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Oxidative DNA damage level in relationship to zinc status in patients complaining hair fall, in Duhok city, Krg-Iraq: A case-control study

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***Abstract*---**Background: Oxidative stress is created form the imbalance between oxidants and antioxidants leading to increase aging and premature cell mortality. Endogenous DNA deterioration due to oxidative stress and DNA aging hasten hair fall. Zinc is an essential trace element that execute a marked role in hair loss, which acts as antioxidant against oxidative stress via involving in DNA repair mechanism. However, the impact of zinc deficiency in pathogenesis of hair loss is still demand further researches. Objective of study: to inspect the DNA oxidative damage relevant to zinc status in patients suffering from hair fall in Duhok city, Kurdistan Region-Iraq. Methods: a case-control study was carried out at department of Dermatology and skin disease, at Azadi teaching Hospital/Duhok on participants visiting the mentioned department from October 2021 till May 2022. 70 (58%) participants [22 males (31.4%) and 48 females (68.5%)] aged from 18-45 years and suffering from hair loss were enrolled in this work. 50 (41.6%) evidently healthy objects [31 males (62%) and 19 females (38%)] whose age and sex matched and showing no history of hair fall were also involved as a control group. Blood samples were gathered from patients and control for determination of serum zinc, DNA oxidative damage (total oxidants) in peripheral blood cells and the biomarker 8-oxoDG. The statistical analysis was implemented using Prism Graph Pad version.5. Results: the data analysis unveiled that levels of total serum zinc were (µg/dl) significantly lower in hair loss patients relative to control (Mean ± SEM= 78.09 ± 2.088 Vs. 88.20 ± 2.539, respectively, p=0.0025). the results also displayed that higher level of serum total oxidants (U/ml) was recorded in the patient of hair loss as compared to control (Mean

± SEM= 10.13 ± 1.803 Vs. 4.405 ± 0.9943, respectively, P=0.0105) whereas the maximum level of 8-oxoDG (ng/ml) was belonged to patients complaining from hair fall in comparison with healthy objects with mean ± SEM between patient and healthy object estimated to be 69,20 ± 33,48 35,72 ± 15,42, respectively p 0.0342. Concerning gender, the female objects with hair fall exhibited lesser levels of serum zinc but more serum total oxidants and 8-oxoDG than male objects. Conclusion: Patients with hair fall seem to be signifcantly affected by oxidative stress that was apparent in increased levels of serum total oxidants and the biomarker 8-oxoDG in their blood over control. Marginal low level of serum zinc in patients of hair fall may propose the important role of this trace element in the pathogenesis of hair loss linked to oxidative stress with more clinical investigation to be implemented in this scope.

***Keywords*---**hair loss, oxidative stress, DNA damage, serum zinc status

Introduction

Hair loss is still one of the most crucial issues to which many individuals are subjected to and which may be controlled or at least minimized by administration of vitamins and mineral supplements. Minerals are considered to be essential for ordinary outgrowth and functioning of the cell and the hair loss problems may create from their inadequacy (Almohanna *et al.,* 2019). Hence, beside to vitamins, trace nutrients are required constituents for our daily dietary value (Mason, 2016).

Hair fall is one of the main public issues among males and females. Clinically, there are many types of hair fall. Androgenetic alopecia (AGA), telogen effluvium (TE) are the two prominent cases of hair loss. Hair buildup and profusion is usually impacted by malnourishment and oxidative stress and hair disturbances such as acute telogen effluvium (TE) as well as sudden weight suppression and reduced intake of protein are all resulted from malnourishment (Mubki *et al.*, 2014).

Zinc is considered as a prestigious element requested by a huge number of enzymes and various transcriptional factors in charge of organization of gene expression (Ogawa *et al.*, 2016). While the precise mechanism of action is still elusive, there is a probability that the zinc is a needed portion of several metalloenzymes sharing in the protein biosynthesis and cell division (MacDonald, 2000). Another suggestive participation of zinc is thought to be in Hedgehog signaling pathway which is an indispensable part of the pathways controlling morphogenesis of hair follicle (St-Jacques *et al.*, 1998). The measurable index of zinc state in the body is the serum zinc which is usually influenced by several factors. The consequences of zinc insufficiency can be observed prior the decrement of serum levels to below ordinary range (Maret and Sandstead, 2006). The reversal of hair loss owed to zinc shortage levels can be achieved by a proper diagnosis and screening of risk agents of serum zin (Karashima *et al.*, 2012).

A number of undertaken studies have unveiled a potent linkage between serum zinc levels and hair disrupted status. Al-Jaff (2017) displayed that there had been an augmented suppression in serum zinc complaining from Alopecia Aeata (AA) in comparison with control. Bosseila *et al.* (2017) inspected the vital impact of micronutrients including zinc on Alopecia Areata and they recorded fewer levels of serum zinc in patients infested with such case matched to healthy objects. Dhaher *et al.* (2018) researched the serum and hair zinc in women screened with Androgenetic Alopecia (APA) and a lesser concentration of serum zinc was determined in ailed women relative to control. Mikhael *et al.* (2020) investigated the serum zinc and biotin levels in certain patients. The research findings pointed out to a magnitude decrement in serum levels of both zinc and biotin in AA patients relative to control. Aiempanakit *et al.* (2017) detected the amount of plasma zinc males with androgenic alopecia and they confirmed a prominent reduction in the plasma zinc levels in patients complaining from such disorder relative to control.

Oxidative stress happens as a result of inadequate antioxidant defendants coincided with extra creation of free radical and had been observed in various dermatological ailments when the skin is chronically susceptible to internal pro-oxidant agents in ordinary metabolic actions or external environmental pro-oxidants driving to the creation of free radicals (Briganti and Picardo, 2003; Prie *et al.*, 2015). Free radicals are maximally reactive molecules with odd electrons which are harmful for numerous cellular architectural membranes, lipids, proteins and DNA leading to critical diseases including skin problems like hair loss (Trueb *et al.*, 2018). studies have confirmed a correlation between zinc status and occurrence of oxidative stress. Murr *et al.* (2012) indicated that the low concentration of serum zinc is usually associated with oxidative stress. Morales-Suárez-Varela *et al.* (2015) detected the association between serum zinc and oxidative stress and revealed that the minimal serum zinc levels were strongly correlated with oxidative stress-generating cellular senescence. Mohammadi *et al.* (2021) displayed that supplying adults with zinc created a reduction in oxidative stress and inflammatory markers. The repairing of oxidative detriment to DNA is usually implemented via the base excision repair pathway pared with the excretion of oxidized by-products in urine (Graille *et al.*, 2020). The biomarkers 8-OH-dG and 8-oxo-dG are efficient markers for quantification of the deteriorating impacts of internal oxidative damage on DNA and they participate in the formation and stimulation of carcinogenesis (Kasai, 1997). Roszkowski *et al.* (2011) displayed that the 8-oxoGua and 8-oxodG were effective as molecular markers of oxidative deterioration of DNA. El-Taweel *et al.* (2020) have measured a relatively greater serum level of 8-OHdG in AA patients than in healthy individuals. Mustafa *et al.* (2021) have demonstrated that the serum 8-OHdG was significantly raised in AA patients relative to control group rendering the serum 8-OHdG as an indispensable predictor for the AA acuteness.

Since the relation of serum zinc to hair loss possibly induced by oxidative exertion is under intensive research, the aim of this study is to inspect the levels of serum zinc in patients having hair fall and to find out the linkage between serum zinc status and oxidative damage to DNA via analysis of total serum oxidants and the biomarker8-oxodG in blood of such patients.

Material and Methods

Materials

A cross-sectional work was implemented established on the case-control design. 70 participants (aged from 18-45 years) having hair loss whose visiting Azadi Teaching Hospital (Duhok, Kurdistan-Region-Iraq), dermatology departments were enrolled in this work. 50 evidently healthy persons (age and sex matched) displaying no history of hair fall were also participated as a control group. The participants involved in this work have been clinically confirmed by dermatologists. Demographic features were gained from each participant and listed down in a specific questionnaire form after they signed on the letter of consent. Blood samples were gathered from patients and control via withdrawing from venipuncture with whole blood transferred into prelabeled gel tube containing clot activator for biochemical analysis to determine serum zinc, total serum oxidants and the oxidative DNA damage biomarker (8-oxoDG). The reagents were prepared for measurement of total oxidants and 8-oxoDG. The buffer wash was made by diluting buffer concentrate 25x with deionized or distilled water to obtain 500 ml of 1x wash buffer. When crystals were produced in the concentrate, it was gently mixed until the crystals had been entirely dissolved. The demography of objects enrolled in the study is clarified in the underneath table:

Table 1. demographics of objects involved in the study

Variables	**Patients, 70 (58.33%) Mean ± SEM**	**Control, 50 (41.7%) Mean ± SEM**	**P Value**
Age (year)	27.73 ± 0.7882	28.88 ± 0.9366	0.3461
BMI	25.78 ± 0.7536	24.91 ± 0.7262	0.4246
Male gender No. (%)	22 (31.4%)	31 (62%)	---
Female gender No. (%)	48 (68.5%)	19 (38%)	---

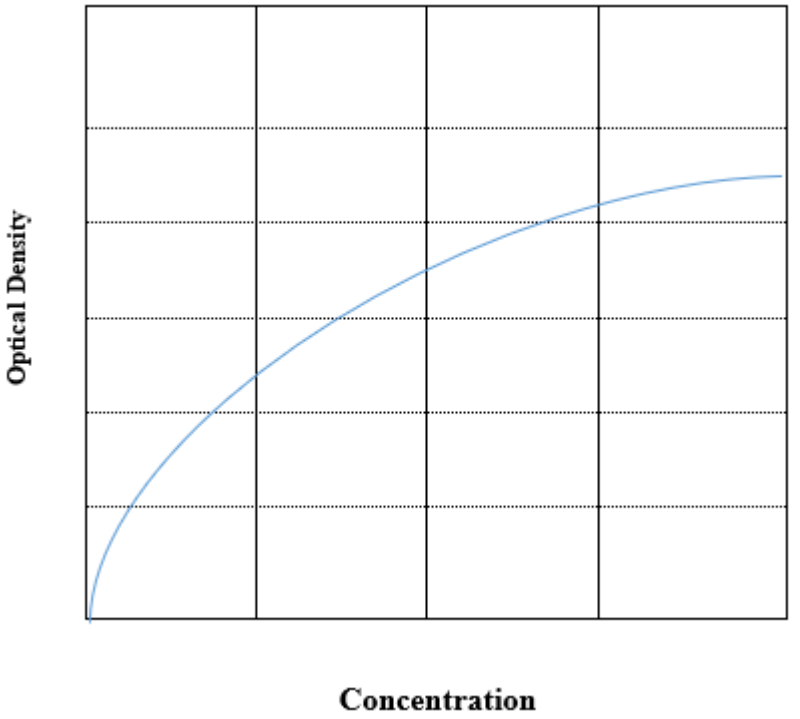
Methods

The serum zinc was measured according to the Cobas 6000 instrument based on zinc barcode and reagents. The biomarker (8-oxoDG) and total oxidants was assessed based on the ELISA assay technique. ELISA (enzyme-linked immunosorbent assay) is a technique utilized for detection of antigens existed in biological samples. This is done by antibodies that are targeting antigen via maximum specific antibody-antigen interference The overall materials and methodology is clarified in the beneath diagram:

Typical Data and Statistical analysis

After the procedure was implemented, a standard curve was created for each essay. the formed standard curve is illustrated below: The statistical analysis was executed with the aid of Prism Graph Pad version.5. Data are expressed as frequencies, percentages, Mean ± SEM and the means between each two groups

were compared statistically using unpaired t-test. P≤0.005 is considers as significant.



Results and Discassion

3.1. Zinc level (µg/dl)

In the present study, serum level of Zinc in all included participants was measured. According to the data displayed in the figure 1, there were statistically significant variation between total individuals complaining hair fall and total healthy ones respective to the level of Zinc in the blood. The serum Zinc level was ranged from (0 µg/dl) to about (90 µg/dl). The control subjects possessed greater Zinc level in the blood for whom the maximal Zinc level closer to (90 µg/dl) was belonged relative to patients suffering from hair fall who has a Zinc level of about (78 µg/dl). Mean ± SEM of Serum Zinc between healthy individuals and patients complaining hair fall were 88.20 ± 2.539 Vs. 78.09 ± 2.088, respectively, p=0.0025.

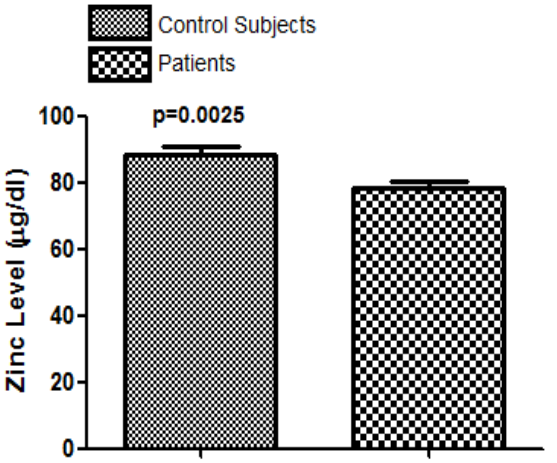


Figure 1: Shows the difference in the Mean ± SEM of Serum Zinc between healthy individuals and patients complaining hairfall, 88.20 ± 2.539 (N=50) Vs. 78.09 ± 2.088, respectively.

3.2. Serum Total Oxidant (U/ml)

Serum level of total oxidants in patients complaining hair fall and healthy control subjects was measured. Figure 2 reveals the levels of serum total oxidants in patients complaining hair fall and healthy control subjects. The measurement and statistical analysis of levels of serum total oxidants showed remarkable differences between individuals complaining from hair fall and those who are free from such disorder. Patients suffering hair fall have had significantly greater serum level of total oxidants (>10 U/ml) in their blood in comparison with healthy subjects (control) whose blood contained significantly lower serum total oxidant (< 5 U/ml). Mean ± SEM of Serum Total Oxidant level between patients complaining hair fall and healthy individuals were 10.13 ± 1.803 Vs. 4.405 ± 0.9943, respectively, P=0.0105. (figure 2).

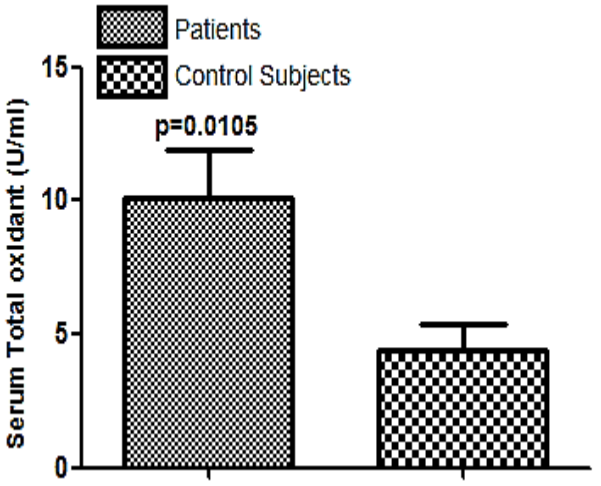


Figure 2: Shows the difference in the Mean ± SEM of Serum Total Oxidant level between healthy individuals and patients complaining hairfall. 10.13 ± 1.803 Vs. 4.405 ± 0.9943, respectively, p=0.0105

3.3. Serum 8-oxoDG (ng/ml)

In the current work serum level of 8 oxoDG was measured in patients suffering from hair fall and healthy control subjects. The data analysis of serum 8 oxoDG unveiled that the serum value of this biomarker in patients was importantly differed from that measured in healthy subjects. The 8-oxoDG range was (0-62) ng/ml. concerning the highest value of serum 8-oxoDG. The hair fall-diseased individuals exhibited the peak value (> 62 ng/ml) which is more than 1.5-fold greater as compared to control (healthy subjects) who statistically had the least serum value of such biomarker (38 ng/ml). Mean ± SEM of Serum 8-oxoDG level between patients complaining hair fall and healthy individuals were 61.27 ± 11.19 Vs. 38.54 ± 6.682, respectively, p=0.1024 as obvious in the figure 3.

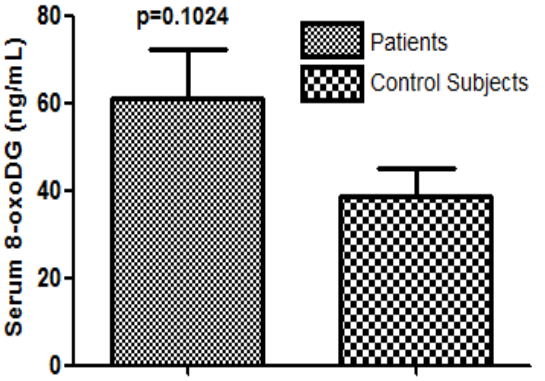


Figure 3: Shows the difference in the Mean ± SEM of Serum 8-oxoDG level between healthy individuals and patients complaining hairfall. 61.27 ± 11.19 Vs. 38.54 ± 6.682, respectivly, p=1024

The above mentioned outcomes displayed that the serum zinc levels in blood of patients complaining from hair fall was fewer than that presented in blood of well objects proposing a linkage between serum zinc status and hair loss problems. This could attributes to the zinc insufficiency could be resulted from either inadequate intake of zinc by such patients or over-utilisation to reduce the free radicals. Transient zinc insufficiency is counted as the major pathogenesis in acrodematitis enteropathica generating hair fall (Cheshire *et al.*, 2009). Hair follicles are distinguished with susceptible and high turnover and meabolism, therefore demanding permanent and enough nourishment and energy. Hence, any caloric disturbance or inadequacy of varied micronutrients, proteins or vitaminc can be a causer of hair-associated disorders (Finner, 2013). Zinc is very urgent micro-mineral that dominates a numerous metabolic actions like participating in the architecture and employment of proteins, bio-production of nucliec acid, enzymes, triggering of transcription agents, sites for hormonal receptors and so forth (Hambidge, 2007).

The depressed levels of serum zinc in persons diseased with hair loss may be referred to the oxidative stress impact created from suppressed activity and levels of prestigious antioxidant enzyme that work to scavenge reactive oxygen species from different tissues within the body. As it was scientifically affirmed, the skin is provided with a vast number of safeguard antioxidants encompassing enzymatic and non-enzymatic types and minerals have a great role in the defense structure of antioxidants. Zinc acts as co factor for over 300 enzymes including antioxidants (Foster and Chu, 2014; Fung and Gildengorin, 2015). Furthermore, it secures cells from hazardous consequences of oxidation via stabilizing the membrane, prohibits the action of a pro oxidant enzymes known as nicotinamide adenine dinucleotide phosphate oxidase (NADPH-Oxidase) as well as stimulating biosynthesis of antioxidant enzymes referred to as metallothionein, which effectively decrease hydroxyl radicals (OH), and finally sequestration of reactive

oxygen species generated under oxidative exhaustion (Chasapis and Loutsidou, 2012; Ruz and Carrasco, 2013). This was confirmed by Mou *et al.* (2015) who displayed that when the serum zinc levels were depressed, the oxidative stress was elevated. Our findings about serum zinc status is consistent with that of Al-Jaff (2017) and Bosseila *et al.* (2017) who recorded an augmented suppression in serum zinc complaining from Alopecia Aeata (AA) relative to control.

The study data unveiled that the serum total oxidants were much higher in patients having hair fall as compared to healthy objects who displayed significantly depressed levels of total oxidants. Our results suggest a potent relationship between hair loss case and total oxidant vitality in the blood. This is maybe because of probable impact of oxidative exertion and imbalance between oxidants and antioxidants within body of infested individuals which in consequence results in the extra deposition of reactive oxygen species (ROS) and emaciates the antioxidant defense architecture to prohibit the occurrence of oxidative damage to various body tissues and organs. The largest level of total oxidants in subjects with hair fall denotes the low functioning of antioxidants, which are steady molecules that can give off an electron to turnover free radicals into an excited status then neutralizing them, hence they become ineffective and do not bring detriment to the susceptible tissue. The assignment of these antioxidants is to retard or prohibit cellular detriment via eradicating free radicals (Abuja *et al.*, 2001). Fattah *et al.* (2011) uncovered depressed antioxidant enzyme functioning in AA patients declared that the raised severity and longevity of the disease generated more decrement in the enzyme activity.

oxidative stress has recently been marked and affirmed in derma papilla of the patients diagnosed with androgenic alopecia (Upton *et al.*, 2015). numerous literatures certifying a potent bind between hair loss and elevated oxidative stress and displayed that hair outgrowth disturbance is concerned with enhanced risk agents for cardiovascular ailments and with elevated appearance of inflammation (Arias-Santiago *et al.*, 2010; Arias-Santiago *et al.*, 2011; Ertas *et al.*, 2015). There are various sources of oxidative stress with influence on the pre-appearing fiber like smoking, oxidative metabolism, ultraviolet radiation (UVR), and inflammation originated from microbial infestations, or irritant resources. precursors of oxidative stress impacting on the post-appearing fiber include UVR, chemicals, and oxidized scalp lipids. The dermatologist is tasked to recognize and treat of pre- and post-appearing agents for perfect scalp and hair sanitation (Trueb, 2015). Moreover, the peak total oxidants in blood of hair fall-suffered objects could be correlated with lower levels of serum zinc that is remarkably influenced by oxidative stress. The same results were showed by Morales-Suárez-Varela *et al.* (2015) who inspected the linkage between serum zinc and oxidative stress and measured minimal serum zinc levels respective with cellular senescence generated from oxidative exertion.

The data analysis relevant to the levels of serum 8-oxoDG in both groups displayed that the levels of this biomarker were significantly greater in hair fall-complaining objects than in healthy objects. This may ascribe the existence of oxidative harm to the DNA architecture of those diseased objects owed to the extra generation and piling of reactive oxygen species (ROS) coincided with depression in entity and function of antioxidants, especially enzymatic ones.

oxidative stress refers to the disturbance in the equilibrium between formation and deposition of harmful reactive oxygen species (ROS) leading to impose demolition upon cell physiology (Lushchak, 2014). 8-oxo-dG is the major dominant portray of oxidative lesions that are motivated by free radicals in nuclear DNA, therefore, can be utilized as biomarkers for oxidation adverse consequences. It is a supreme marker for estimation of the serious negative impact of endogenous sabotage on DNA (Kasai, 1997). Lesions associated to 8-oxo-dG are the commonest dense DNA lesions because of their easily creation. The maximum concentration of serum 8-oxo-dG in hair loss-diagnosed individuals' may prescribe the defense exhibited by cellular architecture versus 8-oxoG within a DNA strand employing base excision repair (BER) that correct small base lesions (Drake *et al.*, 2019). Such operation begins with the oxoguanine glycosylase 1 (OGG1) that targets and exterminate 8-oxoG. The raised levels of biomarker in the body of diseased persons may be linked with the extra levels of serum total oxidants recorded in those persons. The enhanced total oxidants explain that the ratio of ROS within the body tissue and organs is maximal whereas the ratio of antioxidants is relatively depressed making ruin to proteins, lipids and DNA and ultimately, additional accumulation of 8-oxodG. Similar outcomes were demonstrated by Prie *et al.* (2016) who determined maximal levels of reactive oxygen species or oxidants and least antioxidant vitality in patients infested with androgenetic alopecia as compared to control. Our results resemble that of Roszkowski *et al.* (2011) who stated that the 8-oxoGua and 8-oxodG were efficient as molecular markers of oxidative destruction of DNA. El-Taweel *et al.* (2020) also revealed that the serum levels of this biomarker was significantly higher in patients with Alopecia Areata AA over healthy individuals.

Conclusion

The hair is one of the prominent features for aesthetic of human wellbeing appearance. Therefore, the preservation of hair growth following organized perfect diet and frequent medical and physical screening and diagnosis along with definite utilization of chemical cosmetics that harm hair follicles is very necessary to evade hair loss problematic consequences. The study findings displayed that the serum zinc levels in objects with hair fall were lower than that in control but the serum total oxidants and 8-oxodG were bigger in diseased objects as compared to control. This denotes a potential relation between hair loss and oxidative stress that may owed to the inadequate zinc status in such patients pared with disruption in balance between oxidants and antioxidant inside their bodies. However, more researches should be undertaken to assure the precise action of zinc on hair fall and to comprehend more about relationship between zinc status and oxidative stress respective to hair loss.

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