	20.8 (0.18; 929.0)	9.0 (0.7; 69.8)	0.371*

P = Significance level of Mann–Whitney* or Student's t-test**. CRP, C-reactive protein); GPx, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; IL-33, interleukin 33.

Discussion

In this study, children and adolescents with AD predominantly with moderate or severe forms (79.2%) showed a higher frequency of overweight and high zinc levels compared to the control group; a fact not observed for the other biomarkers of antioxidant defense.

The development and phenotypic expression of AD depend on the complex interaction between genetic and environmental factors, including those related to nutrition.[20,21] In individuals with AD, a systematic review showed expressive micronutrient deficiency with a significant role in the immune system, inflammation, and oxidative stress. The authors emphasized the significance of inflammation and oxidative stress in the pathogenesis of AD.[22,23]

With regard to Zn, it is important to highlight its role in cell growth and function and as a cofactor of numerous enzymatic systems. The micronutrient also plays immunomodulatory and antioxidant roles. The immune system cells have high rates of proliferation, apoptosis, and differentiation, and Zn plays an essential role in all processes. T-cell activation as well as differentiation of helper T cells into their different subgroups (Th1, Th2, Th17 and regulatory T cells – Treg) are also influenced by Zn homeostasis.[24]

Studies evaluating serum or intraerythrocytic levels of Zn in individuals with AD compared to controls show contradictory results; some authors report low concentrations,[22,24,25] while others did not observe differences.[26,27] Systematic review and meta-analysis evaluated the association between Zn levels and AD, in addition to the efficacy of oral supplementation in the treatment of the disease. All available studies were considered to be of low or moderate quality. The combined analysis of the studies, in contrary to what we observed, showed lower serum and intraerythrocytic levels in patients with AD compared to controls. Regarding Zn supplementation, the results were inconclusive.[28]

To our knowledge, this study is a pioneer in describing higher concentrations of serum Zn in patients with AD without association with disease severity. Some hypotheses can be suggested to explain the finding: (a) Serum Zn is not a good marker to assess marginal deficiency and chronic deficiency, but for assessing the intraerythrocytic levels; (b) the redistribution of Zn as an acute phase reagent to chronic inflammation may be more exacerbated in moderate or severe forms.[29]

In contrary to what was observed by Sivaranjani et al.,[30] we found no significant difference for the levels of vitamins A, E, and C and antioxidant enzymes (SOD, GPX, and catalase) between patients and controls. It should be considered that the study was conducted predominantly with adult patients (mean age = 35 years) and that it did not address nutritional status, disease characteristics such as severity, or the treatment received.

Regarding vitamin E, the lower concentrations of this vitamin and its ratios with total lipids and fractions in the group with moderate or severe forms compared to the group with mild AD drew attention in the present study. Previous studies have shown that vitamin E can reduce IgE concentrations in individuals with AD.[31,32] A randomized, double-blind clinical trial evaluated the impact of supplementation with 400 IU/day of vitamin E and placebo for 4 months in individuals with AD. The group supplemented with vitamin E showed improvement in all symptoms (pruritus and extent of lesions) except for insomnia and in SCORAD.

The main sources of vitamin E in the diet are vegetables, vegetable oils, and oil seeds. Alpha-tocopherol, naturally present in food, prevents cell membranes from oxidative attack by free radicals. Additionally, vitamin E is involved in the activation of some molecules and enzymes in inflammatory cells and the immune system.[33] Review study highlighted the promising role of vitamin E in the adjuvant treatment for AD and other skin diseases that course with oxidative stress and inflammation.[34]

In our study, we observed excess weight and central adiposity (waist-to-height ratio > 0.5) in 56.2 and 43.8% of the individuals with AD, despite the majority being prepubertal (58.3%). It also drew attention to the association with other atopic diseases in most patients, and the presence of moderate or severe forms in about 80% of patients. A recent study, similar to ours, highlighted the higher prevalence of overweight and dyslipidemia in children with AD.[35] It is known that excess weight can contribute to the exacerbation of the disease and favor the development of other chronic diseases.[36]

We found vitamin D deficiency in about 20% of children and adolescents with AD, with no significant difference compared to controls. Hattangdi-Haridas et al. conducted a systematic review and meta-analysis, describing the concentrations of 25-hydroxyvitamin D (25 [OH]) in individuals with AD, as well as the impact of supplementation on disease severity.[37]

The current study had some limitations, such as the cross-sectional model, limitation of sample size, and lack of evaluation of food consumption and the approximate number of topical corticosteroids used.

Conclusion

Children and adolescents with AD had higher concentrations of elevated levels of zinc compared to controls; a fact not observed for vitamins (A, D, E, and C), copper, and antioxidant enzymes. Moderate or severe forms of AD compared to mild showed lower concentrations of vitamin E, a potent fat-soluble antioxidant. Knowledge of the nutritional status related to antioxidant defense is essential for the future development of intervention studies with a possible impact on the evolution of the disease.

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