

# Vitiligo and Rise in Blood Pressure – a Case–Control Study in a Referral Dermatology Clinic in Southern Iran

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Mohammad Reza Namazi<sup>1</sup>  
Shekoofe Rouhani<sup>2</sup>  
Alireza Moarref<sup>2</sup>  
Mahsa Kiani<sup>1</sup>  
Seyed Sajjad Tabei<sup>3</sup>  
Maryam Hadibarhaghtalab<sup>1</sup>

<sup>1</sup>Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; <sup>2</sup>Cardiology Department, Shiraz University of Medical Sciences, Shiraz, Iran; <sup>3</sup>Student Research Committee, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

**Purpose:** Vitiligo is an acquired hypopigmentation condition in which well-defined macules can develop virtually everywhere on the patients' skin. This analytic case–control study was conducted in Faghihi Hospital outpatient dermatology clinic, affiliated to Shiraz University of Medical Sciences, southern Iran from June to September 2019. Furthermore, we studied the relationship of hypertension with activity, age of onset, duration, affected body surface area and type of vitiligo.

**Patients and Methods:** In the current case–control study, 166 individuals were enrolled in total (the case group was comprised of 83 vitiligo patients and 83 individuals acted as control group). The case group was made up of vitiligo patients (both segmental and non-segmental) between 20 and 50 years of age, no prior history of systemic disease and other hypopigmentation disorders, while individuals with any form of dermatologic findings were excluded from the control group. Individuals aged younger than 20 years old or older than 50, having a dermatologic disease other than vitiligo, being afflicted with the diseases which may lead to secondary hypertension, pregnancy, taking substances, and medication which can lead to hypertension were chosen as the exclusion criteria in this study.

**Results:** Data obtained from our study revealed that vitiligo patients had a higher prevalence of essential hypertension diagnosis than the control group ( $P=0.040$ ). Also, no significant relationship was found between patients' age at the first lesion appearance ( $P=0.856$ ), duration of vitiligo involvement ( $P=0.497$ ), and percentage of vitiligo involvement ( $P=0.681$ ) with hypertension.

**Conclusion:** According to our results, vitiligo patients were more susceptible to hypertension while no association could be found between characteristics of the disease and rise in blood pressure.

**Keywords:** vitiligo, hypertension, catecholamines, metabolic syndrome

## Introduction

Vitiligo is a prevalent acquired pigmentation disorder which is characterized by development of well-defined macules which are ubiquitously found on patients' skin. According to skin biopsies, epidermal melanocytes are diminished in vitiligo patients.<sup>1–3</sup>

Prevalence of vitiligo in males and females is virtually the same. While, There is no preponderance based on specific race, ethnicity or socioeconomic group, it can occur across every age group and the peak of incidence is in the second and third decades of life.<sup>4,5</sup>

Correspondence: Maryam Hadibarhaghtalab  
Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran  
Tel +98 917 101 7912  
Email Maryam\_hadibarhaghtalab@yahoo.com

The exact cause of vitiligo is still unknown, however there are several hypotheses for etiology of vitiligo, such as genetic, autoimmune, neural, biochemical, oxidative stress, viral infection, and melanocyte detachment mechanisms.<sup>3,6,7</sup>

Sympathetic nervous system disturbance could contribute to vitiligo pathogenesis. Excess release of catecholamines can result in melanocyte destruction by two mechanisms: direct cytotoxic effect and indirect effect by stimulation of alpha adrenergic receptors in skin blood vessels which leads to vasoconstriction, hypoxia and increasing free radicals that can be harmful to melanocytes.<sup>3</sup>

The Vitiligo Global Issue Consensus Conference has suggested a detailed classification for vitiligo in 2012, which categorized vitiligo into two types: segmental vitiligo (SV) and non-segmental vitiligo (NSV).<sup>8</sup>

Vitiligo is associated with several diseases, including uveitis, various autoimmune diseases such as autoimmune thyroid diseases, pernicious anemia, Addison's disease, systemic lupus erythematosus, rheumatoid arthritis, and insulin-dependent diabetes. Also, there appears to be an association with dermatological autoimmune diseases like alopecia areata, lichen sclerosis, and halo nevi. Besides, a significant majority of vitiligo patients experience stress and psychological disorders that often require psychiatric and psychological interventions.<sup>9</sup>

Moreover, one of the mechanisms which has been proposed for vitiligo is excess catecholamine release.<sup>3</sup> The rise in sympathetic efflux is one of the influencing factors for hypertension too and researches have shown that hypertensive people have higher levels of catecholamines than normotensive ones.<sup>10</sup>

Although vitiligo has association with several diseases, there has not been adequate research regarding the prevalence of hypertension in vitiligo patients. As higher levels of catecholamines are detected in both vitiligo and hypertensive patients, the aim of this study is to determine the association between vitiligo and hypertension.

## Patients and Methods

This analytic case-control study was conducted in Faghihi Hospital outpatient dermatology department, a referral center for vitiligo patients, affiliated to Shiraz University of Medical Sciences in Fars Province, southern Iran from June to September 2019. The review board of Shiraz University of Medical Sciences approved the study and all recruited patients filled in the informed consent form.

Participants were divided into two groups of patients and controls; group A

& group B respectively. Group A were patients 20 to 50 years of age with any type of vitiligo selected among those referred to Faghihi hospital dermatology clinic. On the other hand, individuals without vitiligo or any other dermatologic condition, systemic diseases and hypopigmented lesions comprised Group B, the control group, that was chosen from healthy individuals. Furthermore, we chose group B to be similar to group A with regards to age, sex and body mass index (BMI). The participants of each group were categorized into four subgroups regarding BMI; less than 18.5 as underweight,  $18.5 < \text{BMI} < 24.9$  as normal,  $25 < \text{BMI} < 29.9$  as overweight, and  $\text{BMI} > 30$  as obese. In order to obtain the final study population, 40 individuals (20 from group A and 20 from group B) were selected as an initial pilot sample. Subsequently, the final sample population was estimated according to the sample size formula in SPSS software as 166 persons (83 persons in group A and 83 persons in group B).

Individuals aged younger than 20 years old or older than 50, having a dermatologic disease other than vitiligo, being afflicted with the diseases which may lead to secondary hypertension, pregnancy, taking substances, and medication which can lead to hypertension were chosen as the exclusion criteria in this study.

The patients group (group A), was further categorized based on their vitiligo type into segmental vitiligo and non-segmental vitiligo. In order to assess percentage of vitiligo involvement, we used the vitiligo area scoring index (VASI). In this scoring system every hand unit (palm plus the volar surface of all digits) is 1% of total body surface area.<sup>11</sup> Also disease activity was determined by new hypo-pigmented lesions appearance or extension of the previous lesions in the previous 3 months. Apart from hypo-pigmented lesions, clinical activity features also consisted of trichrome lesions, quadrichrome lesions and presence of vitiligo ponctué lesions (confetti-like depigmented macules) and lesions resulting from the Koebner phenomenon.

We designed a data collection form that consisted of age, sex, BMI, vitiligo type (segmental versus non-segmental), disease activity, vitiligo involvement percentage and patients' age at the first lesion appearance. After informing the study participants about our study and by their informed consent we collected our required data in accordance with the declaration of Helsinki ethical guidelines.

Blood pressure was measured in two separate visits with a 1-week interval and documented in our data collecting forms. In the first visit blood pressure was checked from both arms and if blood pressure was higher in either of the arms, the second visit blood pressure was checked from that arm. Altogether, we provided a standard condition for blood pressure measurement as much as possible. We calculated the mean blood pressure between the first and second visit and considered systolic blood pressure higher than 130 mmHg and diastolic blood pressure higher than 80 mmHg as hypertension.<sup>12</sup> In line with the American Heart Association's recommendations, patients were advised to refrain from coffee and caffeine derivatives consumption, exercise and smoking for 30 minutes prior to blood pressure measurement. Furthermore, patients were seated in a relaxed position, with feet flat on the floor for 5 minutes before measurement.<sup>13</sup> Due to limited visiting hours, all measurements were taken in the evening.

Those whom were considered as hypertensive were evaluated in a Para clinical setting for ruling out the secondary causes of hypertension. These tests were: TSH for ruling out hyper or hypothyroidism, potassium for hypokalemia and hyperaldosteronism, FBS for DM, BUN and Cr and urine analysis for renal involvement. According to the test results, no one was excluded from the study. Therefore participants were deemed to be essential hypertensives with no specific identifiable cause.

For data analysis we used SPSS software and due to non-normality of our data we used the Mann-Whitney test.

## Results

This case-control study included 166 participants with a case-to-control ratio of 1:1 with 83 patients constituting the case group (group A) and 83 individuals as the control group (group B). Gender distribution was the same in both groups (Females: 60.24%, males: 39.76%). Mean age was 26.33±9.21 years for females and 33.74±8.86 years for males. In this survey six participants were underweight (7.22%), 39 were normal (46.98%), 31 were overweight (37.34%), and 7 participants were obese (8.43%). These characteristics were identical in both case and control groups.

Seventy individuals (84.30%) in group B and 59 (71.10%) in group A had normal blood pressure, whereas 13 (15.70%) in group B and 24 (28.90%) in group A were diagnosed with hypertension. Results obtained from statistical analysis showed that the patients group had a significantly

higher hypertensive population rather than the control group ( $P=0.040$ ) (Table 1).

According to statistical analysis results, there was no significant relationship between type of Vitiligo and hypertension. Moreover, we did not find a meaningful relationship between hypertension and disease activity (Table 2).

Our study also revealed that patients' age at the first vitiligo lesion appearance, duration of the disease and percentage of vitiligo involvement had no significant statistical impact on hypertension diagnosis in the patients' group (Table 3).

## Discussion

In this case-control study we investigated the association between hypertension and vitiligo. We also studied the relationship of hypertension with activity, age of onset, duration, affected body surface area and type of vitiligo. According to our results, there was no meaningful association between hypertension and vitiligo, despite the increased prevalence of hypertension in vitiligo patients in comparison with the normal population.

Higher levels of catecholamines have been detected at the onset of vitiligo and in the active phase of the disease. This could be related to an increase in emotional stress at these phases.<sup>14</sup> One of the mechanisms for hypertension is the rise in sympathetic efflux leading to a higher level of catecholamines in hypertensive patients.<sup>10</sup> We suggest that increase in plasma catecholamine levels in vitiligo patients may lead to higher predisposition to hypertension in these patients.

**Table 1** Relationship Between Vitiligo and Hypertension

	Group A	Group B	P-value
Normal blood pressure	(%10/71) 59	(%30/84) 70	0.040
Hypertension	(%90/28) 24	(%70/15) 13	

**Table 2** Relationship Between Hypertension and Type of Vitiligo, and Relationship Between Hypertension and Vitiligo Activity

	Type of Vitiligo		Disease Activity	
	Segmental	Non Segmental	Active	Inactive
Normotensive	6 (10.20%)	53 (83.80%)	27 (45.80%)	32 (54.20%)
Hypertensive	2 (8.30%)	22 (91.70%)	16 (66.66%)	8 (33.33%)
P-value	0.797		0.084	

**Table 3** Relationship of Hypertension with Patients' Age at the First Lesion Appearance, Duration of Vitiligo Involvement and Percentage of Vitiligo Involvement

		Mean (Min – Max)	P-value
Patients' age at the first lesion appearance	normotensive	22.33±10.58 (5–48)	0.856
	hypertensive	22.79±11.47 (6–45)	
Duration of vitiligo involvement	normotensive	10.54±8.78 (1–39)	0.497
	hypertensive	11.91±9.17 (1–40)	
Percentage of vitiligo involvement	normotensive	7.5±12.96 (0.5%–50%)	0.681
	hypertensive	5.68±9.83 (0.5%–50%)	

Vitiligo is a systemic disease with several mechanisms proposed for its pathogenesis, all of which can be deemed as corresponding mechanisms for other diseases.<sup>15–17</sup> A large variety of vitiligo comorbidities are autoimmune diseases like autoimmune thyroid diseases, pernicious anemia, Addison's disease, systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes, alopecia areata, lichen sclerosis, halo melanocyte nevi.<sup>9</sup> In addition to autoimmune diseases, vitiligo can be associated with other chronic diseases. Al Hossein et al<sup>18</sup> reported higher prevalence of hypothyroidism, diabetes, dyslipidemia, obesity and kidney injury in vitiligo patients. They also studied the association between vitiligo and hypertension. In contrast to our study they did not find any significant relationship between these two diseases. This discrepancy maybe due to the target age range of 20 to 50 years in our study in which hypertension is more prevalent. Hitherto there have been few articles regarding the association of vitiligo and metabolic syndrome with focus on the association of hypertension as one of the aspects of metabolic syndrome with vitiligo.<sup>17,19–21</sup> Atas and Gonul,<sup>19</sup> designed a case control study to investigate association of Vitiligo and metabolic syndrome. According to their results metabolic syndrome was more prevalent in vitiligo patients. They studied all parameters of metabolic syndrome in patients and controls. They found higher values of fasting blood glucose, triglyceride, high density lipoprotein and systolic blood pressure in their cases in comparison to their controls but without statistical significance. Besides diastolic blood pressure, treatment for diabetes, treatment for hypertension and waist circumference in their cases were neither higher than the controls nor had statistical significance. They compared the prevalence of metabolic syndrome with different characteristics of vitiligo (disease activity, body surface area involvement, type of vitiligo, duration of the disease, and concluded that active vitiligo, segmental type, long duration of the disease and more percentage of involvement is

associated with more prevalence of metabolic syndrome.<sup>19</sup> In contrast we did not find any association between vitiligo characteristics and hypertension. Sharma et al<sup>20</sup> also reported a significant association between vitiligo and metabolic syndrome, among the five parameters of metabolic syndrome they did not find significant differences between cases and control for blood pressure and waist circumference. They also claimed that severity of the disease does not raise the chance of metabolic syndrome.<sup>20</sup> These conflicts regarding the association of metabolic syndrome and its parameters with the characteristics of vitiligo need more studies with larger series to prove this possible association.

It is worthy of note that the results of an Indian study by Singh et al<sup>21</sup> was in concordance with ours. Similar to studies conducted by Atas and Gonul<sup>19</sup> and Sharma et al,<sup>20</sup> they worked on prevalence of metabolic syndrome in vitiligo patients. Among the parameters of metabolic syndrome hypertension was significantly more prevalent in vitiligo patients in this survey. Singh et al<sup>22</sup> also investigated the prevalence of atherosclerosis in vitiligo patients and proposed that vitiligo patients are at higher risk for atherosclerosis than the normal population. We propose that due to higher levels of catecholamines in vitiligo and hypertension, hypertension is more prevalent in vitiligo patients. In previous studies it was suggested that due to anti-inflammatory and anti oxidative effects of melanin in adipose tissue, disturbance in melanin production will result in metabolic syndrome.<sup>15,23,24</sup> Therefore this new hypothesis about association of vitiligo and hypertension due to catecholamines excess in both diseases, will be a beginning for more studies in this field. However, it is of utmost importance to recognize that vitiligo is a multifactorial disease, therefore any systemic feature which is diagnosed pertinent to vitiligo, may have a myriad of etiologies which its relationship with vitiligo may have not yet been fully understood. The pathogenesis of vitiligo could be explained by different major hypotheses.



The autoimmune hypothesis elucidates the role of different immune markers such as CD4 and CD8T cells as well as CD68 macrophages. The neurochemical hypothesis demonstrates the role of catecholamines and other molecules in vitiligo development.<sup>25</sup> Although there are possible overlaps in different hypotheses and theories for pathogenesis, in this study we hypothesized the relationship of hypertension and vitiligo on elevated catecholamine levels. Therefore, the focus on neurochemical pathways has been emphasized more than other theories in our study. It is worthy of note that this does not rule out other pathogenic factors as causative agents of vitiligo. In this case, the relationship of vitiligo and hypertension could not be specifically related to a certain biochemical pathway or autoimmune markers as the scope of studies in this regard have been limited. Hitherto, no proven chemical pathway has been recognized as a hypertension pathogenesis factor in vitiligo patients and examples such as stress-induced catecholamine release and sympathetic efflux remain as hypothetical etiologies.

In our study we did not examine other factors that may affect blood pressure like nutrition and stress level in cases and controls. Moreover, we did not consider white coat hypertension, which could be considered as a limiting factor in our study. So in future studies considering other factors that may affect blood pressure, home blood pressure monitoring or holter monitoring may yield more accurate results.

Larger cohort studies on association of vitiligo and hypertension, preferably metabolic syndrome, in the future with a lengthier follow up will possibly produce more detailed information. If such studies confirm this association, earlier metabolic syndrome screening with shorter intervals in vitiligo patients will help us diagnose metabolic syndrome much sooner and by means of medical intervention, we will be enabled to prevent cardiovascular accidents.

## Conclusion

In conclusion, vitiligo is a polygenic, multimodal, and multifactorial disease, in which stress may be one of the contributing factors. We found that vitiligo patients were diagnosed with hypertension more often than the normal population. However, no significant association between hypertension and patients' age at the first vitiligo lesion appearance, duration of the disease and percentage of vitiligo involvement existed.

## Disclosure

The authors report no conflicts of interest in this work.

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