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Investigate the role of Zinc and Ferritin in Iraqi patients with alopecia areata

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Abstract

Alopecia areata (AA) is an auto-immune disease in which there is an inflammation around the anagen phase of hair follicles. Many nutritional elements were found to modulate this immune response. Zinc and ferritin have many vital roles inside the body and are considered among the most important nutritional factors in immune modulation and division of hair follicle matrix cells. This study aimed to investigate the role of zinc and ferritin in patients with alopecia areata. A case control study including a total of 40 patients with AA who were attending the outpatient clinic at Al-Kindy Teaching Hospital, Baghdad during the period from 2nd June 2019 to 31st March 2020. Other 65 age- and gender-matched apparently healthy subjects. Demographic of the patients and controls and clinical data of the patients were recorded through direct interview. Blood samples were collected from all participants, and serum level of zinc and ferritin were measured using enzyme linked immunosorbent assay(Elisa). Results revealed that in three-fourth of the patients, only scalp was involved in the lesion, while mixed lesion was reported in the 25% of the patients. Single and multiple lesions were reported in 42.5% and 57.5% of the patients respectively. Median serum level of ferritin in patients was 23.0 µg/L (range=3-98 µg/L) which was lower than that of controls (median = 27.0 µg/L, range= 10-166 µg/L) with a significant difference. Likewise, median serum level of zinc was 59.5 µg/dl (range= 15-175 µg/dl) in patients compared with 71.5 µg/dl (range= 21-201 µg/dl) in controls with a significant difference. Zinc level showed a significant positive correlation with age (r= 0.334, p= 0.041) and negative correlation with lesion size (r= -0.327, p= 0.045). In conclusion, multiple lesions in the scalp are the most common presentation of patients with AA. Low levels of ferritin and/or zinc could be involved in the pathogenesis of AA and increase the risk of disease severity.

Keywords: Alopecia areata; Ferritin; Zinc; Elisa

1. Introduction

Alopecia, also known as baldness or hair loss, refers to the partial or complete loss of hair over the body, although the hair loss over the head may be the most concerned issue among a large number of people who pursue medical assistance [1]. Many different types of alopecia exist, each with their own symptoms and differing degrees of severity. These include alopecia areata, androgenic alopecia, alopecia barbae, telogen effluvium and trichotillomania. Furthermore, there are other rare types of alopecia such as frontal fibrosing alopecia [2]. The etiology of AA is unknown, even though most evidence is consistent with an autoimmune disease to which both genetic predisposition and environmental factors contribute [3]. Several lines of evidence support the notion that alopecia areata has a genetic basis [4]. Alopecia areata is associated with several concurrent diseases (comorbidities) including depression, anxiety, and several autoimmune diseases including thyroid disease (hyperthyroidism, hypothyroidism, goiter and thyroiditis), lupus erythematosus, vitiligo, psoriasis, rheumatoid arthritis and inflammatory bowel disease [5].

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Treatment studies are difficult to perform because the disease has an unpredictable course and may improve on its own. Nevertheless, guidelines have been established to facilitate research. Numerous therapies are available for the management of alopecia areata, and several can be utilized in combination [6]. Zinc is an essential mineral upon which hundreds of enzymes depend for their catalytic activity and its deficiency can result in extensive hair changes including telogen effluvium (TE) and induction of thin, brittled hair [7]. As with zinc, iron likely exhibits an important role in tissues with high cellular turnover, like the hair follicle matrix. The primary indicator of iron status relied upon in hair loss studies is serum ferritin. Serum levels of this iron-binding protein reflect a patient's total iron storage [8].Therefore, this study aimed to investigate the role of zinc and ferritin in patients with alopecia areata

1.1. Patients and Methods

This a case control observational study including a total of 40 patients with alopecia areata who were attending the outpatients clinic of Al-Kindy Teaching Hospital, Baghdad during the period from 2nd June 2019 to 31st March 2020. The diagnosis of AA was performed by a senior dermatologist at the center. Other 65 age- and gender- matched apparently healthy persons were recruited to represent control group. The study was approved by Arab Board of Health Specialization.

1.1.1. Inclusion Criteria for Patients

- All the consenting patients of age group 3-57years with patchy hair loss
- Both genders were included

1.1.2. Exclusion Criteria for Patients and Controls

- Patients suffering from any other systemic or dermatological disorder.
- Other causes of alopecia including scarring alopecia, androgenic alopecia, telogen effluvium, female pattern hair loss, tinea capitis, and Trichotillomania.
- Patients who had received oral or topical medications during the past 4 weeks (vitamins, iron, folic acid, zinc supplements).
- Pregnant and lactating females, subjects with malnutrition and underweight and those with undergoing chemotherapy or radiotherapy were excluded from patients and controls

1.2. Ethical consideration

A written consent from each participant or his/her parent was obtained prior to data collection after explaining the aim of study. Each patient was given the complete unconditioned choice to withdraw anytime. The confidentiality of data throughout the study was guaranteed and the patients were assured that data will be used for research purpose only.

1.3. Clinical Examination and Data Collection

After taking the complete history of each patient, a thorough physical examination was conducted age, gender, and site of the lesion, lesion pattern. Size was measured by using Tape measure to detect two dimensions for each lesion and used dermoscope especially for children to exclude Tinea capitis or other causes of alopecia.

1.4. Measurement of Serum Levels of Ferritin and Zinc

Five ml of peripheral blood were collected from each participant in plain tube from which sera were separated. A ready kit (Cusabio/ China) were used to measure serum level of ferritin and zinc in each participant using Enzyme-linked immunosorbent assay (ELISA) with an auto-analyzer (SpinReact/ Espain). The manufacturer's protocols were followed precisely.

1.5. Statistical Analysis

Data entry was performed using the Microsoft excel and Statistical Package for Social Sciences (SPSS ver. 25). Continuous data were subjected to normality test (Shapiro Wilk test). Those with normal distribution were expressed as the mean ± standard deviation (SD), while those with non-normal distribution were expressed as a median and range. The categorical data were expressed as a number (percentage). Evaluation of the statistical significance differences in the categorical data between the two groups were performed using the Chi-square ($\chi 2$) test. Data with normal distribution were analyzed with Student t-test, while non-normally distributed data were analyzed with Mann Whitney test. In all test, a p-values of less than 0.05 was considered significant.

2. Results

2.1. Demographic Characteristics of the Study Population

Mean age of the patients was 21.33±13.84 years (range =3-57 years) which did not differ significantly from that of the controls (23.75±11.03 years, range 5-60 years). Stratifying of age into classes revealed that the most common class in both patients and controls was 11-20 years accounting for 27.5% and 32.31%, respectively, while the older age class (41-57 years) was the least common accounting for 7.5% and 4.62% of the patients and controls, respectively. Although some variations occur in the frequency of age classes between patients and control, which was no significant difference (Table 1).

Table 1 Age distribution in AA patients and controls

Age class (years)	Patients (n=40)	Controls (N=65)	p-value
1-10	12(30%)	8(12.31%)	0.105
11-20	11(27.5%)	21(32.31%)	
21-30	5(12.5%)	19(29.23%)	
31-40	9(22.5%)	14(21.54%)	
>40	3(7.5%)	3(4.62%)	
Mean±SD Range	21.33±13.84 3-57	23.75±11.03 5-60	0.323

Males and females represented 57.5% and 42.5% of the patients, respectively compared with 43.08% males and 56.92% females among control group with no significant difference (P=0.151)(Figure 1).

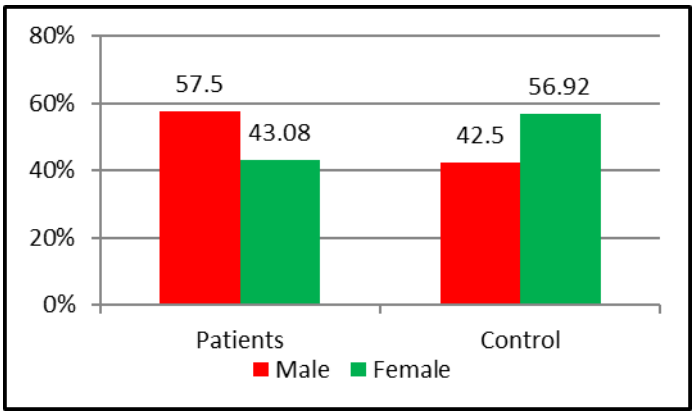

Figure 1 Gender distribution in patients and controls

2.2. Clinical Characteristics of the Patients

In three-fourth of the patients, only scalp was involved, while mixed lesion (involving scalp and beard) was observed in the other 25% of the patients. Single lesion was encountered in 17 patients (42.5%), while 57.5% demonstrated multiple lesions. The overall mean size of the lesion was 5.63±3.71 cm (range 1-13 cm) as shown in table 2.

Table 2 Clinical characteristics of the patients

Variables	Value
Site	
Scalp only	30(75%)
Mixed	10(25%)
Lesion Pattern	
Single Multiple	17(42.5%)
	23(57.5%)
Overall lesion size, cm	
Mean ± SD Range	5.63±3.71
	1-13

2.3. Serum level of Ferritin and Zinc

Data regarding serum ferritin and zinc were subjected for normality test, and were found to be non-normally distributed. Accordingly, non-parametric Mann Whitney U test was used to compare the medians between patients and controls. Median serum level of ferritin in patients was 23.0 µg/L (range=3-98 µg/L) which was lower than that of controls (median = 27.0 µg/L, range= 10-166 µg/L) with a significant difference (Figure 2).

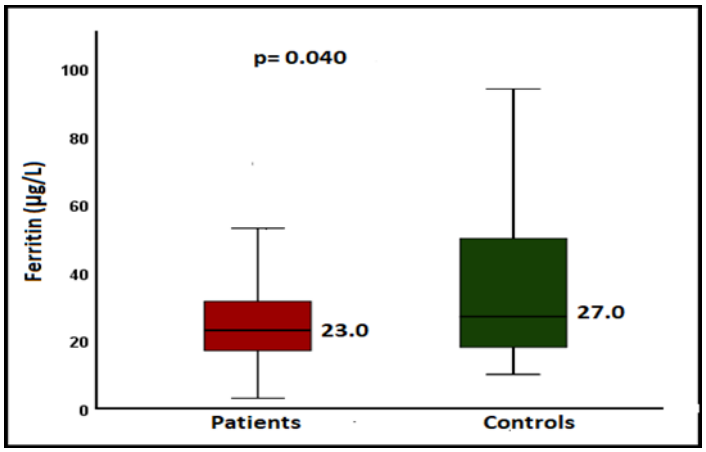

Figure 2 Median serum level of ferritin in patients and controls

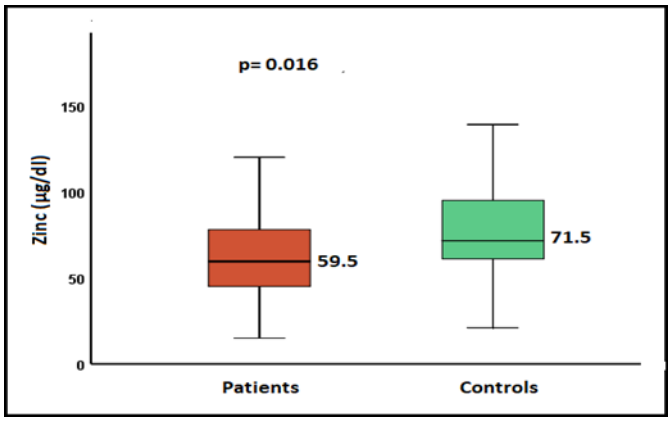

Figure 3 Median serum level of Zinc in patients and controls

Similarly, patients showed a median serum level of 59.5 µg/dl (range= 15-175 µg/dl) for zinc compared with 71.5 µg/dl (range= 21-201 µg/dl) in controls with a significant difference (Figure 3).

2.4. Correlation of Ferritin and Zinc with Other Variables

Pearson's correlation was used to explore the possible correlations between ferritin and zinc with the other variable. For ferritin, there was no significant correlation with any of the included variables. On the other hand, zinc level showed a significant positive correlation with age (r= 0.334, p= 0.041) and negative correlation with lesion size (r= - 0.327, p= 0.045) as demonstrated in table 3, figure 4, 5.

Table 3 Pearson's correlation of ferritin and zinc with other variable in patients with AA

Variable	Ferritin		Zinc	
	r	p-value	r	p-value
Age	0.185	0.259	0.334	0.041
Lesion number	0.145	0.378	0.083	0.619
Lesion size	0.172	0.312	-0.327	0.045

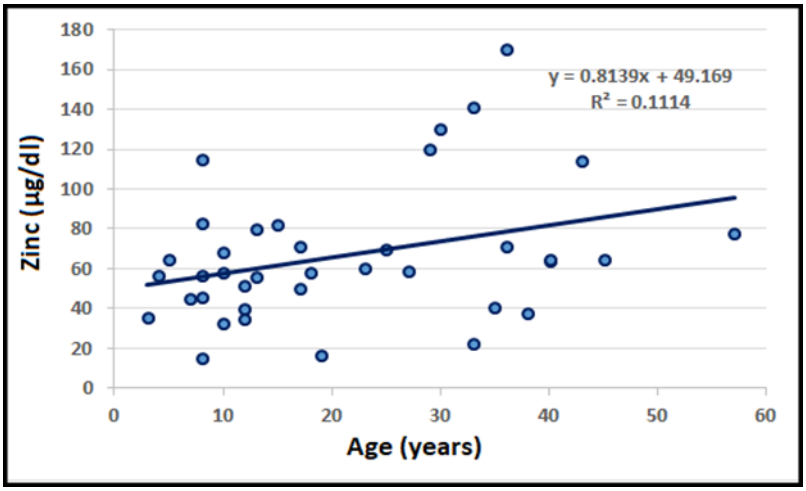

Figure 4 Regression line between age and zinc

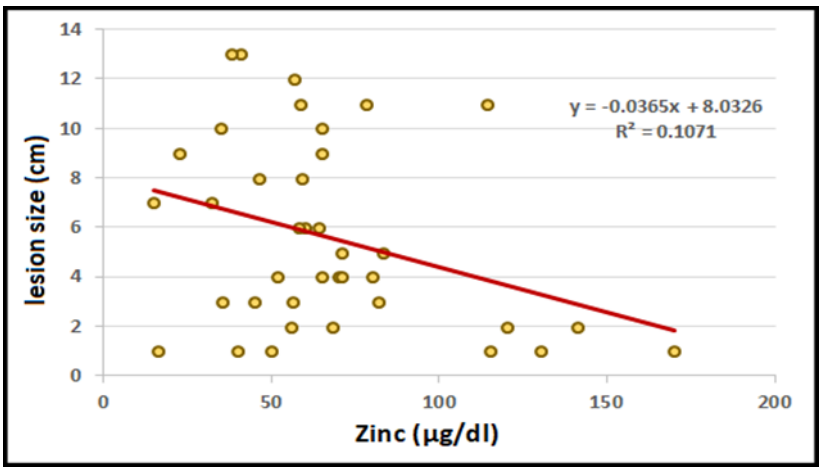

Figure 5 Regression line between zinc and lesion size

2.5. Association of Serum Ferritin and Zinc with Gender and Lesion Site

Although serum ferritin and zinc were remarkably higher in males (median =25.0 µg/L and 64.5 µg/dl, respectively) than females (median 19.0 µg/L and 58.5 µg/dl, respectively), the differences were not significant. Also serum ferritin was no significantly higher in mixed lesion than scalp restricted lesion (27.5 µg/L vs. 21.0 µg/L) as shown in table 4.

Table 4 Association of serum ferritin and zinc with gender and lesion site

Variables	Ferritin, µg/L median (range)	Zinc, µg/dl median (range)
Gender		
Males (n=23) Females (n=17)	25.0(10.8-98.0)	64.5(15.0-170.0)
	19.0(3.0-72.0)	58.5(16.4-115.0)
p-value	0.063	0.271
Lesion site		
scalp (n= 30)	21.0(3.0±98)	59.0(15.0-170)
Mixed (n=10)	27.5(10.8-55.0)	60.0(22.5±115.0)
p- value	0.418	0.277

3. Discussion

In majority of patients, the scalp was involved and more than half of cases have multiple lesions. This results in accordance with a previous local study including 100 patients in which 42% of cases had a single patchy lesion while 52% had multiple lesions. Furthermore, the scalp was involved in 82% while moustache area in only 7% of the cases [9]. In another local study, the percentage of single lesion was 45% and the multiple lesion was 55% [10]. Slightly higher percentage of scalp involvement (96.3%) followed by beard area in 21% of cases were reported in a Kuwaiti study [11].

The presence of multiple lesions is thought to be attributed mainly to the age of patients at first attack. Supporting this assumption is a Chinese study, in which extensive lesion was found in 14 out of 15 cases of the early onset disease but only one case in the late- onset group [12].

The most interesting finding in the present study was that median serum level of ferritin in patients (23.0 µg/L) was significantly lower than that of controls (median = 27.0 µg/L). This agrees with most previous studies. In a local study, Naser [13] recruited 60 patients with telogen effluvium and other 60 healthy subjects to investigate the role of serum ferritin in alopecia. Serum ferritin was found to be very low, low and normal in 73.3%, 16.6% and 10%, respectively among the patients compared with 13.3%, 28% and 40% among controls, with highly significant differences. Globally, in Nepal, 60 female patients of age group 15-50 years with chronic diffuse hair loss with equal number of age- and gender- matched controls were enrolled in hospital based case control study. Patients with AA and androgenetic alopecia had significantly lower serum ferritin than controls [14]. Also in accordance with current study there are two studies by Kantor et al. [15] and Esfandiarpour et al. [16] who also found mean serum ferritin level to be significantly lower in cases than in control. In contrast, Sinclair et al. [17] showed there is no association between alopecia areata and serum ferritin.

Ferritin has been reported to exhibit different immunological activities such as suppression of antibody production by lymphocytes and suppression of delayed type hypersensitivity. Furthermore, iron is a known cofactor in ribonucleotide reductase, a rate limiting enzyme for DNA synthesis. Hair follicle matrix cells are among the most rapidly dividing cells in the body. They may be very sensitive even to a small reduction in iron availability, hence resulting in reduced hair growth in the presence of iron deficiency [18].

Another interesting finding in the current study was that median serum level of zinc in patients was59.5 µg/dl (range= 15-175 µg/dl) compared with 71.5 µg/dl (range= 21-201 µg/dl) in controls with a significant difference.

This result is in accordance with many previous diseases worldwide. In an Indian study included 50 patients with alopecia and 50 controls, serum zinc level was significantly decreased ($p<0.01$) in both females and males as compared to controls [19]. In a meta- analysis including 10 articles with 764 patients indicated that AA patients demonstrated

significantly lower levels of serum zinc and selenium compared with controls [20]. Naginiene et al. [21] found a lower level of zinc in blood and urine of children with alopecia and increased levels of copper and chromium concentrations in their hair compared to healthy individuals. On the other hand, Dastgheib et al. [22] did not detect a significant difference in the serum and hair level of iron, zinc, and copper between patients and controls.

The discrepancy in results of the levels of zinc in various studies can be explained on the basis of sample size, methodology, and population variations.

The variation in serum level of zinc between patients and controls in the present study and many other studies reflects the role of zinc in the growth and maintenance on hair.

Zinc influences the function of hair follicle metabolism by inhibiting follicle regression and accelerating follicle recovery [23]. Moreover, zinc plays an important role in achieving proper function of the immune system in the body [24]. Therefore, the presence of a significant reduction in zinc level of AA patients may lead to impaired immune function of those patients.

In the same context, recent studies found that combination therapy with immunomodulators may be administrated to facilitate enhanced zinc-targeted action, as immunomodulatory therapy may promote tissue zinc redistribution by decreasing the perifollicular CD8+ T-cell infiltrate [25].

In the present study, serum level of zinc correlated positively with age and negatively with lesion size. These results support two facts. Firstly, zinc concentration is in its optimal level during youth, while younger ages and elderly are more susceptible to zinc deficiency [26] Secondly, zinc is not only associated with initial attack of AA, but also with the intensity and development of this disease. Thus, zinc may be more important than ferritin in AA.

According to the result of the study, ferritin was found to have higher concentration in male patients than female patients although the difference did not reach the significant level. Similar observations were found in various studies and reported the decreased value of serum ferritin in alopecia patients and the value was more reduced in female patients as compared to male patients [27,28]. This variation in ferritin but not in zinc between male and females can be explained by the fact that iron storage in female can be reduced through recurrent bleeding during the menstrual cycles, multiparity, pregnancy, and use of some hormonal contraceptives, taking into account that about 70% of the females in the present study have reached menarche.

4. Conclusions

Multiple lesions in the scalp are the most common presentation of patients with AA. Low levels of ferritin and zinc could be involved in the pathogenesis of AA and increase the risk of disease incidence. Serum level of zinc, but not ferritin, correlates positively with age of the patients and negatively with the lesion size.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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