



Research article

Altered serum elements, antioxidants, MDA, and immunoglobulins are associated with an increased risk of seborrheic dermatitis

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ABSTRACT

Background: The exact mechanism for the pathophysiology of seborrheic dermatitis (SD) remains unknown. According to past knowledge, neuropsychiatric disorders, weak immune responses, fungal infections, antioxidants deficiencies, and inadequate nutrition might involve in SD. Here we evaluated serum trace elements, micronutrients, antioxidants, malondialdehyde (MDA), and immunoglobulins in SD patients.**Methods:** This case-control study recruited 75 SD patients and 76 age-and sex-matched healthy controls (HCs). We measured serum micronutrients using atomic absorption spectroscopic methods. Similarly, we assessed serum antioxidants applying the RP-HPLC techniques. Also, serum MDA and immunoglobulins levels were evaluated by UV-spectrophotometric and turbidimetric methods, respectively.**Results:** We observed higher serum levels of copper, manganese, iron, calcium, magnesium, and MDA in SD patients than HCs. Together with vitamin E, we noticed lower serum concentrations of immunoglobulin A, G, and M in SD patients than HCs. The present study detected a positive correlation between serum zinc and calcium levels ($r = 0.365$, $p = 0.009$) in SD patients. However, we identified a negative correlation between serum copper and calcium levels ($r = -0.298$, $p = 0.035$).**Conclusion:** The present study suggests that the altered levels of micronutrients, antioxidants, MDA, and immunoglobulins are associated with the pathophysiology of SD. These changes may not be the cause but the consequences of the disease. These findings might help to understand the etiopathology and management of SD.

1. Introduction

Seborrheic dermatitis (SD) is a common form of skin disorder [1]. The affected skin of SD patients becomes swollen and looks pink. Sometimes we see the yellow-brown scales and crusts over the affected skin [2]. It is a common skin disease in infants (up to 3 months), adults (40–60 years), and puberty [3]. The scalp of SD patients produces an excess amount of sebum. Therefore we see the sebaceous follicle-rich area on the face and shoulder [4]. It is a common skin disease among human immunodeficiency virus (HIV) patients [5]. Though we see some remission and aggravation periods in SD, there is a tendency for lifetime relapses in SD patients [6]. In general, 1–3% of adults suffer from SD, and in all age

groups, males are affected more than females [7, 8]. About 50% of adults suffer from dandruff which is the mildest form of SD [9]. In Bangladesh, the prevalence of SD is of a similar magnitude as in developed countries. Here, 70% of patients with skin disorders suffer from pyoderma or scabies [10]. Hormonal imbalance, fungal infection, nutritional deficiency, neurogenic disorder are the common causes of many skin diseases [11]. The actual cause of SD is still unknown. However, scientists have identified several predisposing factors for this disease, for example, sebaceous gland activity, alteration in fungal colonization and metabolism (*Malassezia spp.*), host responses, and individual susceptibility [12]. Moreover, many researchers consider hot weather, damp humidity, sun exposure, stress, use of cosmetics, processed foods, nutritional

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deficiency as aggravating factors of SD [3, 6, 13]. Since the past knowledge is limited to understand the actual pathophysiology of SD, we need further research on this topic to know more about this disease and to develop new drug molecules to treat it.

Inorganic minerals and nutrients present in the tissue are essential for their regular functions [14]. Sodium, chloride, and calcium are involved in many biochemical and immunological processes. Therefore, they play vital roles in SD [15, 16]. Moreover, several trace elements (TE) and macro-mineral (MM) such as copper (Cu), iron (Fe), manganese (Mn), zinc (Zn), calcium (Ca), magnesium (Mg) can influence oxidative stress through various mechanisms [17]. Three-dimensional structures of many proteins are vital for healthy skin. Some TEs and MMs play essential roles in maintaining this three-dimensional structure of proteins [18]. Altered levels of these TEs and MMs are responsible for developing various skin diseases [19]. A study reported the altered serum Zn levels in SD patients compared to healthy volunteers [20]. Therefore, changes in serum TEs and MMs levels may influence the pathophysiology and development of SD.

Human skin is repeatedly exposed to oxidative stress by the reactive oxygen species (ROS) [21]. This ROS causes several oxidative damages through DNA modification, secretion of inflammatory cytokines, lipid peroxidation, etc. [22]. Many enzymatic and non-enzymatic antioxidants play vital roles in inactivating the free-radicals [23, 24]. Natural antioxidants (vitamins A and E) are lipophilic, thus act as free radical eliminators. However, synthetic antioxidants might have some detrimental effects on the human body [25, 26, 27, 28]. Lipid peroxidation helps to know the oxidative status in the biological system [29].

Immunoglobulins are macromolecular proteins produced by blood cells that neutralize various pathogenic bacteria and viruses [30]. Several studies reported the relationship between immunodeficiency and SD though the actual mechanism behind this is not well established [31, 32, 33]. More specifically, research showed the association between serum immunoglobulin E (IgE) levels and atopic dermatitis [34].

Woefully, the knowledge regarding the role of TEs, MMs, antioxidants, MDA, and immunoglobulins in SD is limited. Therefore, the present study aimed to find the association of these parameters with SD patients.

2. Methods

2.1. Study population

We considered 95% confidence level, 5% margin of error, and 10% population proportion while calculating sample size. Based on this assumption, 139 participants were supposed to include in the present study. We enrolled a total of 151 subjects (75 SD patients and 76 age- and sex-matched HCs) in this case-control study. A dermatologist performed the diagnosis of SD patients based on the location and appearance of lesions. The physician suggested a biopsy to exclude other skin diseases that present similar symptoms. Also, the same dermatologist evaluated the HCs. We excluded treated patients from this study to avoid the possible interference with the concentrations of analyzed parameters. Also, we excluded them from the present analysis who had a previous history of any skin or inflammatory diseases. We used a pre-designed structured questionnaire to record the socio-demographic profile of the participants. The present study analyzed the different biophysical and socio-demographic characteristics such as weight, height, and body mass index (BMI). Following the principles of the Declaration of Helsinki and later amendments, we performed this study [35].

2.2. Blood collection and preparation

After an overnight fast, we collected a 5ml blood sample from the cephalic vein of each participant. We transferred the collected blood samples into a metal-free, pre-cleaned test-tube. The blood samples were allowed to clot for one hour at room temperature (25 °C). We extracted

serum from the blood samples by centrifugation at 3000 rpm for 15 min and placed them into micro-tubes. Then the serum samples were stored at -80 °C until doing further analysis. We performed the sample collection and preservation according to our previous study [36].

2.3. Chemicals and reagents

We purchased standard Cu, Fe, Mn, Zn, Ca, and Mg from Buck Scientific, USA, and the immunoglobulin kits from Chronolab, Switzerland. Sigma Chemical Co., USA, supplied the standard α -tocopherol (vitamin E), α -tocopheryl acetate, and retinol (vitamin A). For HPLC-based analysis, Active Fine Chemicals Limited, Dhaka, Bangladesh, supplied HPLC-grade chemicals and reagents. We purchased other supportive chemicals of the recommended grade from Merck, Germany.

2.4. Determination of serum micronutrients

We measured the serum TEs (Zn, Cu, Mn, and Fe) and MMs (Ca and Mg) levels using flame atomic absorption spectrometry (FAAS) and graphite furnace atomic absorption spectrometry (GFAAS) following the method described in our previous article [37]. We measured serum Ca, Mg, Zn, and Fe in flame AAS. Also, serum Cu and Mn levels were analyzed using graphite furnace AAS. In both cases, we used SpectrAA hollow cathode lamps as the radiation source. We have used acetylene-nitrous oxide flame for FAAS and transversely heated graphite atomizer for GFAAS measurements. We adjusted the gas flow rates and the burner height to get the maximum absorbance signal. Before subjecting the samples to atomic absorption spectrophotometry, we checked the relative standard deviation and instrument parameters. Then we evaluated the linearity, recovery, precision, and limits of detection of serum elements. At first, we diluted the serum samples (1:10) using deionized water. Then we prepared the calibration curve using different concentrations (0.5, 1.0, 2.0, 5.0 and 10.0 mg/L) of TEs and MMs. Finally, we measured the concentrations of Ca, Mg, Cu, Fe, Mn, and Zn at 422.7, 285.2, 327.4, 248.3, 279.8, and 213.9 nm, respectively. We have run one standard solution for every 10 test samples to ensure assay accuracy and quality. We took enough precautions during the handling of serum samples to avoid or minimize contamination.

2.5. Measurement of serum antioxidants

The serum concentrations of vitamin A and E were measured simultaneously at 291nm by the modified RP-HPLC method with UV detection [38]. We prepared serum samples of vitamin A and E levels by liquid-liquid extraction using n-hexane. Then we dried the sample mixture at 40 °C using a concentrator (DB-3, Techne, UK). Afterward, we reconstituted the dried extract in the mobile phase.

2.6. Quantification of serum MDA

We measured serum MDA concentration using thiobarbituric acid (TBA) reagent. The absorbance was taken at 530 nm using UV-spectrophotometry. MDA was measured in terms of TBARS by the modified method described in our past study [39]. We expressed the concentration of MDA as nmol/mL.

2.7. Serum immunoglobulin profiling

We measured serum immunoglobulins by the quantitative turbidimetric method using an immunoglobulin kit. In this method, serum samples containing IgA, IgG, IgM were mixed with the activation buffer and then with anti-human immunoglobulin reagent according to the procedure described in our previous article [40]. We diluted the serum samples (1:4) using saline water. Then we placed the diluted serum samples into a microtiter plate. We used separate microtiter plates to measure each immunoglobulin (IgA, IgG, IgM). Then, we added 10 μ L,

25 μ L, 50 μ L, 75 μ L, and 100 μ L of the calibrator protein into marked wells. 230 μ L of reagent R1 (tris-buffer) was added to each serum and calibrator protein-containing wells of the microtiter plate to make the final volume 240 μ L. Then 15 μ L of each diluted anti-human IgA, IgG, and IgM was added to the respective wells. Finally, we incubated this mixture for about 2–5 min to complete the reaction between samples and reagents. Then, we took the absorbance at 630 nm for IgA; at 405 nm for IgG and IgM.

2.8. Statistical analysis

We presented the data as mean \pm standard error mean (mean \pm SEM). We performed the independent sample t-test, Fisher's exact test, and box-plot graphs for comparing the parameters between SD patients and HCs. Also, we performed Pearson's correlation analysis to obtain the correlation among various study parameters. We used the statistical software package SPSS version 25.0 (Armonk, NY: IBM Corp.) to perform all the statistical analyses.

2.9. Ethics approval and consent to participate

We obtained ethical approval from the ethical committee of Ad-din Women's Medical College, Dhaka, Bangladesh (approval number: AWMC/EC/2018/32). All the participants were well informed about the purpose of the study. Each participant gave a written consent to participate in this study.

3. Results

3.1. Anthropometric and demographic profile of the study population

We presented the anthropometric and demographic characteristics of the SD patients and HCs in Table 1. We observed the average age of SD patients and HCs as 27.13 ± 1.61 years and 26.30 ± 0.92 years, respectively. Though SD can develop at any stage of life, we carried out the present study among 18–35 years of age. We observed the BMI of SD patients and HCs were 22.65 ± 1.57 kg/m² and 22.93 ± 1.31 kg/m², respectively. The percentage of males was highest among the SD patients and HCs. There were no significant differences observed in terms of age, BMI, and sex among the participants ($p > 0.05$). Moreover, both SD patients and HCs were similar in terms of marital status, monthly income, occupation, economic condition, smoking habit, and residence.

3.2. Serum levels of micronutrients, antioxidants, MDA, and immunoglobulins

We presented the serum levels of micronutrients, antioxidants, MDA, and immunoglobulins in Table 2. The concentrations of Cu, Mn, Fe, Ca, and Mg were significantly higher in the SD patients than the HCs. Also, the present study observed elevated serum MDA levels in the SD patients compared to HCs (0.2125 ± 0.31 μ mol/L vs. 0.186 ± 0.28 μ mol/L, respectively). However, serum vitamin E levels were significantly lower in SD patients compared to HCs (5.564 ± 0.39 μ mol/L vs. 7.074 ± 0.37 μ mol/L, respectively). Similarly, we observed lower serum levels of three

Table 1. Anthropometric and socio-demographic profile of the study population.

Parameters	SD patients	Healthy controls	p value
No. of subjects	75	76	
Age (years)	27.13 ± 1.61	26.30 ± 0.92	0.289
BMI (kg/m ²)	22.65 ± 1.57	22.93 ± 1.31	0.432
Sex			0.561
Male	43 (57%)	41 (54%)	
Female	32 (43%)	35 (46%)	
Marital status			0.473
Married	41 (55%)	38 (50%)	
Unmarried	34 (45%)	38 (50%)	
Monthly income (KBDT)			0.258
Below 20	32 (42%)	28 (37%)	
21–30	11 (15%)	13 (17%)	
31–40	12 (16%)	18 (24%)	
Above 40	20 (27%)	17 (22%)	
Occupation			0.326
Service	19 (25%)	15 (20%)	
Business	9 (12%)	8 (10%)	
Student	13 (18%)	10 (13%)	
Jobless	28 (37%)	25 (33%)	
Others	6 (8%)	18 (24%)	
Economic status			0.215
Low	29 (39%)	22 (29%)	
Medium	25 (33%)	31 (41%)	
High	21 (28%)	23 (30%)	
Tobacco user			0.548
Yes	39 (52%)	35 (46%)	
No	36 (48%)	41 (54%)	
Residence area			0.331
Rural	37 (49%)	40 (53%)	
Urban	38 (51%)	36 (47%)	

Values are expressed as Mean \pm SEM, $p < 0.05$ (Significant difference between patient and control groups at 95% confidence interval). BMI: Body mass index, KBDT: Kilo Bangladeshi taka, SD: Seborrheic dermatitis, SEM: Standard error mean.

Table 2. Serum levels of trace elements, macro-minerals, antioxidant vitamins, malondialdehyde and immunoglobulins in the study population.

Parameters	SD patients (n = 75) Mean ± SEM	Healthy controls (n = 76) Mean ± SEM	p value
Zinc (mg/L)	1.430 ± 0.11	1.308 ± 0.09	0.289
Copper (mg/L)	2.136 ± 0.10	0.950 ± 0.05	<0.001*
Manganese (mg/L)	15.830 ± 0.85	7.022 ± 0.46	<0.001*
Iron (mg/L)	2.248 ± 0.14	1.130 ± 0.11	<0.001*
Calcium (mg/L)	185.040 ± 5.89	99.580 ± 1.77	0.001*
Magnesium (mg/L)	29.640 ± 0.55	20.640 ± 0.27	<0.001*
Vitamin A (µmol/L)	0.403 ± 0.07	0.374 ± 0.03	0.707
Vitamin E (µmol/L)	5.564 ± 0.39	7.074 ± 0.37	0.009*
MDA (µmol/L)	0.2125 ± 0.31	0.186 ± 0.28	0.011*
IgA (mg/dL)	212.96 ± 16.38	263.08 ± 10.22	0.001*
IgG (mg/dL)	1208 ± 16.37	2317 ± 10.23	<0.001*
IgM (mg/dL)	119.45 ± 8.57	158.89 ± 9.09	0.003*

*p < 0.05 (Significant difference between patient and control groups at 95% confidence interval). SD: Seborrheic dermatitis, SEM: Standard error mean.

immunoglobulins (IgA, IgG, and IgM) in SD patients compared to HCs (212.96 ± 16.38, 1208 ± 16.37, and 119.45 ± 8.57 mg/dL vs. 263.08 ± 10.22, 2317 ± 10.23, and 158.89 ± 9.09 mg/dL, respectively). We

presented the distribution pattern of micronutrients (Figure 1), antioxidants, MDA, and immunoglobulins (Figure 2) with median, maximum, and minimum value.

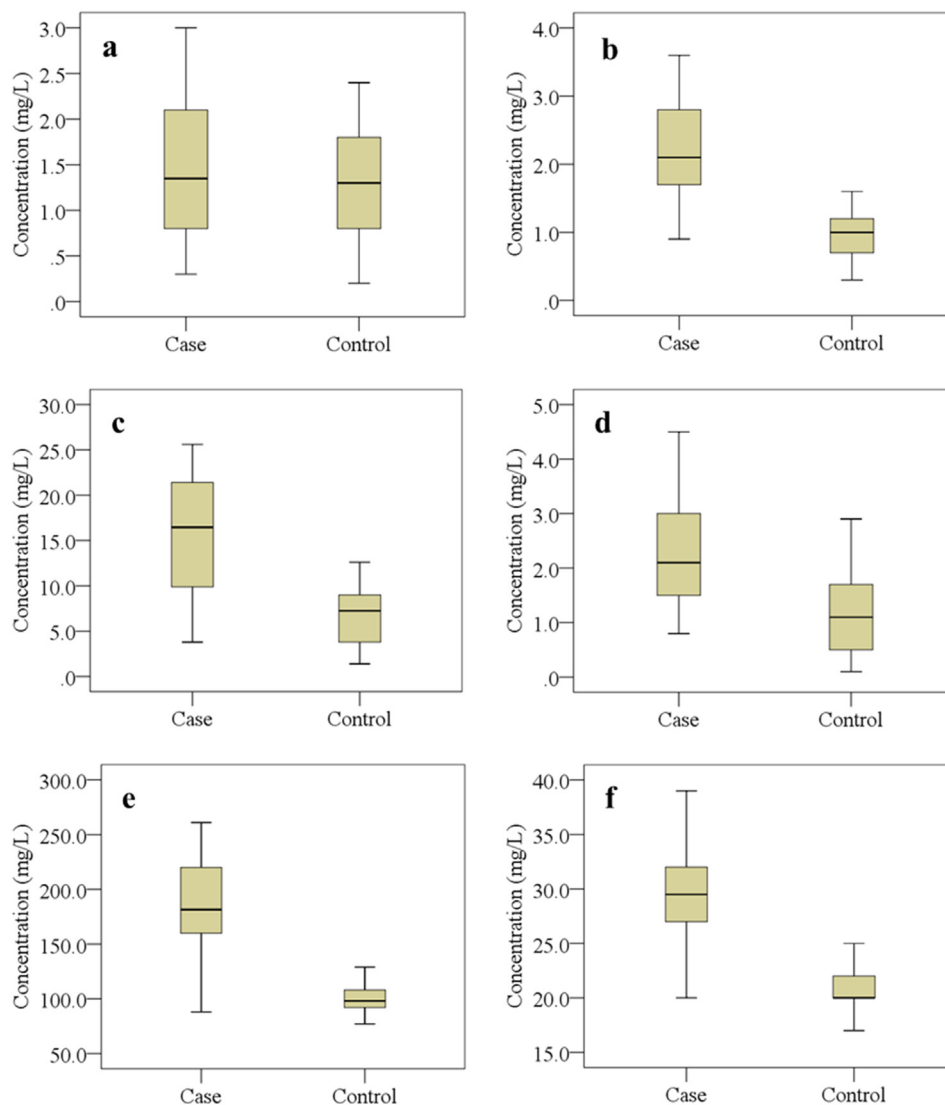


Figure 1. The changes of serum micronutrients levels (mg/L) in the study population. Graphs showing the median, maximum, and minimum value range. a Zinc, b Copper, c Manganese, d Iron, e Calcium, f Magnesium.

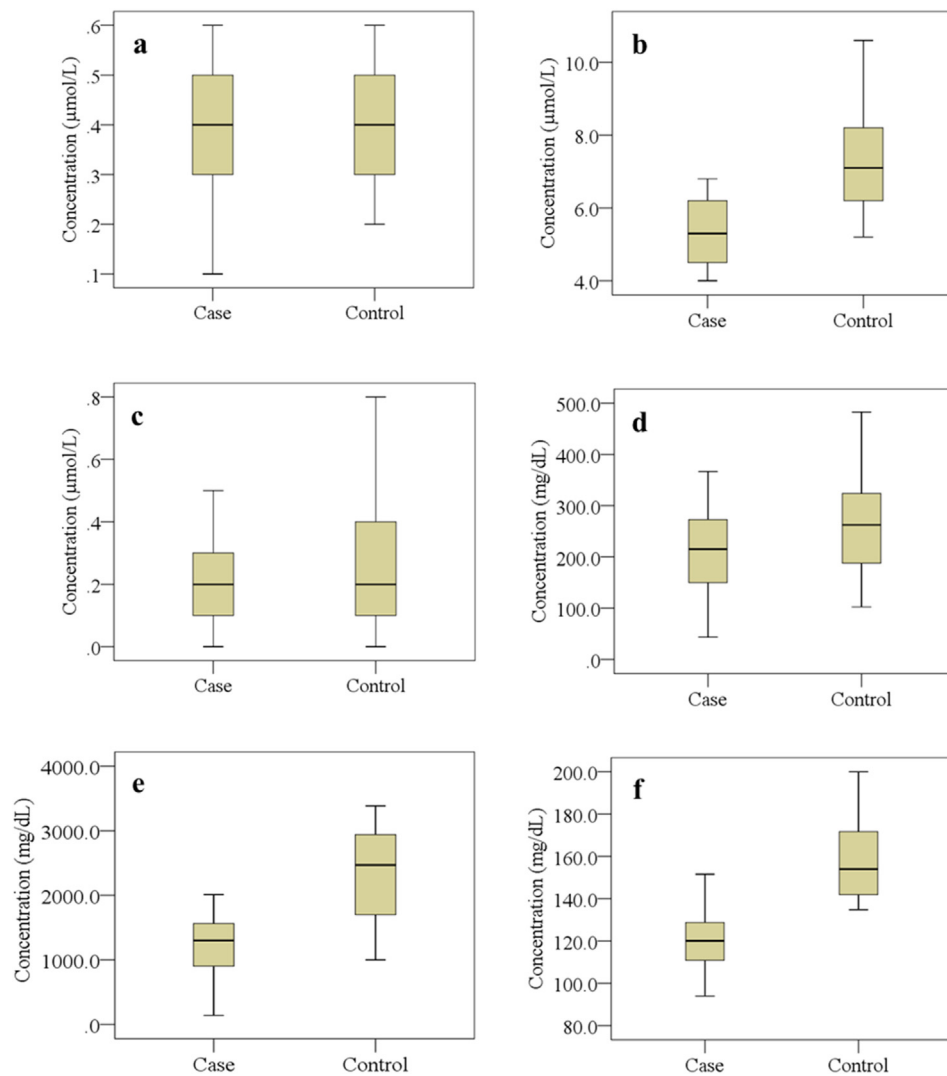


Figure 2. The changes in serum levels of antioxidants (μmol/L), MDA (μmol/L), and immunoglobulins (mg/dL) levels in the study population. Graphs showing the median, maximum, and minimum value range. a Vitamin A, b Vitamin E, c MDA, d Immunoglobulin A, e Immunoglobulin G, f Immunoglobulin M.

3.3. Correlation study

We presented the inter-elemental relationships among the analyzed parameters in Table 3. We found a significant positive correlation between Zn and Ca ($r = 0.365$, $p = 0.009$) in SD patients. We also observed a significant positive correlation between serum Ca and Mg levels ($r = 0.783$, $p = 0.001$) in HCs. However, a significant negative correlation was detected between serum levels of Cu and Ca ($r = -0.298$, $p = 0.035$) in SD patients, and such relations were absent in HCs.

4. Discussion

In the present study, we observed higher serum levels of Cu, Mn, Fe, Ca, and Mg in SD patients than HCs. The role of Zn in SD is obscure. Previous studies reported that serum Zn levels were lower or no change in SD patients than HCs [24, 41]. Another study reported that no change in serum Mn levels in patients with psoriasis and vitiligo than HCs. A study observed high Mn levels in pigmented moles. However, the same study reported no association between Mn level and the severity of melanization in seborrheic warts [42]. Serum Mn catalyzes the conversion of H_2O_2 to potent hydroxyl radicals that may lead to oxidative damage in SD. This process is representing an epiphenomenon related to the pathogenesis of SD [16]. The elevated serum levels of Fe in SD patients might be responsible for inducing free radical-mediated oxidative

damage [43]. Ca plays a vital role during bone formation, blood clotting, and neuromuscular excitability [5, 44]. We noticed significantly higher levels of Ca in SD patients than HCs. A study confirmed the elevated serum levels of two calcium-binding proteins are associated with abnormal keratinocyte differentiation in psoriasis [9]. Ca helps to do the proliferation and differentiation of keratinocytes by gene activation [45, 46]. Both the low or high intake of Cu in our body can cause an imbalance in the immune system [47, 48]. In agreement with the previous studies, the present study suggests that the increased levels of Cu, Mn, Fe, Ca, and Mn may cause inter-elemental homeostasis. Also, this process might lead to the oxidative damage of biomolecules in the skin. Moreover, in SD patients, serum Ca levels were positively correlated with the Zn levels and negatively correlated with the Cu levels.

Biological processes produce ROS that causes cell damage by the free radical chain reaction. Antioxidants counteract the effects of these free radicals [8, 49]. Therefore, antioxidant vitamins play a vital role in maintaining the balance between ROS production and elimination [50]. The present study showed increased MDA and reduced vitamin E levels in SD patients compared to HCs. However, no changes happened in vitamin A levels between these two groups. These results indicate the cell and tissue damage due to oxidative stress through binding the free radicals with the membrane lipids, DNA, and other intracellular components. One study reported lower serum vitamin E levels in SD patients than HCs that contrast the present study results [51]. Another study reported higher

Table 3. Study of inter-element correlations in SD patients and healthy controls.

Correlation parameters	SD patients (n = 75)		Healthy controls (n = 76)	
	r	p	r	p
Zn and Cu	-0.182	0.207	-0.272	0.056
Zn and Mn	0.001	0.996	0.003	0.887
Zn and Fe	0.222	0.121	0.045	0.758
Zn and Ca	0.365	0.009**	0.179	0.213
Zn and Mg	0.231	0.107	-0.127	0.379
Cu and Mn	0.092	0.525	0.022	0.878
Cu and Fe	0.237	0.097	-0.016	0.914
Cu and Ca	-0.298	0.035*	-0.095	0.512
Cu and Mg	-0.072	0.617	-0.029	0.842
Mn and Fe	-0.125	0.385	0.005	0.973
Mn and Ca	-0.127	0.380	0.116	0.422
Mn and Mg	-0.041	0.779	0.054	0.708
Ca and Mg	0.277	0.052	0.783	<0.001*

Here, r = Correlation co-efficient; p = Significance; Negative value indicates opposite correlation; *p < 0.05, Correlation is significant at 95% confidence interval.

scalp MDA levels in SD patients than HCs [5]. According to the above observation, higher MDA and lower antioxidant levels might serve as possible causative factors for SD.

The prevalence of SD is high (83%) among the population with organ transplantation, AIDS, chronic alcoholic pancreatitis, and cancer [52]. This observation indicates the importance of the immune system in the pathogenesis of SD. The present study noticed significantly decreased serum IgA, IgG, and IgM levels in SD patients than HCs. These findings are consistent with several past observations [31, 53]. Moreover, one study reported the prevalence of SD was higher in patients with an impaired immune system [52]. From the above discussion, we can say that the alteration of TEs, MMs, antioxidant vitamins, MDA, and immunoglobulins might harm the immune system. Therefore, the changes of these parameters in serum levels might be associated with the pathophysiology of SD.

The present study has some limitations also. Firstly, we did not evaluate serum inflammatory, pro-inflammatory, and anti-inflammatory cytokines. But ROS can cause different types of oxidative damages and enhance the secretion of these cytokines in SD. Secondly, we should have measured the same parameters after the remission of SD to produce more precise conclusions. Therefore, we recommend the further investigation of these parameters overcoming the above issues for a better understanding of the pathophysiology of SD. Despite few drawbacks, we hope that this work will help to explore the role of micronutrients, antioxidants, MDA, and immunoglobulins in SD.

5. Conclusion

The present study suggests that altered serum levels of micronutrients, MDA, antioxidants, and immunoglobulins are associated with SD. These findings may assist in the understanding of the biochemical basis and etiopathology of SD. Moreover, macro and micronutrients, immunoglobulins, and multivitamins might aid the clinical management of SD patients. The alterations of these parameters in SD patients may be the consequence, and not the cause, of disease. However, further detailed studies are required to discover whether the altered parameters are the cause or outcome of the disease process in SD.

Declarations

Author contribution statement

Ishrat Jahan, Md. Rabiul Islam and Md. Reazul Islam: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Rubaiya Ali and S.M. Matiur Rahman: Performed the experiments; Analyzed and interpreted the data.

Zabun Nahar: Performed the experiments; Wrote the paper.

Abul Hasnat and Md. Saiful Islam: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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