

Serum Levels of Copper, Zinc, Magnesium, Iron and Ferritin in Libyan Patients with Vitiligo Vulgaris: A Case Control Study

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Received date: February 16 2022; **Accepted date:** May 02, 2022; **published date:** May 16, 2022

Citation: Salwa A. El-Dibany, Nadia A. E Sherif, A E S H Greiw. (2022) Serum Levels of Copper, Zinc, Magnesium, Iron and Ferritin in Libyan Patients with Vitiligo Vulgaris: A Case Control Study. *J. Dermatology and Dermatitis*. 7(2); DOI: [10.31579/2578-8949/094](https://doi.org/10.31579/2578-8949/094)

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Abstract

Background: Vitiligo is the most common acquired pigmentary skin disorder, with an estimated worldwide incidence of 0.5-4%. Although the pathogenesis of vitiligo remains largely unknown, there are different theories explaining its pathogenesis, including: genetic, autoimmune, auto-cytotoxic, oxidative stress and neurogenic. Oxidative stress has been postulated to causes cellular disruptions that provoke an autoimmune response in genetically susceptible individuals leading to melanocytes destructions. Trace elements considered as antioxidants protecting the body against cytotoxicity of melanocytes and inhibition of tyrosinase in oxidative stress. **Aim of the study:** to evaluate the serum levels of copper, zinc, magnesium, iron and ferritin in patients with vitiligo vulgaris and compare it with control subjects. Also to determine the association between serums trace elements levels and disease activity. **Patients and Methods:** This study included 50 patients with vitiligo attending the Outpatient Clinic of Dermatology Department, Eljumhoria Hospital, Benghazi, Libya, and 50 healthy age and sex-matched volunteers who had nodermatological or systemic diseases. Blood samples for serum levels of copper (Cu), zinc (Zn), magnesium (Mg), iron (Fe) and ferritin were obtained from patients with vitiligo vulgaris and healthy controls. **Results:** Serum Cu, Zn and Mg were higher in patients, serum ferritin was lower in patients than control subjects and this difference was statistically non-significant ($P < 0.05$). Whereas, there was no difference in serum Fe between patients and control subjects. There was no significant correlation between the serum level of these TE with activity of the disease, duration or family history of vitiligo. **Conclusions:** Serum Zn, Cu and Mg levels in patients with vitiligo were found to be higher than that of controls. The role of trace elements in the pathogenesis of vitiligo needs to be investigated in further large sample sized population-based studies.

Keywords: trace elements; serum; vitiligo

Introduction

Vitiligo is an acquired disorder characterized by depigmented macules and patches that result from a destruction of functional melanocytes [1]. Vitiligo affects approximately 0.5-4% of the general population worldwide with no gender or race predominance [1]. The average age of onset is variable, but peaks in the second and third decades [2]. The precise etiology of vitiligo is still unknown, but the major hypotheses states that stress, accumulation of toxic compounds, infection, autoimmunity, mutations, altered cellular environment, and impaired melanocyte migration and proliferation can all contribute in varying proportions to the pathogenesis of the disease [1]. Increased oxidative stress due to the accumulation of free radicals and reactive oxygen species with deficiency of antioxidant substances in vitiliginous skin have been reported [2,3].

Trace elements are required for the normal functioning of many enzymes and play a significant role in the development of many diseases. They are involved in immunological and inflammatory reactions such as keratinization and melanin formation. Trace elements are also considered as antioxidants protecting against cytotoxicity of melanocytes and inhibition of tyrosinase in oxidative stress. Moreover, disturbances in trace element status and increased oxidative stress in vitiligo may contribute to its development [2,4].

Aims of study

- To evaluate the serum levels of copper, zinc, magnesium, iron and ferritin in patients with vitiligo vulgaris and compare it with

control subjects.

- To determine the association between serum trace elements levels and disease activity.

Patients and Methods

Fifty vitiligo patients and 50 age and sex matched healthy subjects attending in OPD of Dermatology Department, El-Jumhoria Teaching Hospital, in Benghazi, Libya were participated in the present study. All patients had vitiligo vulgaris, based on clinical and wood lamp examination. Exclusion criteria included pregnancy or lactation, taking mineral supplements or receiving any medication that could change serum level of trace elements, metabolic or systemic disorders and skin problems other than vitiligo. A complete history was taken from each patient, which included the demographic data, medical and drug history, duration of vitiligo, and familial history of vitiligo. Laboratory tests were recommended from both patients and control subjects, which comprised complete blood count, serum zinc (Zn), copper (Cu), magnesium (Mg), iron (Fe) and Ferritin levels.

Vitiligo patients were divided into two groups as active and stable according to the progression of the disease in the last three months. A signed consent was obtained from all patients and subjects after explaining the nature of the study to them and manuscript is according to declaration of Helsinki.

Statistical analysis

All statistical analyses were performed using SPSS software for Windows (Version 22.0). Results are presented as mean ± standard deviations for continuous variables and as a number (%) for categorical variables. The Chi-square test and independent t-test were used for statistical analysis. Differences were considered as statistically significant with P values < 0.05.

Results

A total of 50 vitiligo patients and 50 age and sex matched healthy subjects were enrolled in this study. Table 1.

Demographic data	Vitiligo patients	Control subjects	P value
Age mean ± SD yrs	34 ± 6 yrs	32.2 ± 9 yrs	.235
Sex			
Female	26 (52%)	27 (54%)	.902
Male	24 (48%)	23 (46%)	
Duration yrs ± SD	10.5 ± 9 yrs	NA	
Activity of disease			
Active	17 (34%)	NA	
Stable	33 (66%)		

Table 1: Demographic data of vitiligo patients and control subjects under study

Table 2. Represent the serum levels of trace elements under study. Serum Cu and Zn were insignificantly higher in vitiligo patients, whereas serum Mg was significantly higher in patients as compare to control subjects.

No difference was observed in serum iron between two groups and serum ferritin was insignificantly lower in patient as compare to control subjects

Serum level	Vitiligo patients	Control subjects	P value
Zinc (µg/dl)	111 ± 40	90.2 ± 18.9	
Copper (µg/dl)	175 ± 77	156.3 ± 43	.127
Magnesium (mg/dl)	2.6 ± .6	1.9 ± .2	.000*
Hemoglobin (g/dl)	12 ± 2	12.7 ± 2	.668
Iron (µg/dl)	116.9 ± 32	116.8 ± 81	.993
Ferritin (ng/ml)	72.6 ± 80	89 ± 86	.322

Table 2: Serum TE levels in vitiligo patients and control subjects

All serum TE were lower in patients with active disease as compare to patients with stable vitiligo, but this difference was statistically insignificant (Table 3).

Serum level	Active disease	Stable disease	P value
Zinc (µg/dl)	100±46	117±37	.118
Copper (µg/dl)	159±58	184±84	.286
Magnesium (mg/dl)	2.6±.6	2.7±.7	.521
Hemoglobin (g/dl)	11.7±1.5	12.2±2	.365
Iron (µg/dl)	102±47	124±94	.357
Ferritin (ng/ml)	57.5±71	80±84	.339

Table 3: Correlation between the serums TE with vitiligo activity

Female patients had lower serum levels of Zn, Cu, Mg, Fe than male patients but this difference was statistically insignificant. However, female patients had significantly lower blood Hb and ferritin

(Table 4). No statistically significant difference was observed in serum TE with regard duration of the disease, family history of vitiligo.

Serum level	Female patients	Male patients	P value
Zinc (µg/dl)	110±38	112±44	.821
Copper (µg/dl)	173±81	178±73	.796
Magnesium (mg/dl)	2.6±.6	2.6±.7	.953
Hemoglobin (g/dl)	11.7±.6 g/dl	13.5±1.5g/dl	.000*
Iron (µg/dl)	113.9±85	119.8±79	.800
Ferritin (ng/ml)	48±72	99±80	.020*

Table 4: The mean serum TE levels in vitiligo patients according to their gender

Discussion

Vitiligo is an acquired depigmenting skin disorder of unknown origin with an estimated worldwide incidence of 0.5-4% [1]. Moreover, vitiligo has a pronounced impact on the physical and mental health of patients, including loss of skin photoprotection, compromised cutaneous immunity, and an appreciable reduction in quality of life [1,3]. Vitiligo is a multifactorial polygenic disorder with a complex pathogenesis. However, the autocytoxic and the autoimmune theories are at present the most accredited [3]. Current literature reports several evidences suggesting a strict interplay between oxidative stress and immune system, able to trigger and maintain vitiligo depigmentation process and the eventually associated autoimmune diseases [1].

Zinc and copper are important cofactors and modulators of many critical biological functions in skin disorders including dermatitis enteropathica, bullous pemphigoid, decubitus ulcer, alopecia areata, psoriasis, vitiligo and skin cancer [5]. Moreover, they are involved in inflammatory reactions and important for the normal functioning of the immune system [6]. They are integral part of metalloenzymes necessary in the final stage of eumelanin formulation in melanogenesis [6]. Many studies have been made to reveal the effect of trace elements on vitiligo, but these studies provide conflicting results [7].

Serum Zn and Cu in our patients was higher than the control subjects. These findings are in agreement with previous study [8]. Increased Zn serum level was also observed by studies of Ali et al [9] and Basha et al [6]. While many previous studies reported a significantly lower serum Zn among patients with generalized vitiligo (5,10,11). However, Arora et al. in their study reported lower serum Zn in patients with vitiligo but this difference statistically was insignificant [12].

There was no significant correlation between the serum level of Zn with family history of vitiligo, duration or activity of the disease in the present study in agreement with previous studies [5,6]. Shameer et al reported that low Zn levels were more frequent in patients with disease duration of 2–5 years [10], moreover, Mirnezami et al reported that duration of the disease had a strong positive linear relationship with serum zinc levels [11].

Serum Cu was insignificantly higher in vitiligo patients under study as compare to healthy subjects, in agreement of previous study of Praneeth et al [4]. Previous studies reported non-significant difference in the serum level of Cu between patients with vitiligo and healthy controls [2,13]. However, previous studies reported a significant decrease of serum Cu level in vitiligo patients [7,14], and they concluded that low serum levels of zinc and copper could cause vitiligo [7,10,14].

It is well known that the role of Zn and Cu is to protect against reactive oxygen species and promote melanogenesis, moreover, Zn and Cu are cofactors of tyrosinase, which plays a key role in pigmentation process [2]. Melanins are colloidal pigments, known to have a high affinity for certain metal ions such as copper, zinc, and iron which found in high levels in pigmented tissues, however, with the degeneration of melanocytes in vitiligo, there should be decreased zinc and copper in pigment tissues with their defective share in melanin synthesis reflecting their higher serum level [8].

In present study we observed a slight but non-significant decrease in serum ferritin level, whereas the serum level of iron show on difference between patients and control subjects. Similar results were reported by studies of Gonul et al and Boisseau-Garsaud et al and Mansur et al [15,16,17].

Oxidative stress, characterized by an increase in free-radical production exceeding the intracellular antioxidant defense, has been proposed as a possible pathogenetic mechanism for vitiligo [15]. Iron is involved in antioxidative system, it can catalyze the formation of potentially toxic free radicals. However, iron is also biochemically dangerous; it can damage tissues by catalyzing the conversion of hydrogen peroxide to free-radical ions that attack cellular membranes, protein and DNA. This threat is reduced in the healthy state where, because of the fine iron metabolism regulation. Ferritin is an important acute phase reactant and its serum level is increased in some autoimmune disorders [15].

Few studies were done regarding serum level of Mg in vitiligo, in the present study vitiligo patients had significantly higher serum Mg as compare to control subjects, in agreement with previous studies [18,19], however, Namazi et al study reported no significant difference in the mean concentrations of Mg between vitiligo patients and control subjects, although they noticed a positive correlation between serum Mg concentration and Vitiligo Area Severity Index score as well as the total body surface area involved by the disease [20].

The possible explanations for this higher serum Mg in vitiligo patients under study, may be related to stimulation of magnesium reabsorption in the renal tubule, absorption in the gut, and release of the ion from bone by the hyper-production of parathormone due to high prevalence of vitamin D deficiency among vitiligo patients, although not tested in our patients, have been reported in many previous studies [19, 21].

Conclusions

Disturbances in the serum levels of trace elements are notes in patients with vitiligo. Further investigation taking larger number of patients is required to delineate the relationship between trace elements and vitiligo and to evaluate whether these trace elements is a causative factor in vitiligo.

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