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INVESTIGATIVE REPORT

Insulin Resistance is Increased in Patients with Vitiligo

Ayse Serap KARADAG[1], Emre TUTAL[2] and Derun Taner ERTUGRUL[3]
[1]Department of Dermatology, Yuzuncu Yil University, Faculty of Medicine, Van, [2]Department of Internal Medicine, Ankara Baskent University Hospital, Faculty of Medicine, and [3]Department of Internal Medicine, Division of Endocrinology and Metabolism, Ankara Kecioren Research and Training Hospital, Ankara, Turkey

The aim of this study was to evaluate the relationship between vitiligo and insulin resistance (IR). A total of 96 subjects were included in the study; 57 patients with vitiligo and 39 subjects in an age and a body mass index-matched control group. In fasting blood samples, insulin, C-peptide, glucose, total cholesterol, triglyceride, low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) were measured. IR was calculated with the homeostasis model assessment-IR (HOMA-IR) method. Comparison of the vitiligo and the control groups revealed that patients with vitiligo had higher IR (2.3 vs. 2.0, $p < 0.01$), higher insulin and C-peptide levels ($p < 0.001$, $p < 0.001$, respectively), higher LDL/HDL ratio and lower HDL-C levels ($p < 0.01$, $p < 0.0001$, respectively). Systolic blood pressures of patients with vitiligo were also higher compared with control subjects ($p < 0.01$). Further experimental and clinical studies are needed to elucidate the molecular mechanisms underlying this association. ***Key words: HOMA-IR; insulin resistance; vitiligo.***

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Ayse Serap Karadag, Department of Dermatology, Yüzüncü Yıl University, Faculty of Medicine, TR-65300 Van, Turkey. E-mail: drayserem@yahoo.com

Vitiligo is an acquired disorder in which progressive patchy loss of pigmentation of skin, overlying hair, and mucous membranes results from loss of melanocytes from the involved areas (1). Vitiligo affects 1–2% of the world's population (2). Melanocyte destruction in vitiligo seems to have an autoimmune basis, resulting from a combination of genetic and environmental triggering factors (3). Vitiligo is epidemiologically associated with other autoimmune diseases, including autoimmune thyroid disease and adult-onset type 1 diabetes mellitus (4). In patients with vitiligo and in their close relatives, there is a predisposition to this group of autoimmune diseases, suggesting a common genetic background (5). It has also been speculated that pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6, might play a role in the development of vitiligo (6–8).

Even without diabetes, insulin resistance (IR) is a major risk factor for cardiovascular disease and early mortality. Resistance to insulin-stimulated glucose transport in adipose tissue and skeletal muscle is one of the earliest defects detected in IR. Overt hyperglycaemia develops when increased insulin secretion no longer compensates for IR (9). Variable prevalences for diabetes in patients with vitiligo have been reported in different studies (10). However, to our knowledge there is no study examining IR in non-diabetic patients with vitiligo. The aim of the current study was to evaluate the relationship between vitiligo and IR. The homeostasis model assessment-insulin resistance (HOMA-IR) method was used to assess IR in patients with vitiligo and body mass index (BMI)-matched controls (11).

METHODS

A total of 96 subjects were included in the study. Fifty-seven subjects were patients with vitiligo and 39 were in the control group. Patients were diagnosed as having vitiligo through clinical examination by an expert dermatologist. Demographic data, history of disease, family history, distribution of lesions, clinical type, and duration of disease and progression characteristics were recorded. Active/progressive vitiligo and stable disease discrimination was carried out by assessing the presence of activity according to the Koebner phenomenon and the history of new lesions in the last 2 months. The percentage of the body surface area covered by lesions was also recorded during physical examination. The diagnostic criteria for vitiligo were those of the Vitiligo European Task Force, classifying vitiligo vulgaris, acrofacial vitiligo, and vitiligo universalis as subtypes of generalized vitiligo, and segmental and focal vitiligo as subtypes of localized vitiligo (10). Exclusion criteria were: presence of hypertension, diabetes mellitus, thyroid disease, emotional or physical stress, atherosclerotic vascular disease, infections, malignancy, amyloidosis, autoimmune diseases, using corticosteroid treatment or smoking history in both patient and control groups. The control group was selected from healthy volunteers who had no dermatological or systemic disease history, and from patients who were evaluated in our dermatology outpatient clinic for cosmetic complaints and naevi.

Fasting blood samples were drawn from an antecubital vein from participants after 12 h fasting. Total cholesterol (Lot No: B540, Konelab) and triglycerides (Lot No: C186, Konelab) were measured with enzymatic colorimetric tests. Low-density lipoprotein cholesterol (LDL-C) (Lot No: C435, Konelab) and high-density lipoprotein-cholesterol (HDL-C) (Lot No: C136, Konelab) were measured with the homogeneous enzymatic colorimetric test. Fasting serum glucose (Lot No: D426, Konelab) concentrations were measured enzymatically with an automatic

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Table I. *Demographic comparison of study and control groups and clinical characteristics of patients with vitiligo*

Characteristics	Vitiligo ($n=57$)	Control ($n=39$)
Gender (F:M)	31:26	28:11
Age, years, mean ± SD	38.5 ± 14.2	40.2 ± 11.1
Family history of vitiligo, *n* (%)	15 (26.3)	
Vitiligo type, *n* (%)		
Focal	12 (21.1)	
Vulgaris	29 (50.9)	
Acrofacial	9 (15.8)	
Universalis	2 (3.5)	
Segmental	5 (8.8)	
Progressive disease, *n* (%)	29 (50.7)	
Stable disease, *n* (%)	28 (49.3)	
Body surface spread, *n* (%)		
0–4.9%	30 (52.6)	
5–24.9%	21 (36.8)	
25–49.9%	4 (7.0)	
50–100%	2 (3.5)	

SD: standard deviation

analyser (Konelab 60İ, Thermo Fisher Scientific Inc., Waltham, MA, USA). Fasting serum insulin and C-peptide levels were measured by Liaison Immunoluminometric assay (ILMA) (DiaSorin, Saluggia, Vercelli, Italy). HOMA-IR was calculated using the updated model available from the Oxford Centre for Endocrinology and Diabetes (11). Weight, height and waist circumference of all patients were also measured. The study protocol is in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All patients and controls provided their informed consent.

Statistical analyses were performed with SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc, Chicago, IL, USA). Normality of data was analysed by using a Kolmogorov-Smirnov test. All numerical variables with normal distribution were expressed as the means ± standard deviations (SD), while variables with skew distribution were expressed as medians and interquartile range. Categorical variables were given as percentages and were compared with a χ^2 test. Normally distributed numeric variables were compared using the independent samples Student's *t*-test, and skew distributed numeric variables were compared using the Mann-Whitney *U* test. A p-value < 0.05 was considered as statistically significant.

RESULTS

Demographic comparison of the study and the control groups is shown in Table I. Disease types, distribution and other characteristics of the study group are also summarized in Table I. Comparison of the study and the control groups revealed that patients with vitiligo had higher HOMA-IR, insulin and C-peptide levels, higher LDL/HDL ratio and lower HDL-cholesterol levels ($p < 0.01$–0.0001), respectively (Table II, Figs 1A and 1B). Mean systolic blood pressure of patients with vitiligo was also slightly higher compared with control subjects ($p < 0.01$, Table II, Fig. 1C). There was no significant difference in BMI and waist circumference measurements (Table II).

DISCUSSION

Vitiligo is a heterogeneous disease encompassing multiple etiologies (2). Autoimmune aetiology for vitiligo is one of the most intriguing hypotheses. Another possible pathogenetic factor is increased proinflammatory cytokines. Birol et al. (6) and Moretti et al. (7) reported increased TNF-α, IL-1 and -6 expressions at lesion sites of patients with vitiligo in two different studies. Lv et al. (8) reported a patient with ankylosing spondylitis and vitiligo who received infliximab (an anti-TNF-α agent). There was significant improvement in patients' symptoms related to ankylosing spondylitis, while vitiligo lesions faded completely after treatment. The above-mentioned cytokines are also implicated in the pathogenesis of diabetes mellitus and IR states. Inflammatory cytokines inhibit insulin signalling by phosphorylation of the certain serine residues of insulin receptor substrate-1 (12, 13). It is possible that elevated levels of proinflammatory cytokines may cause IR in patients with vitiligo (6, 8). In our study population there was no significant difference between the study and the control groups' BMI and waist

Table II. *Comparison of clinical and laboratory characteristics of study and control groups. Data with normal and skew distribution are shown as mean ± standard deviation (SD) and median and interquartile range (IQR), respectively*

	Vitiligo ($n=57$)	Control ($n=39$)	p-value
Fasting blood glucose, mg/dl	91 (16)	95.5 (12.5)	NS
Homeostasis model assessment-insulin resistance	2.3 (2.6)	2.0 (1.2)	<0.01
Insulin	9.9 (10.5)	7.7 (6.0)	<0.001
C-peptide	2.5 (1.6)	2.0 (0.9)	<0.001
Total cholesterol, mg/dl	172.4 ± 34.6	173.4 ± 34.5	NS
High-density lipoprotein (HDL)-cholesterol, mg/dl	41.3 ± 11.9	51.1 ± 12.4	<0.0001
Low-density lipoprotein (LDL)-cholesterol, mg/dl	102.6 ± 26.6	106.4 ± 27.4	NS
LDL/HDL	2.7 ± 1.1	2.2 ± 0.8	<0.01
Very-low-density lipoprotein-cholesterol, mg/dl	26.0 (30.2)	21.8 (16.3)	NS
Triglyceride, mg/dl	122.0 (154.0)	111.0 (80.2)	NS
Body mass index, kg/m^2	30.0 ± 15.6	31.1 ± 17.8	NS
Waist circumference, cm	93.8 ± 11.7	92.9 ± 11.4	NS
Systolic blood pressure, mmHg	120.0 (17.5)	110.0 (20.0)	<0.01
Diastolic blood pressure, mmHg	70.0 (10.0)	70.0 (7.5)	NS

NS: not significant.

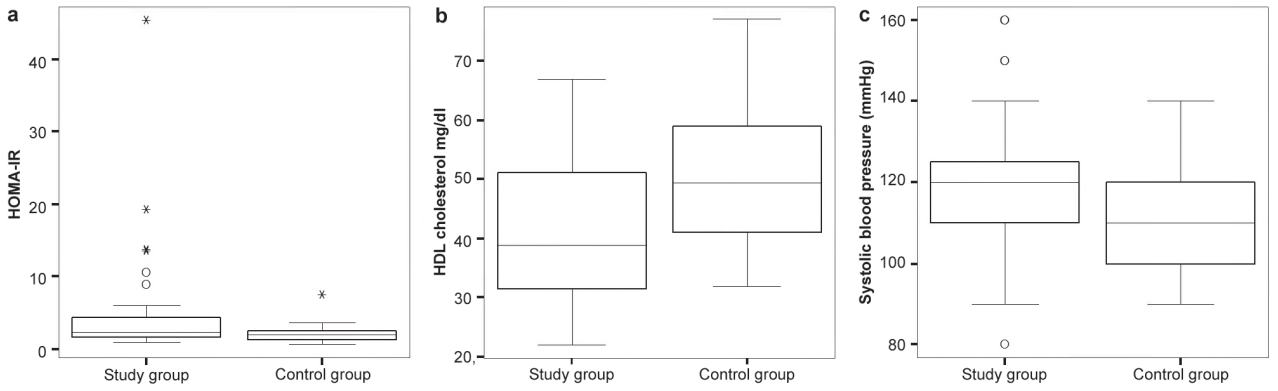

Fig. 1. Box-plot comparing vitiligo and control groups regarding (a) homeostasis model assessment-insulin resistance (HOMA-IR), (b) high-density lipoprotein (HDL)-cholesterol; and (c) systolic blood pressure. *: extreme values; °: outliers.

circumference measurements. Therefore, a different mechanism than obesity and metabolic syndrome may be responsible for higher IR in patients with vitiligo.

There are several studies reporting increased incidence of vitiligo in diabetic patients. Mahajan et al. (10) reported that, in a group of 100 diabetic patients (98 of them non-insulin-dependent), vitiligo incidence was higher compared with 100 healthy controls. Similarly, Vijayasingam et al. (14) reported a 3.3% incidence for vitiligo in diabetic patients. Nine percent of 457 consecutive Italian patients with diabetes had vitiligo in another study (54% type 1 diabetes) (3). On the other hand, diabetes incidence is also higher in patients with vitiligo compared with the general population (2, 15, 16). Several studies have previously reported a significant association between vitiligo and juvenile diabetes mellitus (12), latent autoimmune diabetes in adults (1, 13, 17) and non-insulin dependent type-II diabetes (10, 14). Several case reports have also linked vitiligo with acanthosis nigricans alone, or as a component of HAIR-AN syndrome (hyperandrogenism, insulin resistance, and acanthosis nigricans) (13, 18, 19).

The melanin-concentrating hormone receptor (MCHR) has been identified as a B-cell auto-antigen in patients with vitiligo (20). MCHR auto-antibodies have been shown to induce damage to human melanocytes *in vitro* by antibody-dependent cell-mediated cytotoxicity (21). MCH is expressed in the lateral hypothalamus and zona incerta and has been shown to be important for feeding and energy homeostasis in rodents (22). Mice lacking the pro-hormone are lean and hypophagic, whereas mice overexpressing MCH are obese and insulin resistant (23, 24). MCH and its receptor MCHR1 were found in primary human and mouse islets, suggesting a potential role for this appetite-regulating neuropeptide in modulating islet mass and function. The ability of exogenous MCH to stimulate insulin secretion, in both human and mouse islet tissue, provides additional evidence that MCH may regulate islet secretory function (25). There may be a link between MCHR1 auto-antibodies and hyperinsulinaemia in patients with vitiligo. Further experimental studies may reveal this hypothetical association between MCHR1 antibodies and islet cell function. MCHR1 antibodies, which were found in patients with vitiligo, may have a stimulatory effect on islet cells.

In conclusion, in this study we found that patients with vitiligo had higher IR than BMI- and waist circumference-matched controls. Increased insulin levels may be related to other mechanisms than obesity, such as cytokines or autoimmune reaction to melanocytes, in patients with vitiligo. Further experimental and clinical studies are needed to clarify this subject.

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