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ORIGINAL PAPER

Patients with alopecia areata show signs of insulin resistance

Mohammad Shahidi-Dadras[1] · Negin Bahraini[1] · Fateme Rajabi[1,2] · Shima Younespour[3]

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Abstract

Alopecia areata (AA) is an autoimmune disease associated with high levels of proinflammatory cytokines. Since chronic inflammation plays a major role in the pathogenesis of insulin resistance, AA can theoretically increase the risk of diabetes. We sought to investigate this theory by conducting a case–control study. Sixty patients with alopecia areata and 60 healthy volunteers (matched for age, sex, and body mass index) were evaluated. Fasting blood glucose (FBS), C-peptide, plasma insulin, and homeostasis model assessment for insulin resistance (HOMA-IR) were measured for each individual. Plasma levels of insulin [median (interquartile range IQR): 11.22 (7.28–18.15) µIU/ml vs. 4.80 (3.20–9.00), $p < 0.0001$)], C-peptide [median (IQR): 2.10 (1.61–3.00) ng/ml vs. 1.40 (1.20–1.88), $p < 0.0001$)] and HOMA-IR [median (IQR): 2.70 (1.58–3.96) µIU/ml vs. 1.01 (0.64–1.98, $p < 0.0001$)] were significantly higher in patients with AA compared to controls. The differences remained significant even after controlling for age, gender, and BMI. Patients with a more severe disease (alopecia totalis/universalis) had higher levels of insulin [median (IQR): 15.80 (9.68–21.55) vs. 9.30 (5.33–14.40), $p = 0.02$)] and HOMA-IR [median (IQR): 3.30 (2.20–4.84) vs. 2.15 (1.29–3.52), $p = 0.01$] compared to those with patchy hair loss. Our data suggest that individuals with AA are at a higher risk of developing insulin resistance. This may be due to common inflammatory pathogenesis or a shared genetic background.

Keywords Insulin resistance · Diabetes · Alopecia areata · C-Peptide · Homeostasis model assessment for insulin resistance

Abbreviations

AA	Alopecia areata
AT	Alopecia totalis
AU	Alopecia universalis
HOMA-IR	Homeostasis model assessment for insulin resistance
IQR	Interquartile range

Introduction

Alopecia areata is a chronic inflammatory disease of the hair follicles that affects about 2% of the general population [19].

AA is becoming increasingly recognized as a systemic condition due to its strong association with comorbidities such as vitiligo, type 1 diabetes, lupus, autoimmune thyroid disease, and Addison's disease [7, 9, 24].

Aside from these immune-mediated conditions, few observational studies and case reports have linked AA to type 2 diabetes, a polygenic metabolic disease [12]. This association, if confirmed, can greatly change our perception of the pathophysiological events in AA and seriously impact our current therapeutic strategies. To determine the risk of developing diabetes in patients with AA, we performed a case–control study. We evaluated insulin resistance (IR) since it allowed us to detect earlier stages of metabolic deterioration.

We used a paradigm physiological model called the homeostasis model assessment of insulin resistance (HOMA-IR) to quantify insulin insensitivity [6, 23].

✉ Negin Bahraini
negin_bahraini@sbmu.ac.ir

[1] Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Network of Dermatology Research (NDR), Universal Scientific Education and Research Network (USERN), Tehran, Iran

[3] National Institute of Health Research, Tehran University of Medical Sciences, Tehran, Iran

Materials and methods

Participants were consecutively recruited from two referral dermatology clinics. Individuals with a confirmed diagnosis of AA who were aged 18 or over were enrolled as the case group and a set of age, sex, and BMI (body mass index) matched healthy volunteers were selected as the control group. The exclusion criteria were as follows: diabetes, history of diabetes in first-degree relative, any coexisting inflammatory disease other than AA, renal impairment, hypothyroidism, malignancy, hypertension, atherosclerosis, pregnancy, lactation, and polycystic ovary syndrome. Patients who were receiving systemic anti-inflammatory drugs or topical steroids and those with previous exposure to a systemic medication were also excluded from the study.

Documented factors for each individual included age, sex, height, weight, BMI, and disease characteristics such as duration from onset of symptoms and family history. The severity/pattern of hair loss was assessed by a trained dermatologist and was classified as one of the following: patchy, ophiasis, alopecia totalis (AT), and alopecia universalis (AU).

A venous blood sample was drawn from each individual after 12 h of fasting. The serum was separated from the collected blood samples by centrifugation for 10 min at 2000 rpm and stored at − 20 °C. Fasting serum glucose concentration (FBS) was measured enzymatically. C-Peptide and insulin levels were measured via chemiluminescent immune assay (immulite 2000 analyzer). HOMA-IR was calculated using the following formula: (fasting insulin [μIU/ml] × fasting glucose [mg/dl])/405.

The sample size was calculated according to the following parameters: prevalence of insulin resistance in the Iranian population, the presumed prevalence of insulin resistance in AA based on other similar autoimmune diseases [19], α error of 0.05 and β error 0.20.

All analyses were performed using the statistical software JMP, version 7 (SAS Institute Inc., Cary, NC, 1989–2007). Two-sided p values less than 0.05 were considered statistically significant. Categorical data were summarized as the number of subjects (percentage). For continuous variables, values were reported as median, total and interquartile ranges (25th–75th percentiles). The normality assumption of the continuous variables was examined using the Shapiro–Wilk's test. The nonparametric Mann–Whitney U test was employed to compare the continuous variables between the patients and controls. Fisher's exact test was carried out wherever appropriate. Spearman correlation test was used to detect the association between duration of disease and laboratory results. Binary logistic regression analysis was performed to determine the association between the occurrence of AA and study parameters.

Results

The study included 60 patients with alopecia areata and 60 age and sex-matched healthy control subjects. The serum levels of FBS were roughly equal in patients and healthy controls (Table 1). Individuals with AA had higher levels of insulin, C-peptide, and HOMA-IR than the control subjects (Table 1, Fig. 1). These findings remained statistically significant even after controlling for the effects of age, gender and BMI ($p = 0.01$ for insulin, $p = 0.001$ for C-peptide, and $p = 0.03$ for HOMA-IR).

A subgroup analysis demonstrated that individuals with severe forms of the diseases (AT/AU) had higher levels of insulin and HOMA-IR compared to those with patchy hair loss [insulin: median (IQR): 15.80 (9.68–21.55) vs. 9.30 (5.33–14.40), $p = 0.02$, and HOMA-IR: median (IQR): 3.30 (2.20–4.84) vs. 2.15 (1.29–3.52), $p = 0.01$] (Fig. 2). However, the AT/AU patients did not differ from milder cases in the median serum levels of FBS [median (IQR): 94.00 (85.00–99.50) vs. 94.00 (85.00–98.00), $p = 0.99$, respectively] and C-peptide [median (IQR): 2.10 (1.62–3.40) vs. 2.10 (1.70–2.80), $p = 0.69$].

There was no correlation between duration of disease and serum levels of FBS ($r = 0.23$, $p = 0.08$), insulin ($r = 0.24$, $p = 0.06$), C-peptide ($r = 0.001$, $p = 1.00$), or HOMA-IR ($r = 0.25$, $p = 0.06$).

According to the results of binary logistic regression analyses, the occurrence of AA was significantly associated with levels of insulin, C-peptide, and HOMA-IR (Table 2).

Discussion

In the present study, individuals with AA had a median HOMA-IR of 2.70 that is slightly higher than the estimated cutoff value for defining metabolic syndrome in non-diabetic adults [5]. The median of HOMA-IR was even higher (3.30) in individuals with severe forms of hair loss (AT and AU).

These findings are in line with a previous study by Karadag et al. [12] that reported higher levels of insulin (12.5 vs. 8.3 μIU/ml), c-peptide (2.7 vs. 2.1 ng/ml) and HOMA-IR (2.8 vs. 1.9) in AA patients compared to healthy controls [12]. Moreover, higher levels of HOMA-IR have been documented in studies on many other immune-mediated diseases such as vitiligo, psoriasis, rheumatoid arthritis, and systemic lupus erythematosus [1, 2, 8, 13].

The higher incidence of insulin resistance in alopecic patients can be explained by their similar immunopathogenesis. AA is an autoimmune disease that results from a collapse in the immune privilege of the hair follicles. The most important mediators in this process are interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) and a set of

Table 1 Baseline demographics, clinical characteristics and laboratory results of patients with alopecia areata and healthy controls

	Patients with AA ($n=60$)	Healthy controls ($n=60$)	p value
Gender, no. (%)			1.00
Female	26 (43.33%)	26 (43.33%)	
Male	34 (56.67%)	34 (56.67%)	
Age, years	30.50 (25–36); (18–64)	32.50 (27–37.75); (17–65)	0.32
BMI	25.02 (22.92–27.70); (20.30–37.46)	24.50 (22.48–26.54); (19.11–36.33)	0.46
Duration of disease, years	5 (1–11.75); (0.3–25)	–	
Subgroups of hair loss duration			
< 3 months	–	–	
3–12 months	8 (13.33%)	–	
12–24 months	11 (18.33%)	–	
2–5 years	10 (16.67%)	–	
5 years and more	31 (51.67%)	–	
Pattern of hair loss, no. (%)			
Patchy	23 (38.33%)	–	
Ophiasis pattern	4 (6.67%)	–	
Totalis	10 (16.67%)	–	
Universalis	23 (38.33%)	–	
Positive family history of AA, no. (%)	11 (18.33%)	0 (0.00%)	0.001
FBS, (mg/dl)	93.00 (85.00–98.75); (69.00–127.00)	90.50 (84.25–97.00); (58.00–122.00)	0.45
Insulin, (μIU/ml)	11.22 (7.28–18.15); (0.30–71.11)	4.80 (3.20–9.00); (1.20–86.90)	< 0.0001
C-peptide, (ng/ml)	2.10 (1.61–3.00); (0.70–6.23)	1.40 (1.20–1.88); (0.70–7.80)	< 0.0001
HOMA-IR	2.70 (1.58–3.96); (0.06–22.30)	1.01 (0.64–1.98); (0.23–25.32)	< 0.0001

Values are median (IQR); (range) unless otherwise noted

AA alopecia areata, *IQR* interquartile range (25th–75th percentiles), *BMI* body mass index (calculated as weight in kilograms divided by height in meters squared), *HOMA-IR* homeostasis model assessment of insulin resistance

interleukins (IL) such as IL-1, IL-6, and IL-15 [17]. Insulin resistance is a state of low sensitivity to insulin-stimulated glucose uptake by the liver, muscle, and adipose tissue. In this pre-diabetic state, the pancreatic cells are still able to compensate for the reduced response by increasing the production and secretion of insulin. Obesity is one of the main factors that provoke insulin resistance in the peripheral tissue. Excessive fat accumulation in adipocytes compromises the tissue oxygenation. Hypoxia can then alter cellular signaling and cause inflammation by releasing IL-1β, TNF-α, and IL-6 [16, 21]. These cytokines interfere with the functions of the insulin receptor and its downstream signaling pathway [3, 16]. It seems that elevated levels of systemic cytokines in AA could result in insulin resistance by the very same mechanism. Clear benefits of anti-inflammatory agents in diabetes can be regarded as evidence for this theory [4]. Similarly, anti-TNF alpha treatment in patients with rheumatoid arthritis [11] and psoriasis [15] has led to improvement of the concomitant type 2 diabetes. Anti-interleukin-1 antibodies are also beneficial in treating pre-diabetic and diabetic individuals [22].

AA and type 2 diabetes may also share common genetic backgrounds [25]. *ERBB3*, *PTPN22*, and *CTLA4* are three genes that are associated with both AA and type 2 diabetes in genome-wide association studies [17, 18].

Behavioral attitudes in individuals with AA may also contribute to the increased risk of insulin resistance. AA greatly impacts quality of life and individuals with alopecia have significantly higher rates of depression and anxiety [10]. Depressed individuals are more likely to choose a sedentary lifestyle and behavioral habits that cause obesity and diabetes [14, 20].

Conclusion

In conclusion, our data suggest that individuals with AA are at a higher risk for developing insulin resistance. However, more comprehensive studies with a larger sample size are required to confirm these results.

None the less, physicians should encourage lifestyle modification in individuals with chronic autoimmune diseases such as AA to reduce their risk of insulin resistance. Moreover, dermatologists should also reconsider using systemic steroids in treating patients with extensive forms of AA.

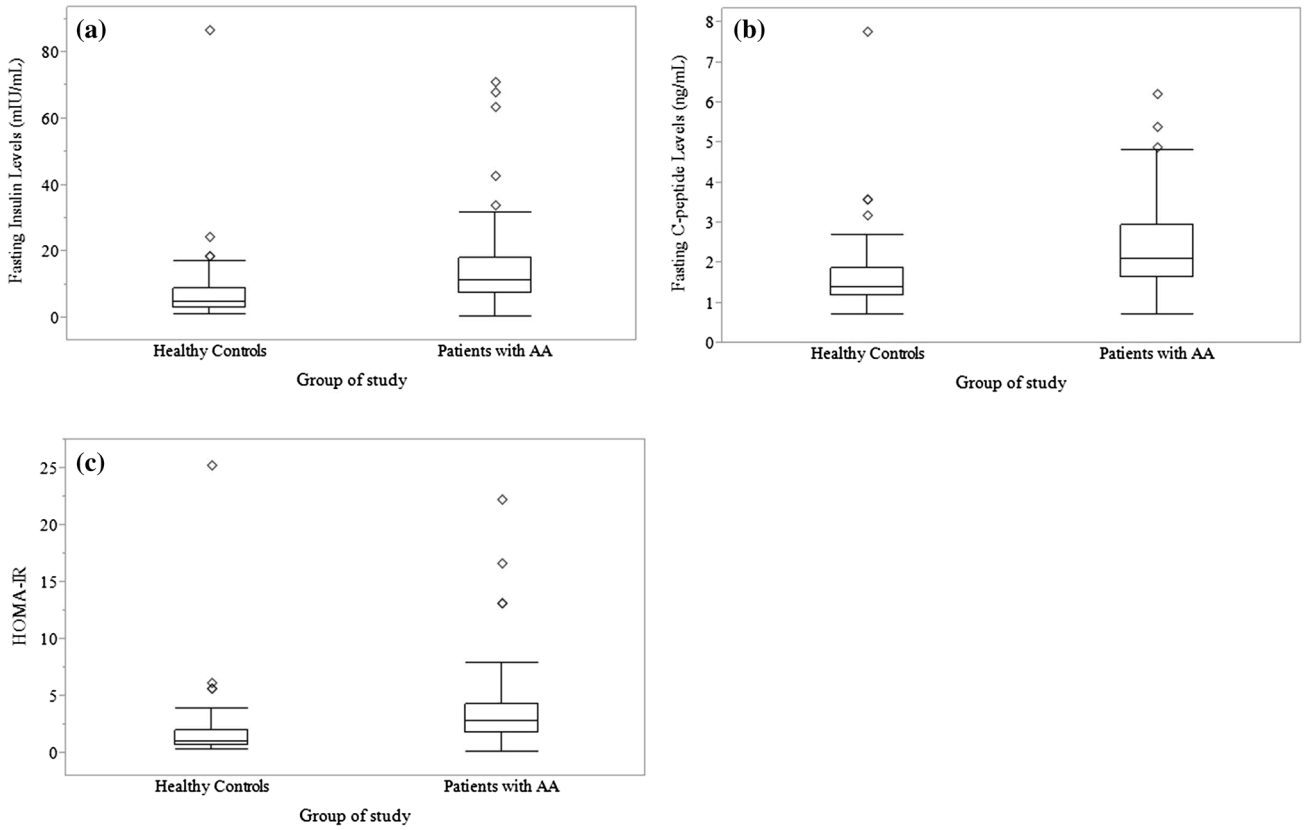

Fig. 1 **a** Fasting insulin levels in patients with AA and healthy controls. Middle point: median, box: interquartile range (25–75 percentiles), whisker: range (excluding outliers). **b** Fasting C-peptide levels in patients with AA and healthy controls. Middle point: median, box: interquartile range (25–75 percentiles), whisker: range (excluding outliers). **c** HOMA-IR levels in patients with AA and healthy controls. Middle point: median, box: interquartile range (25–75 percentiles), whisker: range (excluding outliers)

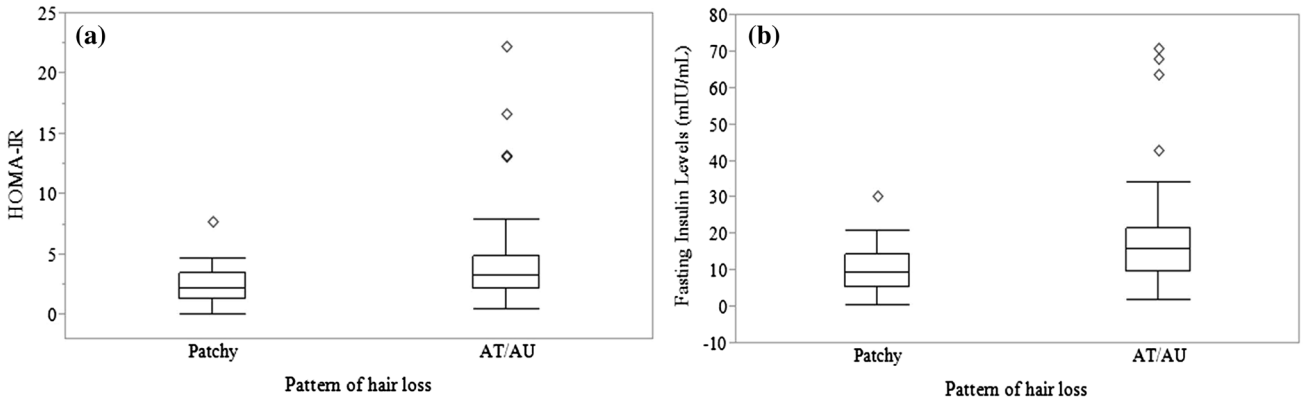

Fig. 2 **a** Levels of fasting insulin (μIU/ml) by the pattern of hair loss in patients with AA; middle point: median, box: interquartile range (25–75 percentiles), whisker: range (excluding outliers). The width of the boxes is proportional to the number of patients contributing to the box, showing the different sample sizes in the two groups. **b** Levels of HOMA-IR by the pattern of hair loss in patients with AA; middle point: median, box: interquartile range (25–75 percentiles), whisker: range (excluding outliers). The width of the boxes is proportional to the number of patients contributing to the box, showing the different sample sizes in the two groups

Table 2 Association of demographic and laboratory tests with the presence of AA

	OR (95% CI for OR)
Age	0.98 (0.95–1.02)
Gender (male vs. female)	1.00 (0.49–2.06)
BMI	1.04 (0.95–1.14)
FBS, (mg/dl)	1.02 (0.98–1.05)
Insulin, (μIU/ml)	1.07 (1.02–1.12)
C-peptide, (ng/ml)	2.11 (1.33–3.35)
HOMA-IR	1.22 (1.02–1.46)

AA alopecia areata, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index (calculated as weight in kilograms divided by height in meters squared), *FBS* fasting blood sugar, *HOMA-IR* homeostasis model assessment of insulin resistance

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical standards The Ethics Committee of Shahid Beheshti University of Medical Sciences approved this study and the study was conducted according to the latest revision of the Helsinki Declaration.

Informed consent Written informed consent was obtained from all participants before enrolment.

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