



ASSOCIATION OF VITILIGO DISEASE ACTIVITY AND SEVERITY WITH METABOLIC SYNDROME: A CASE-CONTROL STUDY

Dermatology

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ABSTRACT

Background: Vitiligo is an acquired depigmenting disorder. Shared mechanisms such as oxidative stress and immune dysregulation may link vitiligo with metabolic syndrome (MetS). **Aims:** To evaluate association between vitiligo and MetS and examine its relationship with disease activity, severity, and duration. **Methods:** In this prospective case-control study, 126 adult vitiligo patients and 126 controls were enrolled. Clinical data and metabolic parameters were recorded. Disease activity and severity were assessed using VIDA and VASI scores. MetS was diagnosed using IDF and NCEP ATP III criteria. **Results:** MetS was significantly more prevalent in vitiligo patients than controls by both IDF (33.3% vs 13.5%; $p < 0.001$) and NCEP ATP III criteria (38.1% vs 16.7%; $p < 0.001$). Patients had higher systolic blood pressure and triglyceride levels. MetS was associated with greater disease severity using both criteria and with higher disease activity using NCEP ATP III criteria only. No association was found with disease duration or clinical subtype. **Conclusion:** Vitiligo is significantly associated with MetS, particularly in active and extensive disease. Routine metabolic screening may be warranted to support comprehensive patient care.

KEYWORDS

vitiligo, metabolic syndrome, oxidative stress, VIDA, VASI

INTRODUCTION

Vitiligo is a common acquired depigmenting disorder characterised by milky-white macules and patches resulting from the loss of functional melanocytes. Although benign, its conspicuous appearance and associated social stigma significantly impair quality of life.^[1] The etiopathogenesis of vitiligo is multifactorial, involving genetic susceptibility, immune dysregulation, oxidative stress, and environmental triggers.^[2]

Metabolic syndrome (MetS) is a clustering of cardiometabolic abnormalities—including central obesity, dyslipidemia, hypertension, and impaired glucose metabolism—that predisposes individuals to cardiovascular disease, diabetes, and stroke.^[3] Increasingly, vitiligo is recognised not merely as a cutaneous disorder but as a condition with systemic inflammatory underpinnings. Shared mechanisms, such as chronic oxidative stress and pro-inflammatory cytokines (e.g., TNF- α , IL-6), are central to both melanocyte destruction in vitiligo and the development of insulin resistance and metabolic dysfunction, providing a plausible biological link between the two conditions.^[4]

Despite this plausibility, evidence for an association between vitiligo and MetS remains inconsistent. While several studies report a higher prevalence of MetS among vitiligo patients, others fail to demonstrate a significant relationship. These discrepancies may stem from differences in study design, diagnostic criteria, ethnicity, and background population risk. As vitiligo is often perceived primarily as a cosmetic concern, its potential systemic comorbidities may be under-recognised in clinical practice.

Clarifying this association is crucial for the early identification of cardiovascular risk and the holistic management of vitiligo patients. Given that variability in MetS diagnostic criteria contributes significantly to inconsistent findings across studies, we employed both the IDF and NCEP ATP III definitions to allow for direct comparison and a more robust assessment.

In this context, the present study was conducted with the following objectives: (1) to investigate the association between vitiligo and MetS by comparing its prevalence in vitiligo patients against age- and sex-matched controls, using both IDF and NCEP ATP III criteria; (2) to compare key metabolic parameters (including fasting plasma glucose, blood pressure, waist circumference, HDL cholesterol and serum triglycerides) between the two groups; and (3) to evaluate the relationship between MetS and vitiligo disease activity, severity, and duration

Study Design and Setting

This prospective case-control study was conducted in the Dermatology Outpatient Department of a tertiary care teaching hospital from October 2022 to March 2024 (18 months). The study protocol was approved by the Institutional Human Ethics Committee (Registration No. IHEC/22/IN/SRPG040). Written informed consent was obtained from all participants, and data confidentiality was strictly maintained.

Participants

We enrolled adult patients (>18 years) of either gender with clinically diagnosed vitiligo, confirmed by Wood's lamp examination, irrespective of their MetS status. Age- and sex-matched healthy volunteers without vitiligo served as controls. Exclusion criteria included pregnant and postpartum females, immunocompromised individuals, and patients receiving medications known to affect metabolic parameters (atypical antipsychotics, corticosteroids, oral contraceptive pills, tacrolimus, cyclosporine, or thiazolidinediones).

Sample Size Calculation

An a priori sample size calculation was performed using Epitools epidemiological calculators. Based on a recent Indian study reporting a 5.37-fold increased odds of MetS in vitiligo patients (95% CI: 3.1-9.3)[5], we selected a more conservative target odds ratio of 3.5. To ensure robust power across potential population variations, a conservative control prevalence estimate of 5% was used. With 80% power and 95% confidence level (two-sided $\alpha = 0.05$), this calculation yielded 126 participants per group (total N=252). The observed effect size in our study exceeded these conservative assumptions.

Study procedure

Detailed demographic and clinical histories were recorded, including vitiligo onset, duration, progression, comorbidities, addictions, and drug history. Blood pressure was measured as the average of two readings taken five minutes apart after a 15-minute rest. Waist circumference was measured in the erect posture at the end of normal expiration, midway between the inferior margin of the last palpable rib and the iliac crest, using a non-stretchable tape. After 12 hours of fasting, venous blood samples were collected for estimation of fasting blood glucose, serum triglycerides, and HDL cholesterol using an Erba CHEM-7 semi-automated analyser.

Vitiligo disease activity was evaluated using the Vitiligo Disease Activity (VIDA) score, a six-point scale based on patient-reported disease progression.[6] The score ranges from -1 to +4, where:

- +4: Active disease within the past 6 weeks

Methods:

- +3: Activity within the past 6 weeks to 3 months
- +2: Activity within the past 3–6 months
- +1: Activity within the past 6–12 months
- 0: Stable disease for more than 1 year
- -1: Stable disease with spontaneous repigmentation for more than 1 year

The severity of vitiligo was assessed using the Vitiligo Area Scoring Index (VASI). VASI quantifies disease extent by estimating the affected body surface area using hand units, where one hand unit (palm plus volar surface of all fingers) represents approximately 1% of the total body surface area. Assessment was performed across six body regions: head and neck, trunk, upper extremities, lower extremities, hands, and feet. For each region, the area of vitiligo was multiplied by the degree of depigmentation, graded as 0 (no depigmentation), 10%, 25%, 50%, 75%, 90%, or 100% (complete depigmentation). The total VASI score was calculated by summing the scores of all regions, with higher scores indicating greater disease severity.^[7]

The duration of vitiligo was determined based on the patient's reported history and defined as the time interval (in years) between the onset of the first depigmented lesion and the date of clinical evaluation. Patients were assisted in recalling the onset of their disease using landmark events when necessary to improve recall accuracy. For analytical purposes, disease duration was categorised into two groups: <5 years and ≥5 years, consistent with prior studies assessing the impact of chronicity on systemic comorbidities.^[5]

MetS was identified using the International Diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria.^[3,8] (Boxes 1 and 2)

Box 1: International Diabetes Federation criteria for MetS

Central obesity (mandatory criterion):
Ethnicity-specific waist circumference cut-offs (For South Asians: Male ≥90 cm; Female ≥80 cm)

Plus Any Two of the Following

Raised Triglycerides
≥150 mg/dL (1.7 mmol/L) or receiving treatment for hypertriglyceridemia

Reduced HDL Cholesterol
<40 mg/dL (1.03 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females, or receiving treatment for low HDL cholesterol

Raised Blood Pressure
Systolic ≥130 mmHg and/or diastolic ≥85 mmHg, or treatment for previously diagnosed hypertension

Raised Fasting Plasma Glucose
≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes mellitus

Box 2: Modified National Cholesterol Education Program ATP III criteria for MetS

MetS is diagnosed when any three or more of the following criteria are present:

Abdominal Obesity
Waist circumference >102 cm in men and >88 cm in women

Hypertriglyceridemia
Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or ongoing treatment for elevated triglycerides

Low HDL Cholesterol
<40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, or receiving therapy for low HDL cholesterol

Elevated Blood Pressure
Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, or treatment for previously diagnosed hypertension

Impaired Fasting Glycemia
Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed diabetes mellitus

Statistical analysis

Statistical analysis was performed using MS Excel 2021 and EPI Info

(CDC version 7). Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies/proportions. Associations were assessed using the chi-square test for categorical variables and the independent sample t-test for continuous variables, with a p-value <0.05 considered statistically significant.

Results:

Participant Demographics

A total of 252 participants were enrolled in the study, including 126 vitiligo patients (cases) and 126 age- and sex-matched controls. Both groups comprised 72 females (57.14%) and 54 males (42.86%), yielding a female-to-male ratio of 1.33:1. The mean age of participants was 45.87 years (SD = 16.78) in both groups. The most common age group was 21–30 years (19.84%), followed by 31–40 years (19.05%).

Vitiligo characteristics

Among cases, 45 patients (35.71%) reported a positive family history of vitiligo. Disease onset occurred before 30 years of age in 67 cases (53.18%) and before 20 years in 28 cases (22.23%), with the highest frequency of onset in the 20–29-year age group (30.95%). Vitiligo vulgaris was the most common clinical type (49.21%), followed by acrofacial vitiligo (11.11%). The head and neck were the most frequently involved site (28.22%), followed by lower extremities (21.47%) and trunk (19.02%). Disease activity assessment showed that VIDA score +4 was the most common (26.19%), followed by VIDA score 0 (22.22%). VASI scores were distributed across all severity categories, with an equal proportion of patients in the higher severity groups.

Prevalence of MetS

MetS was significantly more prevalent among vitiligo patients than controls. As per IDF criteria, MetS was present in 33.3% of cases compared to 13.5% of controls (p<0.001). Using NCEP ATP III criteria, 38.1% of cases and 16.7% of controls fulfilled the criteria for MetS (p<0.001). Gender-wise comparison did not show a statistically significant difference in the prevalence of MetS between males and females within either group using either definition. (Figures 1 & 2)

Figure 1: Prevalence of MetS among vitiligo patients and controls according to IDF criteria.

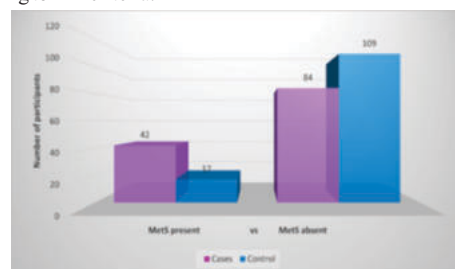
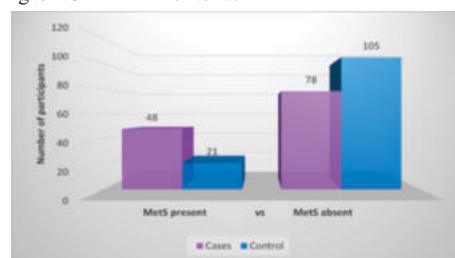


Figure 2: Prevalence of MetS among vitiligo patients and controls according to NCEP ATP III criteria.



Individual metabolic parameters are highlighted in Table 1.

Table 1: Comparison of individual metabolic parameters between vitiligo patients and controls

Variable	Case Mean ± SD (n=126)	Control Mean ± SD (n=126)	p-value
Systolic BP (mm Hg)	126.91 ± 14.39	122.70 ± 11.10	0.01
Diastolic BP (mm Hg)	81.52 ± 7.89	80.65 ± 6.46	0.339
Waist circumference(cm)	90.23 ± 11.80	89.75 ± 10.20	0.73

Fasting Plasma Glucose (mg/dL)	107.48 ± 31.74	105.19 ± 45.24	0.642
S. Triglyceride level (mg/dL)	134.77 ± 64.93	115.97 ± 53.07	0.012
S.HDL (mg/dL)	45.70 ± 10.08	44.24 ± 10.69	0.266

Association of MetS with Clinical and Disease Characteristics

MetS did not show a significant association with addiction patterns, clinical type of vitiligo, or site of involvement using either IDF or NCEP ATP III criteria ($p>0.05$). Disease activity assessed by VIDA score showed no significant association with MetS using IDF criteria ($p=0.42$); however, a significant association was observed using NCEP ATP III criteria ($p=0.025$), with higher VIDA scores (+3 and +4) demonstrating a greater prevalence of MetS. (Table 2) Disease severity assessed by VASI score showed a statistically significant association with MetS using both IDF ($p=0.007$) and NCEP ATP III criteria ($p=0.012$), with the highest prevalence observed in patients with VASI scores between 3.86 and 100. (Table 3) (Figure 3) Duration of vitiligo (<5 years vs ≥ 5 years) was not significantly associated with MetS using either definition ($p>0.05$). (Table 4)

Figure 3: Distribution of MetS across Vitiligo Area Scoring Index (VASI) categories.

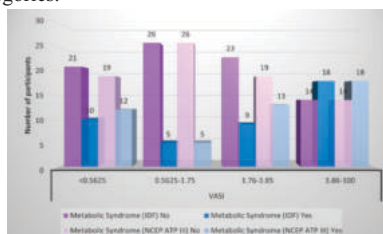


Table 2: Association between Vitiligo Disease Activity (VIDA) score and MetS according to IDF and NCEP ATP III criteria

VIDA score	MetS IDF		p-value	MetS NCEP ATP III		p-value
	Present	Absent		Present	Absent	
-1, 0	11 (26.2%)	26 (31%)	0.42	10 (20.8%)	27 (34.6%)	0.025
+1, +2	12 (28.6%)	30 (36%)		13 (27.1%)	29 (37.2%)	
+3, +4	19 (45.2%)	28 (33%)		25 (52.1%)	22 (28.2%)	

Table 3: Association between Vitiligo Area Scoring Index (VASI) and MetS according to IDF and NCEP ATP III criteria

VASI score	MetS IDF		p-value	MetS NCEP ATP III		p-value
	Absent	Present		Absent	Present	
<0.5625	21 (25.0%)	10 (23.8%)	0.007	19 (24.4%)	12 (25.0%)	0.012
0.5625-1.75	26 (31.0%)	5 (11.9%)		26 (33.3%)	5 (10.4%)	
1.76-3.85	23 (27.4%)	9 (21.4%)		19 (24.4%)	13 (27.1%)	
3.86-100	14 (16.6%)	18 (42.9%)		14 (17.9%)	18 (37.5%)	

Table 4: Association between duration of vitiligo (<5 years vs ≥ 5 years) and MetS according to IDF and NCEP ATP III criteria

	MetS IDF		p-value	MetS NCEP ATP III		p-value
	Present	Absent		Present	Absent	
< 5 years	14	38	0.201	17	35	0.370
≥ 5 years	28	46		30	44	

DISCUSSION:

Vitiligo is an acquired depigmenting disorder resulting from the loss of functional melanocytes.^[9] MetS represents a cluster of cardiometabolic risk factors predisposing to cardiovascular disease, diabetes mellitus, and stroke.^[10] Increasingly, vitiligo is being viewed as a systemic condition rather than a disease limited to the skin. Reduced melanogenesis and a lower melanocyte count may diminish the anti-inflammatory and antioxidant functions of melanocytes, leading to increased oxidative stress and thereby contributing to the development of MetS.^[11,12]

The demographic profile of our cohort was comparable to previously published studies. The mean age of participants was similar to that reported by Atas et al.^[13] and Sharma et al.^[14], while slightly higher than that observed by Sallam et al.^[15] This variation likely reflects population differences and healthcare-seeking behaviour. Female predominance, as seen in our study, has also been reported by Bathina et al., Sallam et al., and Atas et al.^[11,13,15] Although vitiligo itself has no inherent gender predisposition,^[16] sociocultural factors in India may lead to higher clinical reporting among females. Additionally, autoimmune diseases are known to be more prevalent in women. Conversely, Sharma et al.^[14] reported male predominance, attributing this to sociocultural barriers limiting healthcare access for women unless cosmetically significant areas are involved.

A positive family history was observed in 35.71% of cases, slightly higher than the 20–30% reported by Spritz et al.,^[17] reinforcing the role of genetic susceptibility. Early onset was common, with more than half of patients developing vitiligo before 30 years of age, consistent with Taieb et al., who reported onset before 20 years in nearly half of patients.^[9]

No significant difference in addiction patterns was observed between cases and controls. Interestingly, alcohol and nicotine use were more common among controls, contrasting with findings by Tanacan et al., who reported higher alcohol consumption among vitiligo patients.^[18] Vitiligo vulgaris was the most frequent subtype, similar to observations by Bathina et al.^[11]

A key finding of this study is the significantly higher prevalence of MetS among vitiligo patients using both IDF and NCEP ATP III criteria. This association aligns with multiple studies by Bathina et al., Varma et al., Tanacan et al., and Atas et al.^[11,13,18,19] However, Rashed et al. and Sallam et al. did not observe a significant association.^[15,20] A systematic review and meta-analysis including six studies similarly reported no significant overall association between vitiligo and MetS ($p=0.01$), though fasting glycemia and diastolic blood pressure were significantly higher in cases.^[21] (Table 5)

Table 5: Comparison of the prevalence of MetS in vitiligo patients across published studies

MetS	Year	Place	Criteria	Cases	Control	p-value
Present study	2024	Vadodara	IDF	33.33 %	13.50%	<0.01
			NCEP ATP III	38.10 %	16.70%	<0.01
Bathina et al. ^[11]	2024	Andhra Pradesh	Harmonization criteria	36%	24.20%	0.015
Thakur et al. ^[5]	2024	Himachal Pradesh	NCEP ATP III	49.30 %	15.30%	<0.001
Varma et al. ^[19]	2021	Madhya Pradesh	NCEP ATP III	37.50 %	15%	0.022
Tanacan et al. ^[18]	2020	Turkey	IDF	40%	26.50%	0.011
			NCEP ATP III	37.40 %	19.40%	<0.001
Rashed et al. ^[20]	2019	Egypt	NCEP ATP III	35.60 %	33.30%	0.779
Atas et al. ^[13]	2017	Turkey	NCEP ATP III	38.10 %	21.50%	0.04
Sallam et al. ^[15]	2017	Egypt	Harmonization criteria	20.60 %	30.30%	0.084
Sharma et al. ^[14]	2016	Pune	NCEP ATP III	24%	12%	0.027

These conflicting findings may be explained by differences in ethnicity, background cardiometabolic risk, diagnostic criteria, and study design. Indian studies—including those by Bathina et al., Thakur et al., Varma et al., Sharma et al., and the present study—consistently demonstrate a significant association, whereas Egyptian studies do not. Publication bias may further contribute to this heterogeneity.^[5,11,14,15,19,20]

Female predominance of MetS among vitiligo patients in our study is consistent with Thakur et al., Bathina et al., and Atas et al., whereas Rashed et al. reported higher prevalence among males. Although

vitiligo vulgaris showed the highest absolute prevalence of MetS, the association was not statistically significant, echoing findings by Thakur et al.^[5,11,13,20]

Disease activity emerged as an important correlate. Higher VIDA scores were associated with increased MetS prevalence, particularly with scores of 3 and 4, consistent with findings by Thakur et al., Bathina et al., Tanacan et al., and Ataş et al.^[5,11,13,18] In contrast, Rashed et al. reported a greater prevalence in non-progressive disease, while Sharma et al. did not find any association.^[14,20] Similarly, higher VASI scores were associated with MetS in our study, supporting the role of disease severity as a marker of systemic inflammation.

No significant association was observed between disease duration and MetS, consistent with Bathina et al., although Ataş et al. and Varma et al. reported a higher prevalence with longer disease duration.^[11,13,19] This discrepancy may reflect the influence of disease activity and severity rather than duration alone.

Vitiligo is characterised by complex genetic, autoimmune, inflammatory, and oxidative mechanisms that may predispose to systemic comorbidities.^[22,23] Shared genetic susceptibility loci, including ACE, catalase, IFIH1, SH2B3, IKZF4, CASP7, BTNL2, IL2RA, and ZMIZ1, link vitiligo with diabetes and metabolic disorders.^[15] Pro-inflammatory cytokines such as TNF- α , IL-1, and IL-6 further promote insulin resistance and atherosclerosis.^[12,24]

Among metabolic parameters, triglyceride levels were significantly elevated in cases, consistent with Ataş et al. and Thakur et al.^[5,13] In contrast, fasting plasma glucose and HDL cholesterol did not differ significantly, possibly reflecting Gujarat's high background prevalence of dysglycemia and metabolic risk. Similar variability has been reported across studies^[12,25,26]

Higher systolic blood pressure in vitiligo patients supports a possible link with autonomic dysfunction and increased sympathetic activity.^[5,27] White adipose tissue dysfunction and altered adipokine secretion further contribute to metabolic derangements.^[28] Emerging evidence suggests that melanocytes in adipose tissue play a role in oxidative defence, and their loss may exacerbate reactive oxygen species-mediated damage^[12,24,29,30]

Therapeutically, narrowband UV-B phototherapy has been associated with reduced cardiovascular risk, though causality remains uncertain.^[31] Experimental approaches targeting melanogenesis and inflammation, including alpha-MSH analogues and statins, warrant further investigation.^[24,32]

From a clinical perspective, dermatologists play a crucial role in identifying vitiligo patients at risk for MetS and facilitating early referral and intervention. A multidisciplinary approach addressing both cutaneous and systemic inflammation may improve long-term outcomes. Further longitudinal studies are required to clarify causality and therapeutic implications.

Limitations

This single-centre case-control study lacks long-term follow-up, limiting generalizability and causal inference. Advanced metabolic biomarkers were not measured due to cost constraints.

CONCLUSION

Our study demonstrated a significant association between vitiligo and metabolic syndrome, with higher prevalence among patients with greater disease activity and severity. Elevated systolic blood pressure and triglycerides were more frequent, indicating an adverse metabolic profile. These findings support routine metabolic screening in patients with active or extensive vitiligo, reinforcing the concept: "Look at the skin but think systemic."

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