ORIGINAL ARTICLE

Is the severity of alopecia areata associated with arterial stiffness?

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Background: This study aimed to evaluate the severity of alopecia areata (AA) associations with metabolic syndrome, body composition evaluated by bioimpedance techniques, and arterial stiffness based on pulse-wave velocity analysis. **Materials and Methods:** This cross-sectional study was conducted on patients referred to AA Clinic at Razi Hospital in 2021 and 2022. Patients with AA with the Severity of Alopecia Tool (SALT) score above 20% and receiving no systemic therapy were included. Patient demographic and clinical information, symptoms of metabolic syndrome, and bioimpedance factors were collected, and the relationship between disease severity, metabolic syndrome, and bioimpedance indicators was evaluated. **Results:** In this study, 59 patients were examined, with 26 (44.07%) being female and 33 (55.93%) being male. The mean age of the patients was 37.42 years (standard deviation [SD] =11.28). The severity of the disease was assessed using the SALT score, with the mean severity in terms of the percentage being 69.83% (SD = 28.57%). In the regression model, SALT score was independently related to the severity of vascular stiffness after adjusting for the effect of other variables (beta = 0.033, 95% CI = 0.009–0.057, P = 0.046). Moreover, SALT score was significantly related to metabolic syndrome after adjusting for the effect of other variables (OR = 1.035, 95% CI = 1.012–1.059, P = 0.002). **Conclusion:** This study found that AA severity is associated with a higher chance of having metabolic syndrome and arterial stiffness which may lead to cardiovascular diseases in patients with AA, and screening patients regarding cardiometabolic diseases is mandated.

Key words: Alopecia areata, arterial stiffness, bioimpedance factors

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INTRODUCTION

Alopecia areata (AA) is an autoimmune dermatological disorder resulting in nonscarring loss of hair on the scalp and other body parts.[1,2] Despite the importance of genetic factors, environmental factors also have a role in the development of AA.[3,4] It is estimated that 2% of people worldwide are affected by AA.[5] The condition can be emotionally distressing and lead to social anxiety and depression, affecting the quality of life of those affected.[6,7]

Skin conditions such as AA may predispose patients to other diseases and disorders. Studies have shown that patients with skin disorders such as psoriasis, acne vulgaris, androgenetic alopecia, acanthosis nigricans, and atopic dermatitis are at a higher risk of cardiometabolic diseases, such as metabolic syndrome.[8,9] It is suggested that chronic inflammation involving molecular mechanisms such as adipokines and pro-inflammatory cytokines mediates the association between skin conditions and cardiometabolic diseases.[9,10] Recent studies have focused on the association between androgenic alopecia and cardiovascular diseases.[11,12] However, there are only limited studies on the relationship between other types of alopecia, such as AA, and cardiovascular diseases.

While the primary focus of AA research has been on understanding the immune system dysregulation that causes hair loss, recent studies have suggested a link between AA and cardiovascular risk factors[13-17] such

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as obesity,[18] insulin resistance,[19] and dyslipidemia.[20] There are also studies showing the association between the severity of AA and future cardiovascular events.[14,15,21] There is also increasing evidence that AA may be associated with endothelial dysfunction, a predictor of cardiovascular events.[22] However, these studies have conflicting findings, and the mechanism of possible cardiometabolic dysregulation in AA patients is not yet discovered.

In brief, there are only limited studies on cardiometabolic disorders in patients with AA. The association between AA severity and arterial stiffness, vascular age, and body composition as predictors of future cardiovascular events has not been previously studied.[23-25] Therefore, this study was conducted to evaluate the association between severity of AA and arterial stiffness based on pulse-wave velocity analysis along with the body composition evaluated by bioimpedance techniques and metabolic syndrome.

METHODS

Overview

This cross-sectional study was done after approval of the Ethics Committee of Tehran University of Medical Sciences (Ethics Code: IR.TUMS.MEDICINE.REC.1401.078(. The study was performed in the largest dermatology center in our country, Razi Dermatology Clinic, Tehran, Iran, in the years 2021 and 2022.

The inclusion criteria for our study were as follows: participants had to be above 18 years old and have been diagnosed with AA by a dermatologist, and the severity of alopecia was more than 20% based on the Severity of Alopecia Tool (SALT).[26]

We also had exclusion criteria, including systemic treatments within the past 3 months, presence of other autoimmune and inflammatory diseases such as rheumatoid arthritis and psoriasis, and having a cardiac pacemaker. These criteria were carefully considered to ensure the safety and validity of our study.

Measurements

The patients' demographic characteristics, such as age, sex, age of disease onset, family history of alopecia, concomitant systemic disease, medications, smoking, and alcohol consumption, were recorded. The severity of their alopecia was determined according to the SALT criteria.

Laboratory tests, including liver and kidney function tests, lipid profile, fasting blood sugar, and Vitamin D3 tests, were performed after 12 h of fasting. Anthropometric indicators such as weight and waist circumference were recorded. Blood pressure was also measured after a 10-min rest period.

Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) was performed using the InBody S10 device (Biospace Co., Ltd., Seoul, Korea), which is a noninvasive and quick method for assessing body composition. Before the measurements, participants were instructed to fast for at least 6 h, avoid alcohol consumption for 24 h, and not engage in vigorous physical activity for 12 h. Participants were in supine position with their feet slightly apart and arms placed freely at their sides. Shoes and socks were taken off and electrodes were placed after scrubbing contact sites with alcohol. The device then sends a small electrical current through the body to measure the impedance of different tissues. The test takes approximately 1–2 min to complete and provides data on body fat mass, lean body mass, body mass index, and bioimpedance parameters. Measurements were done based on the guidelines set forth by the European Society of Parenteral and Enteral Nutrition.[27]

Pulse-wave velocity

Pulse-wave velocity (PWV) was measured using the PulsePen diastolic device (DiaTecne s.r.l., Milan, Italy), which is a noninvasive and reliable method for assessing arterial stiffness. We individuals in three groups – normal (<75 percentile), borderline stiffness (75–95 percentile), and stiff (>95 percentile). Participants were instructed to lie in the supine position for at least 10 min before the examination. Electrocardiography leads were attached to the wrists and ankles of each participant to record the R-wave of each heartbeat. A handheld probe was placed sequentially over the carotid and femoral arteries to record the pulse waveforms. The transit time between the two arterial sites was determined from the delay between the feet of the two waveforms. The distance between the carotid and femoral sites was measured with a measuring tape. The carotid-femoral PWV was calculated as the distance divided by the transit time. The measurements were performed by trained specialists who were blinded to the participants.

Clinical characteristics

All study participants underwent diagnostic procedures at a single center to measure these variables including percent body fat (PBF), visceral fat area (VFA), and phase angle (PhA) calculated from the BIA measurements and PWV, vascular stiffness, and vascular age using the PulsePen Diatecne device.

Statistical analysis

In this manuscript, we described the descriptive statistics for both quantitative and qualitative variables. Mean and standard deviation were reported for quantitative variables, while frequency and frequency percentage were reported for qualitative variables.

To evaluate the relationship between the severity of AA using the SALT score index and the metabolic indices described earlier, we used the Pearson correlation coefficient along with the corresponding 95% confidence intervals (CIs). In addition, we utilized a multiple linear regression model to conduct multivariate analysis.

In this study, a statistical significance level of 0.05 was considered. All statistical calculations were performed using the SPSS ver.22 (IBM Corp. Armonk, NY) software. These analyses were conducted to investigate the relationship between the severity of AA and metabolic, bioimpedance, and cardiovascular indices.

RESULTS

The patients' demographics are listed in Table 1 along with the mean SALT score. The study evaluated the presence of metabolic syndrome, revealing that 28 (47.46%) patients had metabolic syndrome, while 31 (52.54%) patients did not. The distribution of specific criteria of metabolic syndrome is demonstrated in Table 2.

Measurement results of body composition using bioelectrical impedance analysis and pulse-wave velocity

The study found that the average percentage of body fat (PBF) in the patients was 26.66% with a standard deviation of 9.99%. The average level of visceral body fat (VFA) was 101.60 cm^2 with a standard deviation of 94.78 cm^2. The PhA of the patients was 5.88° on average with a standard deviation of 0.81°. The PWV of the patients was on average 8.11 m/s with a standard deviation of 1.48 m/s. The vascular age of the patients was 40.24 on average with a standard deviation of 11.52 years. The study also found that 18 patients had normal vascular stiffness, 24 patients had borderline stiffness, and 9 patients had complete vascular stiffness.

Table 1: Demographics

	n (%)/mean±SD
Number of cases	59 (26 women, 33 men)
Age (years)	37.42±11.28
Height (cm)	168.71±10.58
Weight (kg)	71.08±15.02
BMI (kg/m^2)	24.08±3.98
Smoker	
Yes	11 (18.64)
No	48 (81.36)
Alcohol	
Yes	7 (11.86)
No	52 (88.14)
SALT score	69.83±28.57

BMI=Body mass index; SD=Standard deviation; SALT=Severity of Alopecia Tool

Table 2: Prevalence of metabolic syndrome criteria in patients

Criteria	Males, *n* (%)	Females, *n* (%)
Increased abdominal circumference	8 (24.24)	13 (50)
TG ≥150 mg/dL	11 (33.34)	7 (26.92)
HDL <50 mg/dL	17 (51.51)	17 (65.38)
FBS >100 mg/dL	18 (54.54)	11 (37.93)
SBP ≥130 mmHg or DBP ≥85 mmHg	13 (39.39)	9 (31.03)

SBP=Systolic blood pressure; DBP=Diastolic blood pressure; TG=Triglyceride; FBS=Fasting blood sugar; HDL=High-density lipoprotein

Association between quantitative factors and bioimpedance and Severity of Alopecia Tool score indicators

The results showed that among the quantitative factors, BUN, T3, and aspartate aminotransferase had a significant correlation ($P < 0.05$) with the severity of the disease. Table 3 provides information on the association of each of the studied quantitative factors with bioimpedance and SALT score indicators based on the Pearson test.

The results of the Mann–Whitney *U* and Kruskal–Wallis *H* tests are presented in Table 4, which indicates the relationship between the studied qualitative factors and each of the bioimpedance and SALT score indices. Gender was found to be significantly associated with PhA, VFA, and PBF factors. The mean values for males were 6.36 for PhA, 72.83 for VFA, and 21.62 for PBF, whereas for females, the mean values were 5.30, 135.37, and 32.57, respectively. In contrast, smoking did not show any association with the studied factors. Interestingly, alcohol consumption was found to have a significant association with SALT score, with alcohol users having a higher mean SALT score (90.00%) than nonalcoholics (67.12%). In addition, all factors, including PBF, VFA, PWV, SALT score, and vascular age, had significantly higher mean values in patients with metabolic syndrome compared to those without it. The mean values for patients with metabolic syndrome were 30.37 for PBF, 136.77 for VFA, 8.75 for PWV, 83.36% for SALT score, and 44.36 for vascular age, while for patients without metabolic syndrome, the corresponding mean values were 23.75, 73.96, 7.60, 57.61%, and 37.00, respectively.

Vascular stiffness

Patients with severe vascular stiffness had significantly higher mean SALT score and PWV than the other groups. The mean SALT score was 89.88% in the severe group, compared to 69.42% and 57.67% in the borderline and normal groups. Similarly, the mean PWV was 10.06 in the severe group, compared to 8.22 and 7.09 in the borderline and normal groups. Furthermore, the SALT score and presence of metabolic syndrome were significantly different among the normal, borderline, and extreme groups of the vascular stiffness factor. Table 5 shows all factors associated with vascular stiffness in each of these degrees.

Table 3: Association of each of the studied quantitative factors with bioimpedance and Severity of Alopecia Tool score indicators based on the Pearson test (r)

Index	Vascular age	*P*	PWV	*P*	PhA	*P*	VFA	*P*	PBF	*P*	SALT score	*P*
Age	0.97***	0.001	0.49***	0.001	−0.26	0.07	0.01	0.92	0.44***	0.001	0.16	0.23
Height	−0.09	0.55	0.03	0.84	0.51***	0.001	−0.12	0.42	−0.34**	0.02	0.03	0.84
Weight	0.17	0.25	0.07	0.65	0.49***	0.001	0.12	0.39	0.21	0.15	0.08	0.54
BMI	0.34*	0.02	0.1	0.5	0.3*	0.03	0.3*	0.04	0.61***	0.001	0.07	0.59
Waist circumference	0.32*	0.03	0.09	0.54	0.26	0.07	0.26	0.07	0.57***	0.001	0.12	0.35
SBP	0.39*	0.01	0.41***	0.001	0.17	0.23	−0.14	0.32	0	0.97	0.01	0.93
DBP	0.18	0.22	0.3*	0.04	0.11	0.45	−0.08	0.6	0.02	0.9	−0.01	0.92
FBS	0.08	0.56	0.06	0.69	0.05	0.71	0.14	0.32	0.13	0.37	0.14	0.3
HDL	−0.03	0.86	−0.24	0.1	−0.26	0.06	−0.13	0.36	−0.07	0.65	−0.11	0.39
TG	0.25	0.08	0.22	0.13	0.13	0.37	0.22	0.12	0.21	0.14	0.23	0.07
SALT score	0.18	0.21	0.24	0.09	−0.19	0.2	0.17	0.23	0.1	0.51		
LDL	0.2	0.16	0.2	0.17	0.01	0.94	0.12	0.4	0.24*	0.09	0.03	0.81
Cholesterol	0.29*	0.04	0.04	0.79	−0.19	0.19	0.13*	0.36	0.32*	0.03	0.08	0.53
AST	0.21	0.14	0.17	0.23	0.2	0.17	0.08	0.6	0.04	0.79	0.28*	0.03
ALT	0.07	0.63	0.17	0.25	0.29*	0.04	0.05	0.74	−0.07	0.61	0.23	0.08
BUN	0.17	0.23	−0.05	0.73	0.04	0.81	−0.04	0.81	−0.03	0.83	0.39***	0.001
Creatinine	0.3*	0.03	0.34*	0.02	0.19	0.19	0.08	0.59	0.17	0.23	0.17	0.2
TSH	0.37*	0.01	0.18	0.22	−0.11	0.45	−0.02	0.89	0.14	0.33	−0.11	0.41
T4	−0.05	0.75	0.07	0.61	−0.04	0.79	0.1	0.5	0.02	0.89	0.16	0.23
T3	−0.07	0.64	−0.16	0.26	0.2	0.16	−0.15	0.29	−0.19	0.2	−0.32*	0.01
Vitamin D3	−0.01	0.95	−0.22	0.13	0.23	0.1	−0.23	0.12	0.04	0.76	−0.04	0.75

*P-value<0.05; **P-value<0.01; ***P-value<0.001. BMI=Body mass index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; FBS=Fasting blood sugar; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; TG=Triglyceride; SALT=Severity of Alopecia Tool; AST=Aspartate transaminase; ALT=Alanine transaminase; BUN=Blood urea nitrogen; TSH=Thyroid-stimulating hormone; PWV=Pulse-wave velocity; PhA=Phase angle; VFA=Visceral fat area; PBF=Percent body fat; T4=Thyroxine; T3=Triiodothyronine

Table 4: The relationship between the studied qualitative factors and each of the bioimpedance and Severity of Alopecia Tool score indices (U)

	Vascular age	PWV	PhA	VFA	PBF	SALT score
Sex						
Mann–Whitney *U*	212.500	278.500	70.500***	166.500**	114.500***	401.000
P	0.56	0.533	<0.001	0.005	<0.001	0.664
Alcohol consumption						
Mann–Whitney *U*	87.500	130.000	83.000	107.500	87.500	78.500*
P	0.184	0.952	0.143	0.465	0.184	0.014
Cigarette smoking						
Mann–Whitney *U*	120.500	148.000	144.000	92.500	102.000	246.500
P	0.401	0.944	0.856	0.105	0.175	0.73
Metabolic syndrome						
Mann–Whitney *U*	202.500*	182.500*	272.000	155.000**	193.000*	219.000***
P	0.039	0.014	0.481	0.003	0.025	0.001
Vascular stiffness (normal, borderline, severe)						
Mann–Whitney *U*	3.545	25.426***	0.1720	0.2340	0.7040	8.496*
P	0.17	<0.001	0.918	0.889	0.703	0.014

*P-value<0.05; **P-value<0.01; ***P-value<0.001. PWV=Pulse-wave velocity; PhA=Phase angle; VFA=Visceral fat area; PBF=Percent body fat; SALT=Severity of Alopecia Tool

Regression test

In the multiple backward stepwise ordinal regression model, SALT score was independently related to the severity of vascular stiffness after adjusting for the effect of other variables (beta = 0.033, 95% CI = 0.009–0.057, P = 0.046). Moreover, in the multiple backward stepwise binary regression model, SALT score was significantly related to metabolic syndrome after adjusting for the effect of other variables (excluding the defining factors of metabolic syndrome itself) (odds ratio = 1.035, 95% CI = 1.012–1.059, P = 0.002).

DISCUSSION

This is the first study evaluating body composition by bioimpedance techniques and arterial stiffness based on pulse-wave velocity analysis in patients with AA and assessing their associations with the severity of AA. In

Table 5: Factors associated with vascular stiffness

Index	Vascular stiffness			*P*
	Severe	Borderline	Normal	
Demographic				
Age	40.50	36.25	39.44	0.215
Height	166.50	168.42	167.56	0.890
Weight	68.09	71.75	70.78	0.813
BMI	24.13	25.17	24.94	0.938
Severity of alopecia areata				
SALT score (%)	90	69	58	0.014
Lab tests				
LDL	110.88	105.63	99.28	0.431
Cholesterol	179.63	171.04	170.33	0.731
AST	21.50	22.42	18.67	0.265
ALT	21.88	22.38	20.50	0.660
BUN	14.99	15.65	15.82	0.946
Creatinine	1.08	1.02	0.96	0.248
TSH	2.55	2.89	2.74	0.451
T4	129.38	109.19	106.44	0.384
T3	1.29	1.64	1.57	0.104
Vitamin D3	25.73	25.58	32.94	0.076
Sex (frequency)				
Female	3	12	8	0.817
Male	5	12	10	
Alcohol consumption (frequency)				
Yes	2	3	1	0.369
No	6	21	17	
Cigarette smoking (frequency)				
Yes	1	4	2	0.869
No	7	20	16	
Metabolic syndrome (frequency)				
Yes	6	13	3	0.008
No	2	11	15	

BMI=Body mass index; LDL=Low-density lipoprotein; SALT=Severity of Alopecia Tool; AST=Aspartate transaminase; ALT=Alanine transaminase; BUN=Blood urea nitrogen; TSH=Thyroid-stimulating hormone; T4=Thyroxine; T3=Triiodothyronine

this study, the relationship between vascular age, vascular stiffness based on PVW, PhA, visceral fat, and total body fat percentage with the severity of AA was evaluated for the first time. The main finding of this study was the relationship between vascular stiffness and SALT score and PWV. Specifically, individuals with severe vascular stiffness had a significantly higher mean SALT score compared to other groups, and PWV was also significantly higher in individuals with severe vascular stiffness compared to other groups.

In this study, the severity of AA was associated with an increased risk of metabolic syndrome and arterial stiffness, consistent with previous studies. A significant correlation was also found between AA severity and endothelial dysfunction in a study in Poland, which could be an early finding for cardiovascular diseases in the future.[22] The prevalence of metabolic syndrome was also higher in individuals with AA compared to the control group in another study by Nasimi *et al*.[20] Previous studies have also shown a relationship between AA and other diseases, including diabetes mellitus and autoimmune disorders such as systemic lupus erythematosus, psoriasis, rheumatoid arthritis, celiac disease, and inflammatory bowel disease.[28-32] Although the association between metabolic syndrome and AA is weaker than that with androgenetic alopecia,[30,33] it seems that these patients are still at a higher risk of developing metabolic syndrome and cardiovascular problems than the normal population. Given the burden of cardiovascular and metabolic problems, especially in individuals with severe AA, these patients need further evaluation.[30,34] In severe forms of AA such as universalis and totalis, which are characterized by extensive hair loss, a stronger relationship with autoimmune diseases, cardiometabolic disorders, and metabolic syndrome has been demonstrated, consistent with the present study's findings.[30] Therefore, AA seems to put individuals at risk of developing cardiovascular diseases by impairing endothelial function and increasing arterial stiffness. Lifestyle modifications can be one of the helpful interventions in this regard. For example, in this study, the average SALT score was significantly higher in individuals who consumed alcohol than in those who did not. Alcohol consumption is one of the causes of an increased risk of metabolic syndrome.[35] Therefore, interventions aimed at reducing alcohol consumption in patients with AA can effectively reduce the risk of metabolic syndrome and cardiovascular diseases in the future.[36-39]

We did not find a significant correlation between the severity of AA and visceral fat, total body fat, PWV, arterial age, and PhA. Some previous studies have reported different findings regarding the association between the severity of AA and cardiometabolic factors. However, the results in this regard are controversial, and there are differences among populations. A study conducted in the United States evaluated the risk of acute myocardial infarction and stroke in patients with AA compared to the control group. However, this association was not statistically significant.[14] On the other hand, in a 12-year cohort in South Korea, the risk of acute myocardial infarction was higher in patients with AA compared to the healthy control group.[21] Similarly, in a study in Taiwan, the hazard ratio of stroke incidence in patients with AA was 1.61 compared to the control group, and the incidence of stroke in patients with AA was 5.44 per 1000 people, compared to 2.75 in the control group.[15] These findings suggest the role of genetic factors in the susceptibility of individuals with AA to cardiometabolic disorders. While the results in East Asian countries indicate a significant association between the incidence of stroke and ischemic heart diseases and the severity of AA, the findings of this study indicate that the severity of AA is not associated with visceral fat, arterial stiffness, or arterial age. Considering the similar findings in the United States, it can be hypothesized that the genetic background of

individuals with AA living in East Asian countries places them at a higher risk of cardiovascular disease.[40,41] Future international studies controlling for confounding factors of ethnicity can help understate the association between the severity of AA and cardiometabolic diseases. Another reason for the differences in the findings of these studies might be due to shorter times elapsed since the start of the patients' diseases. Future studies that consider the duration of AA can help to understand better the effects of AA severity on the level of arterial fat and stiffness.

This study has several limitations worth noticing. It was conducted in a single center, which is one of its main limitations. Razi Hospital is a referral dermatology hospital in Iran where patients might have unique characteristics.[42] Therefore, the findings of this study may not be generalizable to all patients with AA. Thus, future multicenter studies are needed to assess the relationship between the severity of AA and bioimpedance analyses and metabolic indices. Furthermore, this study was cross sectional, and a causal relationship between variables could not be evaluated. Longitudinal studies such as cohort studies can help better understand the relationship between cardiometabolic factors and the severity of AA. In addition, only individuals with moderate-to-severe AA were evaluated in this study, and future studies including patients with mild AA and using healthy control groups are needed.

CONCLUSION

In this study, the severity of AA disease was associated with a higher risk of developing metabolic syndrome and increased arterial stiffness which may further lead to cardiovascular diseases in individuals with AA, making patient cardiometabolic screening crucial in this regard. The lack of significant statistical association between the severity of AA disease and other factors may be due to the genetic features of the Iranian population, other confounding factors, the duration of AA in patients, and small sample size. Therefore, future studies with larger sample sizes, more comprehensive evaluations of confounding factors and cardiometabolic factors, longer follow-up periods, and using a control group can be helpful.

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Conflicts of interest
There are no conflicts of interest.

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