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ORIGINAL ARTICLE

Serum Levels of E-selectin and P-selectin In Alopecia Areata: A Case Control Study

Heba El-sayed Ismail Ali[*1], Amr Nazir Saadawi[2], Ahmed Said Abdel Shafy[2], Hanan Samir Ahmed[3]

1. Dermatology, Venereology and Andrology Department, Abu-Hammad Hospital, Zagazig, Egypt
2. Dermatology, Venereology and Andrology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
3.Clinical and Chemical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

Corresponding author:
Heba El-sayed Ismail Ali[1]

Dermatology, Venereology and Andrology Department, Abu-Hammad Hospital, Zagazig, Egypt
drh_angel89@yahoo.com

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ABSTRACT

Background: Alopecia areata (AA) is an inflammatory, nonscarring form of hair loss. Important variations in the clinical presentation of alopecia areata have been detected, extending from small, well-circumscribed blotches of hair loss to a complete absence of scalp and body hair. AA is a changeable, immunologically mediated disease that causing damage of hair follicles and lead t hair loss. Etiology of Alopecia areata is not well known.To measure serum levels of (P-selectin and E-selectin) in patients with AA in relation to the control group. We try to find out the relation between serum levels of P-selectin and E-selectin) and selected clinical considerations, including the severity and the activity of alopecia areata.

Methods: This case-control study was performed on 56 subjects of both sexes at Dermatology, Venereology and Andrology Department outpatient clinic & Department of Clinical Pathology at Zagazig University during the period from May 2018 to November 2018. The 56 subjects were divided into: Case group: 28 patients with different types of Alopecia areata were included in this study. Control group: 28 healthy subjects with age and sexes matched with AA patients

Results: Statistically significantly high levels of P and E-selectins were found in AA patients as compared with the control group. Serum levels of soluble forms of E- and P-selectins correlated with the activity and severity of AA.

Conclusions: This study shows that P and E-selectin can play a significant role in the pathogenesis of AA and may possibly be a target of upcoming therapies in this disease.

Keywords: E-selectin, P-selectin, Alopecia Areata.

INTRODUCTION

Alopecia areata (AA) is an inflammatory, nonscarring form of hair loss. Important variations in the clinical presentation of alopecia areata have been detected, extending from small, well-circumscribed blotches of hair loss to a complete absence of scalp and body hair. AA is a changeable, immunologically mediated disease that causing damage of hair follicles and lead t hair loss. Etiology of Alopecia areata is not well known. **[2]**. Histopathological investigation revealed that injury to the hair follicle happens along with lymphocytic infiltration. Another pathogenic factor is correlated with decreased vascular supply to hair follicles with a very important role of selectins**[3]**. Selectins (CD62) are carbohydrate-binding particles that bind to fucosylated and sialylated glycoprotein ligands, found on leukocytes, endothelial cells and platelets. They are involved in transferring of cells of T lymphocytes, the innate immune system, and platelets **[4]**. An interesting pathogenic concern is associated with elevated serum levels of selectins (E, P, and L-selectin), which are identified as first adhesion molecules involved in lymphocyte immigration through vessels wall and may reveal vascular abnormalities in AA**[5]**.Significance of E and P selectin was mainly measured in psoriasis, but their abnormal serum levels have also been demonstrated in systemic lupus erythematosus, urticaria, graft versus host disease, scleroderma, eczema, lichen planus, pemphigus vulgaris, bullous pemphigoid. There are still few studies regarding the assessment of serum levels P-selectin and E-selectin forms in patients with AA**[6]**.selectins play an important role in the development of AA**[7]**. E-selectin is a cell adhesion molecule present on endothelial cells that activated by cytokines. It plays a vital role in inflammatory process. E-selectin is coded by gene known as the SELE gene. E-selectin also

identified as CD62E (cluster of differentiation 62E) or endothelial-leukocyte adhesion molecule 1 (ELAM-1)**[8]**. P-selectin is amember of the selectin family of and its ligand PSGL-1 is found on leukocytes and platelets and. It plays an important role during ongoing inflammation **[9]**.E-selectin is one of the main markers of endothelial cell damage, while P-selectin is an indicator of ongoing inflammation [2]. E selectin mediates monocytes, neutrophil, and memory T-cell adhesion to cytokine-activated endothelial cells, while P selectin mediated the adhesion of monocytes and neutrophils to endothelial cells and activated platelets **[10]**.This case-control study was performed on 56 subjects of both sexes at Dermatology, Venereology and Andrology Department outpatient clinic & Department of Clinical Pathology at Zagazig University during the period from May 2018 to November 2018. The practical part of this study was completed in Clinical Pathology Department. Venous blood samples were taken from all subjects. A written informed consent was taken from all subjects after explaining to them the details about the nature of study and after obtaining approval from Institutional Review Board (IRB). The number of IRB approval is (4587). The work has been carried out in accordance with the code of Ethics of the World Medical (Declaration of Helsinki) for studies involving humans.The 56 subjects were divided into two groups:- **First group:** Twenty eight patients with different types of Alopecia Areata were included in this study. Patients were with age ranged from 5 to 58 years. **Second group**: Twenty-eight healthy subjects with age and sexes matched with AA patients. The age of that group ranged from 14 to 58 years.

I -Inclusion criteria: 1-Age: any age. 2-Gender: males and females. 3-Patients with any type of alopecia areata.

II- Exclusion criteria: 1-Patients with a history of systemic treatment affecting selectins level 6 weeks before the study such as: **a)** Corticosteroid which in vitro down regulate selectins levels**, b)** Phototherapy which decreases E-selectin levels**, c)** Cyclosporine (A) which decrease the expression of selectins on human umbilical vein endothelial cells**.**

2- patients having another illness causing elevation of selectins serum levels such as atopic dermatitis, psoriasis and vitiligo**.**

3-Patients treated with vascular drugs or antihistamines 6 weeks before the study because they can affect the concentration of selectins.

PATIENTS AND METHODS

All patients were subjected to:

I-Full history taking:

1- Personal history: Name, sex, age, occupation, marital status, residence and habits of clinical importance. 2- Present history: Onset and course, Site of the lesion, Duration of present lesion 3-Past history: Number of previous lesions of AA if present, Age of onset of AA, Disease duration. 4-Family History: Family history of AA.

II. General Examination:

General examination was done to discover predisposing factors and other associated medical conditions.

III. Detailed Dermatological examination:

Proper diagnosis of alopecia areata with its typical signs in the form of single or multiple rounded patches of hair loss was done.

Clinical assessment of lesions including: Site of lesions, Number of the lesions, Percentage of bald skin area. Examination for associated dermatologic abnormalities as atopy was done.

Dermatological examination of scalp skin, eye brows, eye lashes, facial and body hair**.**

Classification according to types into single patchy alopecia areata, multiple patchy alopecia areata, alopecia Ophiasis, alopecia reticularis, alopecia universalis, and alopecia totalis.

Evaluation of severity was based on SALT "Severity of Alopecia Tool Score" **[11].**

SALT scoring is based on a scoring system. The scalp is divided into the next 4 areas:

Vertex represents 40% (0.4) of scalp surface area. Right profile of scalp represents 18% (0.18) of scalp surface area. Left profile of scalp represents 18% (0.18) of scalp surface area. Posterior aspect of scalp represents 24% (0.24) of scalp surface area.

The percentage of hair loss in any area of them equals the percentage hair loss × percent surface area of the scalp in that area.

The SALT score = the sum of the scalp hair loss in the 4 areas. Further subgrouping of hair loss of the scalp is divided into the following subclasses:

* S0 means no hair loss * S1 means that the hair loss is less than 25% * S2 means that the hair loss range from 25 up to 49%

* S3 means that the hair loss range from 50% up to 74 % * S4 means that the hair loss range from 75% up to 99% * S5 means 100% hair loss.

Evaluation of alopecia areata activity:

Evaluation of disease activity the 3 months' time was taken into consideration. According to **Olsen et al**[11] the disease is active when in the last 3 months a new area of hair loss appeared, or the expansion of the existing ones is observed.

IV- Patient Photograph: alopecia areata patches were photographed by Canon IXUS 175 digital camera.

V- Patients and control: were subjected to determination of serum E-selectin and P-selectin levels using Enzyme-linked immunosorbent assay (ELISA) technique. ELISA reader used in this study was sun rise TECAN (Grodig, Austria).

Laboratory examination

Determination of serum level of E-selectin and P-selectin by ELISA kits :(sun red biotechnology company / china)**:**

Test principle

The kits use a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human endothelium Selectin (E-Selectin) and Human platelet Selectin (P-Selectin/CD62P) in samples.

Statistical analysis

Data were checked, entered and analyzed using SPSS version 23 for data processing

The comparison was done using:

I- Chi- square test (X^2): Used to find the relationship between column and row variables.

II- ANOVA (F-test) test was used to calculate difference between quantitative variables in more than two groups.

III- Mann-Whitney U test; was used to calculate difference between not normally distributed quantitative variables in two groups instead of T-test.

P- value of < 0.05 was considered statistically significant.

RESULTS

This case-control study was conducted on 56 subjects of both sexes divided into two grups. The case group included 10 females (35.7%) and 18 males (64.3%). Their age ranged from (5-58) years with mean ± SD (27.6±14.5) years. The control group included 17 females (60.7%) and 11 males (39.3%). Their age ranged from (14-58) years with mean ± SD (29.8±11.5) years **.**There was no statistical significant difference between the two groups as regarding age and sex as P-value was 0.5 for age and 0.06 for sex(**Table 1**).

Table (2) shows that In case group**:** The serum level of E- selectin ranged from (307.1to 2767.4) ng/ml with mean ± SD (704.7±578.8). In control group: The serum level of E- selectin ranged from (40.95 to 366.3) ng/ml with mean ± SD (268.9±85.7).There was highly statistical significant difference between cases and control groups in E selectin serum levels **(p=0.001**).**

Table (3) shows that In case group: The serum level of P- selectin ranged from (13.4 to 221.6) ng/ml with mean ± SD (47.1±53.1). In control group: The serum level of P- selectin ranged from (8.88 to16.2) ng/ml with mean ± SD (12.5±1.5). There was highly statistical significant difference between cases and control groups in p selectin serum levels (p=0.001**). In **table (4)** E-selectin levels between active and non-active cases were Statistically significant different (**P-value 0.04) ,** where E-selectin in active cases ranged from (328.7 to 2767.4)ng/ml with median 704.7 and in non-active cases ranged from (307 to 950.9) ng/ml with median 412.9. In **table (5)** P-selectin levels between active and non-active cases were Statistically significant different **(P-value 0.03),** where P-selectin in active cases ranged from (13.9 to 221.5) ng/ml with median 47.1 and in non-active cases ranged from (13.4 to 66.4) ng/ml with median 17.6.

The area under curve was 0.97 for E-selectin and 0.98 for P-selectin. The significant cutoff of E-selectin (>317.9) and p-selectin (>13.5) for case detection with them.Both of E-selectin and P-selectin are highly significant (p=0.001**) for case detection **(table 6)**

Tables and figures

Table(1): Demographic data of the two studied groups:

Variable	**Case (28) mean ± SD (Range) Median**		**Control (28) mean ± SD (Range) Median**		**Test**	**p-value**
Age	27.6±14.5 (5-58) 26.5		29.8±11.5 (14-58) 29		M.W 0.6	0.5
Variable	**Case No(28)**	**%**	**Control No(28)**	**%**	**χ^2**	**p-value**
Sex **Male** **Female**	18 10	64.3% 35.7%	11 17	39.3% 60.7%	3.5	0.06

Table (2): Comparison of E-Selectin serum levels between case and control groups:-

Variable	Case (28) mean ± SD (Range) Median	Control (28) mean ± SD (Range) Median	M.W Test	p-value
E-Selectin	704.7±578.8 (307.1-2767.4)ng/ml 441.3	268.9±85.7 (40.95-366.3)ng/ml 291.2	3.9	**0.001****

Table (3) Comparison of P-Selectin serum levels between case and control groups

Variable	Case (28) mean ± SD (Range) Median	Control (28) mean ± SD (Range) Median	M.W Test	p-value
P-Selectin	47.1±53.1 (13.4-221.6)ng/ml 22.9	12.5±1.5 (8.88-16.2)ng/ml 12.3	3.4	**0.001****

Table (4): Comparison of Serum levels of E-selectin between active and non-active cases

Variable	*Active disease* (16) mean ± SD (Range) median	*Not active disease* (12) mean ± SD (Range) median	Mann-Whitney Test	p-value
E-Selectin	885.5±707.3 (328.7-2767.4) 704.7	463.6±170.7 (307.1-950.9) 412.9	2.1	**0.04***

Table (5): Comparison of Serum levels of P-selectin between active and non-active cases:

Variable	Active disease (16) mean ± SD (Range) median	Not active disease (12) mean ± SD (Range) median	Mann-Whitney Test	p-value
P-Selectin	65.6±63.7 (13.9-221.5) 47.1	22.3±14.3 (13.4-66.4) 17.6	2.3	**0.03***

Table 6: Cutoff with area under the curve regarding E-selectin and p-selectin

Test Result Variable(s)	Area	Cutoff	P	95% CI% Confidence Interval
E-_selectin	**0.97**	>**317.9**	**0.001****	**0.93-1.00**
P-_selectin	**0.98**	>13.5	**0.001****	0.96-1.00

Table 7: Comparison between E-selectin and P- selectin according to specificity and sensitivity for case detection:

Variable	Sensitivity	Specificity	PVP	PVN	Accuracy
E-selectin	96%	80%	82.6%	94.5%	89.5%
p-selectin	***96.4%***	***85%***	***86.4%***	***95.5%***	***90.5%***

P-selectin is little more sensitive, more specific and more accurate for case detection than E-selectin.

DISCUSSION

Alopecia areata is a common form of non- scaring hair loss. It is supposed to be an immune-mediated stimulus, including auto reactive T-cells against antigens that present in the hair follicle**[12]**.Alopecia areata (AA) is an unpredictable disease. It is usually a patchy hair loss condition that may affect any hair-bearing area**[13]**.Many pathogenic processes have been proposed to clarify the etiology of AA, such as immunological, environmental, psychological, and genetic factors[14]. In addition to disruption of immune function, complex connections between predisposing enviromental and genetic factors act as triggers for the disease advancement. Perifollicular vasculature and nerves, viruses, endocrine disorders, element alterations, and thyroid dysfunction also have been theorized. These multiple factors involved in its pathogenesis lead to consider AA as a psychosomatic illness **[15,16]**.AA is considered the second most common type of alopecia.AA incidence is higher than 2% in both sexes[17]. **Papadopoulos et al[18]** categorized AA according to the extent of hair loss into: localized or patchy AA, alopecia universalis (AU) with total body hair loss and alopecia totalis (AT) with complete loss of the scalp hair. Inflammation and Impairment of angiogenesis are examples of a lot of causes of alopecia areata. The histological examination of alopecia areata patients' skin reveals the large cell infiltration around the hair follicles with inceasing number of T cells and other inflammatory cells. Their presence may lead to the release of cytokines within the hair follicle**[7]**.A significant pathogenic finding is linked to elevated serum levels of selectins, which are known as adhesion molecules responsible for lymphocyte migration through the vessel wall and support vascular theory of AA and reveal vascular abnormalities in AA. E-selectin is considered one of the main markers of endothelial cell damage, while soluble forms of E-selectin and P-selectin are considered as indicators of current inflammation [2].**Toyoda et al[19]** detected an increased expression of E-selectin on perifollicular endothelial cells in skin samples obtained from the center of the AA areas. **Ghersetich et al[20]** reported also increasment in the expression of E-selectin in the skin of the scalp not involved in the disease process only in the active phase of the disease. This proposes the subclinical type of AA which is described by no hair loss, but in immunohistochemistry by attendance of several inflammatory cells around the blood vessels within the seeming healthy skin and spared in the perifollicular region.

P-selectin plays an essential role in the initial recruitment of leukocytes to the site of injury for the duration of inflammation [21].So, the aim of our study was to measure serum levels of (P-selectin and E-selectin) in patients with alopecia areata in relation to the control group. Moreover, we try to find out the relation between serum levels of selectins (E-selectin and P-selectin) and selected clinical considerations, including the activity and the severity of the disease.In our study, we found that there were statistically highly significant difference levels of soluble forms of E-selectin in the patient group compared with control (p=0.001**). In case group: The serum level of E-selectin ranged from (307.1to 2767.4) ng/ml with mean ± SD (704.7±578.8). In control group: The serum level of E- selectin ranged from (40.95 to 366.3) ng/ml with mean ± SD (268.9±85.7). Elevated serum levels of E-selectin in alopecia areata patients may be induced by scaling of E-selectin from the surface of endothelial cells and may revealing an ongoing inflammation inside the vessels. These significant high levels of E-selectin in the serum of AA patients may confirm the theory of vascular pathogenesis of alopecia areata. These findings were in agreement with the finding of **sundik et al[7]** who found Statistically high significant difference of serum levels of E-selectin in AA patients compared to healthy control (p=0.0003*).

In our study, there was a highly significant difference according to the severity of cases regarding serum levels of E-selectin which may be related to lymphocytic infiltration severity in different types of AA. Among the different types of lesions , Alopecia universalis ,the most severe form had the highest level of E-selectin ranged from (1436.6-2767.4) ng/ml with mean ± SD (957.3±568.6) and patchy alopecia the mild form had the lowest level of E-selectin ranged from (307.1-441.3) ng/ml with mean ± SD (391.1±41.5).

Regarding SALT score: S5, the highest score had the highest level of E-selectin ranged from (950.9-2767) ng/ml with mean ± SD (1631.8±669.7) and S1, the lowest score had the lowest level of E-selectin ranged from (307.1-452.7) ng/ml with mean ± SD (390.5±44.7) and with (P=0.001*).

These results were in accordance with the finding of **sundik et al[7]** who found Statistically significantly higher levels of E-selectin in the AU group as compared with the other of AA (p=0.0001*). In the present work, there was a high statistically significant difference between active and non-active cases as regarding serum levels of E- selectin with higher level in active cases compared to non-active cases (p=0.04**) where E-selectin in active cases ranged from (328.7 to 2767.4) ng/ml with median 704.7 and in non-active cases ranged from (307 to 950.9) ng/ml

with median 412.9. These results were matching with the finding of **sundik et al[7],** they reported significantly higher concentrations of the soluble form of E-selectin between the active and non-active phase of the disease ($p < 0.0001$*).

These results suggest that E-selectin can play a very important role in the development of disease and may be a marker for alopecia areata activity, So we may consider the probability of initiation of treatment target to blockage the activity of E-selectin. We found out that there was statistically significant positive correlation between E-selectin with increasing age of the cases (r= 0.04, P=0.03*) (Increasing of age associated with increasing in E-selectin serum levels. There was highly statistically significant positive correlation between E-selectin with P-selectin levels (P=0.001 & r= 0.4) "High levels of E-selectin serum leves are associated with high levels of P-selectin". There was no statistically significant difference in E-Selectin, between male and female patients (P=0.08). There was no statistically significant difference in E Selectin serum levels between cases with and without family history of AA (P=0.07). The second marker we estimated was the serum levels of P-selectin in cases and control groups ($p = 0.001$**). We found out that there was highly significant level of soluble form of P-selectin in the patient group compared to healthy control. In case group, The serum level of P-selectin ranged from (13.4 to 221.6)ng/ml with mean ± SD (47.1±53.1). In control group, the serum level of P-selectin ranged from (8.88 to16.2) ng/ml with mean ± SD (12.5±1.5).These soluble forms (serum forms) of P-selectin may rise from damaged platelet membranes or simple shedding from the cell surface. P-selectin glycoprotein ligands/P-selectin interaction may offer stimulus that cause thrombosis and local inflammation**.** P-selectin helps in the recruitment of monocyte*derived micro-particles, which are a rich source of the clotting element to the forming thrombus**.** This can lead to formation of blood clots in the capillaries of the affected hair follicles and thickening of their wall. This can lead to partial occlusion of their lumen and reduction in blood supply to hair follicles leading to AA. These significant high levels of P-selectin in the serum of AA patients may confirm the theory of vascular pathogenesis of AA. **Ramacciotti et al[22]** consider the possibility of initiation of treatment aimed at blockage the activity of P-selectin as Inhibiting P-selectin causes an increase in thrombus regression.These findings were in agreement with the finding of **sundik et al[7]** who found Statistically high significant difference of serum levels of p-selectin in AA patients compared to healthy control (p=0.0026*).

Maraee et al[23] also found statistically high significant difference of serum levels of P-selectin in AA patients compared to healthy control ($p<0.001$).

In our study, there was a highly significant difference according to severity of cases regarding serum levels of P-selectin. Among the different types of lesions , Alopecia universalis ,the most severe form had the highest level of P-selectin ranged from (112.6-221.5) ng/ml with mean ± SD (158.8±45.6) and patchy alopecia the mild form had the lowest level of P-selectin ranged from (13.4-24.33) ng/ml with mean ± SD (17.4±3.2).

Regarding SALT score: S5, the highest score had the highest level of P-Selectin ranged from (66.46-221.5)ng/ml with mean ± SD (135.6±52.4) and S1, the lowest score had the lowest level of P-Selectin ranged from (13.4-26.3)ng/ml with mean ± SD (17.9±4.1) and with (P=0.001*).

These results were not in accordance with the finding of **sundik et al[7]** who found that there was no significant difference in mean P-selectin levels between patients with patchy AA and Alopecia totalis/Alopecia universalis and that the measurement of P-selectin serum level seems to be inappropriate to assess the disease severity, and this may be due to difference in sample size and method of determination.

In the present work there was a high statistically significant difference between active and non-active cases regarding serum levels of P- selectin where there was high level in active cases compared to non-active cases (p=0.03**). P-selectin in active cases ranged from (13.9 to 221.5)ng/ml with median 47.1 and in non-active cases ranged from (13.4 to 66.4) ng/ml with median 17.6. On the other hand these results were not matched with the finding of **sundik et al[7].** They reported non-significant concentrations of the soluble form of P-selectin between the active and inactive phase of the disease (p= 0.1577).

The ROC (Receiver Operating Characteristic) curve for E-selectin in detection of alopecia in patients showed that: The significant cutoff of E-selectin (>317.9), Sensitivity (96%) specificity (80%), Positive predictive value (82.6), negative predictive value (94.5%), accuracy (89.5%), and the area under curve (0.97) (excellent diagnostic power). The ROC curve for P-selectin in detection of alopecia in patients showing that: the significant cutoff of P-selectin was (>13.5), sensitivity (96.4%), specificity (85%), Positive predictive value was (86.4%), negative predictive value (95.5%), accuracy (90.5%) and the area under curve (0.98) (excellent diagnostic power). According to ROC curve both of E-selectin and P-selectin were highly significant (p=0.001**) for case detection in alopecia areata

CONCLUSION

An interesting pathogenic issue in alopecia areata is related to elevated serum levels of selectins, which are identified as adhesion particles involved in lymphocyte immigration through the vessel wall and they may reveal vascular abnormalities in alopecia areata. Both of soluble forms of E- and P-selectin are elevated in AA. Both of P-selectin and E-selectin were found to be significant markers for revealing of alopecia areata activity and severity.

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