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Evaluation of the Risk of Subclinical Atherosclerosis in Vitiligo Patients by Measuring Carotid Artery Intima Media Thickness via Ultrasonography

Vitiligo Hastalarında Ultrasonografi ile Karotis Arter İntima Media Kalınlığının Ölçülerek Subklinik Ateroskleroz Riskinin Değerlendirilmesi

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ABSTRACT

Objective: Vitiligo is an autoimmune disease characterized by the destruction of melanocytes. It is often associated with other autoimmune diseases and systemic metabolic disorders. This study aimed to evaluate the increased risk of subclinical atherosclerosis in vitiligo patients.

Material and Method: In this prospective study, 70 vitiligo patients and 70 healthy control subjects, who were over the age of 18 years and without cardiovascular disease risk factors, underwent carotid artery ultrasonography, between 2022 and 2023. Carotid artery intima-media thickness which is an indicator of subclinical atherosclerosis was measured bilaterally. Vitiligo patients were grouped according to the presence of vitiligo vulgaris, acrofacial disease, focal vitiligo, family history, duration of disease, and age of the patient at disease onset.

Results: The mean carotid artery intima-media thickness in vitiligo patients was significantly greater than healthy controls ($p<0.001$). In particular, intima-media thickness was greatest in vitiligo patients with a disease duration less than one year, but this difference was not statistically significant ($p>0.05$).

Conclusion: This study revealed the risk of subclinical atherosclerosis in vitiligo patients with the carotid artery ultrasonography, which is a radiation free, inexpensive imaging method. There are few studies on the risk of cardiovascular diseases in vitiligo patients. The main difference of our study is that we excluded the subjects with any risk factors for cardiovascular diseases to identify the vitiligo as an independent risk factor for subclinical atherosclerosis and therefore cardiovascular diseases. At this point, we think that our study makes an important contribution to the literature.

Keywords: Atherosclerosis, carotid artery, intima media, ultrasonography, vitiligo.

ÖZET

Amaç: Vitiligo, melanositlerin yıkımı ile karakterize otoimmün bir hastalıktır. Genellikle diğer otoimmün hastalıklar ve sistemik metabolik bozukluklarla birlikte görülür. Bu çalışmada vitiligoda artmış subklinik ateroskleroz riskinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu prospektif çalışmada, 18 yaş üstü, kardiyovasküler hastalık risk faktörü olmayan 70 vitiligo hastası ve 70 sağlıklı kontrole 2022-2023 yılları arasında karotis arter ultrasonografisi uygulandı. Subklinik aterosklerozun bir göstergesi olan karotis arter intima-media kalınlığı bilateral olarak ölçüldü. Vitiligo hastaları vitiligo vulgaris varlığı, akrofasiyal hastalık, fokal vitiligo, aile öyküsü, hastalık süresi ve hastalığın başlangıç yaşına göre gruplandırıldı.

Bulgular: Vitiligo hastalarında ortalama karotis arter intima-media kalınlığı sağlıklı kontrol grubu ile karşılaştırıldığında istatistiksel olarak anlamlı derecede yüksekti ($p<0.001$). Özellikle hastalık süresi bir yıldan az olan vitiligo hastalarında intima-media kalınlığı en yüksekti, ancak istatistiksel olarak anlamlı değildi ($p>0.05$).

Sonuç: Bu çalışma, radyasyon içermeyen düşük maliyetli bir görüntüleme yöntemi olan karotis arter ultrasonografisi ile vitiligo hastalarında subklinik ateroskleroz riskini ortaya koymaktadır. Vitiligoda kardiyovasküler hastalık riski ile ilgili az sayıda çalışma bulunmaktadır. Çalışmamızın temel farkı ise kardiyovasküler hastalıklar için risk faktörleri olan bireylerin çalışmaya dahil edilmeyerek, subklinik ateroskleroz ve dolayısıyla kardiyovasküler hastalıklar için vitiligonun bağımsız bir risk faktörü olarak ortaya konmasıdır. Bu noktada çalışmamızın literatüre önemli katkı sağladığını düşünmekteyiz.

Anahtar Sözcükler: Ateroskleroz, intima media, karotis arter, ultrasonografi, vitiligo.

Introduction

Vitiligo is a chronic skin disease which is characterized by acquired depigmentation disorder caused by the loss of melanocytes (1). The incidence of vitiligo is approximately 0.5-2% worldwide (2). Many conditions including genetic factors, neural factors, oxidative stress, and autoimmunity are thought to be responsible for the pathogenesis of vitiligo, which has not yet been confirmed (3-7).

Vitiligo is characterized by circumscribed white patches because of the destruction of melanocytes in the skin. Some areas containing melanocytes such as hair follicles, the eyes, the inner ear, and the brain are usually spared because of the immune context there (3,6). To determine the disease activity, the 'vitiligo disease activity score' (VIDA) and to evaluate the disease severity and treatment, the 'vitiligo area severity index' (VASI) scores are used by dermatologists (8). Patients with vitiligo are prone to complications, such as diabetes, obesity, hyperlipidemia, and hypertension (1). In particular, nonsegmental vitiligo, which is characterized by depigmented patches with a diameter of a few centimeters that are symmetrical and involve both sides of the body, is associated with autoimmune diseases, several systemic and metabolic disorders, insulin resistance, lipid abnormalities, and metabolic syndrome (9, 10).

Autoimmunity and oxidative stress which may cause skin findings with inflammatory and immunological responses in patients with vitiligo, can also cause certain systemic manifestations (10). Increased reactive oxygen species (ROS) and inefficiency in antioxidant mechanisms have been shown in vitiligo (11). Intracellular oxidative stress can cause melanocyte destruction as an immune response (12). Several observations have confirmed the systemic inflammatory process, and that IFNγ, in particular, demonstrates important contribution to the pathogenesis of the disease (13). Additionally, the chemokines CXCL9 and CXCL10 are biomarkers of disease activity (13). Inflammatory cytokines in the systemic circulation such as IL-1, IL-6 and TNF-α, which play a role in vitiligo, have been associated with atherosclerosis (13, 14). The expression of chemokines and cytokines, increased oxidative stress and inflammatory processes are the main pathways involved in the pathogenesis of atherosclerosis and vitiligo, in fact, atherosclerosis is the main cause of many cardiovascular diseases (9). Inflammation, oxidation, endothelial disfunction are considered to be functional triggers for atherosclerosis (15-17). Early phase of atherosclerosis can be quantified by the ultrasonographic measurement of carotid artery intima-media thickness (CIMT) (15-17).

Ultrasonography of the carotid artery is widely used for detailed evaluation arterial wall changes, for detecting subclinical atherosclerosis by measuring the intima-media thickness, and also for evaluating the atherosclerotic plaques (18). Many factors, such as sex, age, lifestyle, food habits, and ethnicity, etc. affect the CIMT (19). CIMT is an accepted predictor for future cardiovascular diseases (CVDs) (20). Ultrasonographic measurement of CIMT is an accurate and applicable method for subclinical atherosclerosis from childhood to early adulthood before carotid artery plaques occur (20).

Vitiligo is considered to be a systemic metabolic disorder, not just a skin disease, with accompanying comorbidities. There are currently very few studies on CVDs in individuals with vitiligo (9, 21, 22). The aim of the present study was to verify the presence of subclinical atherosclerosis in vitiligo patients via carotid artery ultrasonography, which is a noninvasive, radiation-free imaging method.

Material and Method

Study population

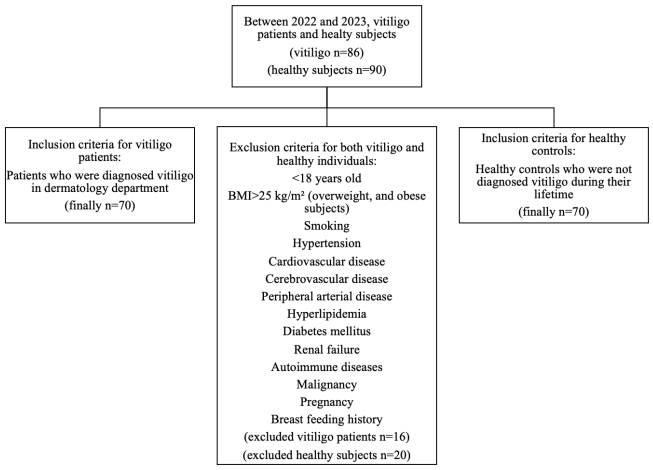
In this prospective study, between 2022 and 2023, 70 individuals with vitiligo, and 70 healthy subjects were included. The patients who were diagnosed with vitiligo were referred to the radiology department by the dermatologist with 15 years of experience. The control group included healthy subjects who applied to the dermatology department for other reasons (acne, bacterial skin infections, fungal nail infections, scabies, etc.). All of the vitiligo patients had nonsegmental vitiligo, and were divided into vitiligo vulgaris, acrofacial, and focal vitiligo groups. Additionally, family history, duration of the disease, and age of the patient at disease onset were added to the study. This study was carried out in accordance with the principles outlined in the latest version of the Declaration of Helsinki. This study was approved by

the local institutional ethics committee (Protocol no: 2022-13, approval date: 23 February 2022). Informed consent was obtained from the individuals included in the study.

Inclusion and exclusion criteria

The patients who were diagnosed with vitiligo, and for controls, subjects who were not diagnosed with vitiligo during their lifetime, were included in the study. In both the vitiligo and healthy control groups, the exclusion criteria were as follows: younger than 18 years, hyperlipidemia, and known history of CVD, cerebrovascular disease, renal failure, diabetes or hypertension, other autoimmune diseases, smoking, pregnancy, breast-feeding, and malignancy. Body mass index (BMI) was calculated for each group. Individuals who were overweight (BMI 25-29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) were excluded. A flow chart is presented in Figure I.

Figure I. Flow chart (BMI: Body mass index)



Ultrasonography protocol

Carotid artery ultrasonography was performed by the radiologist with 10 years of experience who was blinded to the patient's clinical status with a linear transducer (3-12 MHz) in the B-mode, pulsed Doppler mode and color mode. The CIMT was measured when the patient was lying in the supine position. The transducer was positioned longitudinally 1 cm proximal to the carotid bifurcation, and CIMT measurements were obtained from three contiguous sites bilaterally. The mean values were used for statistical analysis (Figure II).

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences, version 26 (SPSS Inc., Chicago, IL, USA). Ratio comparisons between categorical variables were analyzed via the chi-square test. The normality of the distribution of the data was evaluated with the Kolmogorov-Smirnov test. Student's t-test and the Mann Whitney U test were used for data normally distributed and nonnormally distributed data, respectively, to compare numerical variables between two independent groups. For comparisons between more than two groups, analysis of variance (ANOVA) test was used. A post-hoc test was used for multiple comparisons between groups to detect least significant differences when ANOVA test was used. Descriptive statistics of continuous variables were presented as the means±standard deviations (SDs). Categorical variables were reported as numbers (n) and percentages (%). The statistical significance was set at the *p<0.05* level.

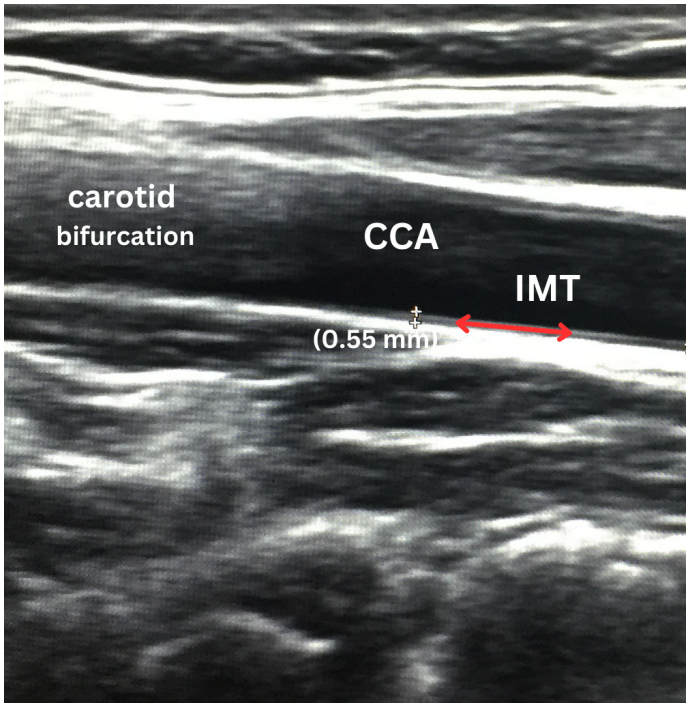


Figure II. Ultrasonographic measurement of carotid artery intima-media thickness (red line), the space between "(+) – (+)" (CCA: Common carotid artery, IMT: intima-media thickness)

Table I. Demographic Characteristics of the Participants

Variables (mean±SD)	Vitiligo (n=70)	Controls (n=70)	*p values*
Age (years)	32.74±9.275	30.16±8.196	*0.083*
Female [n (%)]	38 (54.3%)	35 (50%)	*0.612*
Male [n (%)]	32 (45.7%)	35 (50%)	*0.612*
BMI (kg/m^2)	24.51 ±3.46	24.62±3.17	*0.852*

(BMI: Body mass index, SD: Standard deviation)

Results

Seventy patients with vitiligo and 70 healthy

subjects were evaluated prospectively in the present study. The demographic data were presented in Table I. No significant differences in age, sex or BMI were observed between vitiligo patients and control subjects (*p>0.05*). All individuals underwent carotid ultrasonography. No atherosclerotic plaques were detected. CIMT values, both right and left, were significantly different between the vitiligo patients and control groups (*p<0.001*) (Table II). The patients with vitiligo had greater CIMT values than control group.

Table II. The Mean CIMT Among Vitiligo and Healthy Controls

Variables (mean±SD)	Vitiligo (n=70)	Controls (n=70)	*p values*
CIMT (right) (mm) CIMT (left) (mm)	0.571±0.084 0.592±0.092	0.517±0.046 0.518±0.046	*<0.001* *<0.001*

(CIMT: Carotid artery intima-media thickness, SD: Standard deviation)

Table III. The Mean CIMT between Vitiligo Subgroups

Vitiligo	CIMT (right) (mm) (mean±SD)	CIMT (left) (mm) (mean±SD)
Family history (yes) (n=20) Family history (no) (=50) *p value*	0.559±0.083 0.576±0.085 *0.524*	0.573±0.091 0.599±0.093 *0.201*
Duration of the disease Less than one year (n=9) 1-5 years (n=37) 6-10 years (n=12) More than 10 years (n=12) *p value*	 0.602±0.107 0.553±0.060 0.595±0.096 0.582±0.111 *>0.05*	 0.648±0.119 0.575±0.075 0.594±0.086 0.599±0.116 *>0.05*
Onset of the disease before the age of 18 Yes (n=19) No (n=51) *p value*	 0.581±0.109 0.568±0.074 *0.931*	 0.595±0.105 0.590±0.088 *0.878*
Focal disease (yes) (n=21) Focal disease (no) (n=49) *p value*	0.579±0.077 0.568±0.088 *0.688*	0.589±0.087 0.593±0.095 *0.928*
Acrofacial disease (yes) (n=25) Acrofacial disease (no) (n=45) *p value*	0.557±0.071 0.579±0.090 *0.771*	0.585±0.085 0.595±0.097 *0.862*
Vitiligovulgaris (yes) (n=22) Vitiligovulgaris (no) (n=48) *p value*	0.574±0.084 0.570±0.085 *0.803*	0.598±0.090 0.589±0.094 *0.653*

(CIMT: Carotid artery intima-media thickness, SD: Standard deviation)

Vitiligo patients were divided into subgroups according to their family history, duration of the disease, onset of the disease before the age of 18, focal disease, acrofacial disease, and vitiligo vulgaris. The results of the subgroup statistical analysis were presented in Table III. CIMT values were not significantly different between the vitiligo subgroups (*p>0.05*). The highest mean CIMT value was recorded in patients with a disease duration of less than one year (right: 0.602 mm, left: 0.648 mm). Patients who were diagnosed with vitiligo before 18 years of age at disease onset, patients with vitiligo vulgaris, patients without a family history had greater CIMT values.

Discussion

In this prospective study, CIMT was significantly greater in vitiligo patients than in healthy controls. The presented results indicate the risk of subclinical atherosclerosis in vitiligo patients. The relationships between vitiligo and CVDs have been reported in some literature reports (9, 21, 22). CVDs continue to increase due to the factors such as lifestyle habits, other concomitant diseases, and genetic factors, and they are responsible for approximately one-third of all deaths worldwide (23). It is important to identify possible risk factors and prevent them before the disease occurs.

High levels of inflammatory markers such as homocysteine, C-reactive protein, and the neutrophil/lymphocyte ratio have been reported in vitiligo patients (24, 25). Furthermore, some inflammatory cytokines: such as IL-1, IL-6, and TNF-α are associated with the pathogenesis of both vitiligo and atherosclerosis, insulin resistance, and other metabolic disorders (26). In the present study, the statistically significant increase in CIMT in vitiligo patients may be due to the presence of inflammatory chemicals in the systemic circulation. Additionally, a higher rate of metabolic syndrome was reported in vitiligo patients than in control groups in previous studies (8, 10, 21, 27). Sharma et al. reported a significant increase in the rates of metabolic syndrome, hypertriglyceridemia, low HDL levels, and impaired glucose tolerance in patients with vitiligo (27). Bathina et al. reported that metabolic syndrome was more common in vitiligo patients than in controls; in particular, the patients with vitiligo vulgaris had the highest ratio in their study (8). Metabolic syndrome is an independent risk factor for CVD, and the combination of these risk factors elevates the rates and severity of CVD (28). Therefore, the associations between metabolic syndrome and vitiligo reported by Bathina et al. and Sharma et al. were in concordance with our finding that the risk of subclinical atherosclerosis has been increased in vitiligo patients (8, 27).

Azzazi et al. investigated the association between vitiligo and atherosclerotic cardiovascular disease in Egyptian population (9). They reported that the mean CIMT for nonsegmental vitiligo patients was significantly greater than that for controls, which was consistent with our study. To explain this condition, they used the significantly high levels of malondialdehyde and hydrogen peroxide and significantly low level of total antioxidant capacity as indicators of oxidative stress in vitiligo patients. Namazi et al. reported that CIMT was greater and that subclinical atherosclerosis was more common in vitiligo patients than in controls (21). However, their results about CIMT values were not statistically significant. The mean age and BMI values in their study population were greater than those in our population. Additionally, total cholesterol and low-density lipoprotein (LDL) levels were high in their study population. For secondary analysis of CIMT values, they excluded all the subjects with metabolic syndrome from the vitiligo and control groups to eliminate their contribution to atherosclerosis. Compared with the healthy subjects, vitiligo patients in their study population had high CIMT values which was not statistically significant, and they had significantly more frequent subclinical atherosclerosis. In the present study, the patients and healthy controls with high lipid profiles were not included in the study. Therefore, our study may contribute to the literature in determining the effect of vitiligo as an independent factor for subclinical atherosclerosis without known risk factors such as hyperlipidemia.

We also evaluated the relationship between the disease duration and CIMT. CIMT was high in patients with a disease duration of less than one year and had the highest mean value among the vitiligo subgroups. In contrast, Namazi et al. reported a significant positive correlation between the duration of the disease and subclinical atherosclerosis; the mean duration of vitiligo was significantly longer in patients with subclinical atherosclerosis (21). This mismatch may be due to the small number of subjects in the study subgroups. The correlation between disease duration and the risk of subclinical atherosclerosis should be investigated by further studies with large sample sizes.

Fraczek et al. identified 94 cardiovascular diagnoses (cardiomyopathies, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, heart conduction disorders, heart valve diseases, heart failure, ischemic heart diseases, etc.) with a prevalence of ≥1% in patients with vitiligo in their retrospective study based on the basis of data from electronic health records (22). They reported that individuals with vitiligo were at increased risk of developing atherosclerosis as supported by the elevated CIMT values in our study. As a result, people with vitiligo may be prone to developing CVDs in the future.

The sample size of the study population was the main limitation of the study. While performing subgroup analysis, the small sample size limited the statistical analysis. The ultrasound, which we used during the study did not have an automatic measurement software program, so CIMT was measured manually. Measurements were performed by the same expert radiologist to exclude examiner bias. However, CIMT measurements could be performed by two or more radiologists to verify interobserver agreement in future studies.

Conclusion

The potential influence of other comorbidities might have an impact on the development of CVDs in vitiligo patients. This study focused on subjects, both controls and vitiligo patients, who do not have any risk factors for possible CVDs, such as smoking, obesity, hyperlipidemia, renal failure, cerebrovascular disease, other autoimmune diseases, etc. This was the main factor that distinguished our study from other studies in the literature. Therefore, the statistically significant increase in carotid artery intima-media thickness in vitiligo patients revealed by our study makes an important contribution to the literature in terms of vitiligo being a predisposing factor for subclinical atherosclerosis. Additionally, with the support of further large sample studies, a follow-up procedure should be performed in vitiligo patients for the prevention and treatment of cardiovascular diseases. To detect the risk of subclinical atherosclerosis, carotid artery ultrasonography which is a radiation-free, fast and inexpensive imaging method, can be used periodically in vitiligo patients.

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