Original Article

A Notorious Trio! Inflammation, Metabolic Syndrome and Vitiligo

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Abstract

Background: There is evidence to support that vitiligo is linked to metabolic syndrome (MS), confirming its systemic nature. However, the underlying pathogenic mechanisms remain unknown. **Objectives:** To reveal the possible association of MS with vitiligo. We also attempted to study the connection between some inflammatory markers and MS in vitiligo patients to evaluate their utility in predicting MS risk. **Materials and Methods:** The study included 100 vitiligo patients with an age range between 18 to 60 years and 100 controls with matched age, gender, and body mass index. All subjects were tested for MS components. Serum visceral adipose tissue-derived serine protease inhibitor (vaspin), fatty acid binding protein 4 (FABP4), vascular adhesion protein 1 (VAP-1), chitinase-3-like protein 1 (YKL-40), and high-sensitivity C-reactive protein (hs-CRP) were also measured. **Results:** Regarding MS, it was observed in 22.0% of vitiligo patients and 2.0% of control subjects ($P < 0.001$). Serum FABP4, VAP-1, YKL-40, and hs-CRP concentrations were higher in patients than in the control group ($P < 0.05$ each), and their levels showed high sensitivity and specificity to differentiate MS when using the receiver operating characteristic (ROC). Levels of these markers, except serum vaspin, were significantly positively correlated with lipid profile markers (except high-density lipoprotein cholesterol) and fasting blood glucose levels ($P < 0.05$ each). **Conclusion:** MS was more common in vitiligo patients. The levels of the biomarkers studied were significantly higher in vitiligo patients. Furthermore, their levels accurately predicted MS in vitiligo patients. According to current research, these markers may be useful in assessing MS risk in vitiligo patients. Extensive research, however, is required.

Keywords: *Inflammation, metabolic syndrome, vitiligo*

Introduction

Vitiligo is known to be a depigmenting skin disorder with a multifactorial etiology that not only affects the skin but also causes metabolic irregularities such as glucose and lipid abnormalities and metabolic syndrome (MS), confirming the disease's systemic nature.[1] It is believed that inflammation has a significant role in vitiligo etiology and its associated comorbidities like MS.[2] Adipose tissue's melanocytes may have not only anti-inflammatory capabilities but also the ability to reduce reactive oxygen species.[3] It has been postulated that metabolic problems could occur in vitiligo patients along with the decrease in melanocytes and melanogenesis in adipose tissue.[4] Adipokines are hormonal bioactive molecules secreted by adipose tissue causing chronic low-grade inflammation and interacting with numerous processes in various organs. Although the exact pathophysiology is unknown, dysregulated adipokine production or secretion could contribute to the development of MS.[5]

Visceral adipose tissue-derived serine protease inhibitor (vaspin) is an adipokine found in visceral and subcutaneous white adipose tissues of obese and diabetic patients and has been demonstrated to suppress the expression of inflammatory mediators.[6]

Adipocyte fatty acid-binding protein 4 (FABP4) is another adipokine produced primarily by adipocytes and can regulate some lipid-mediated activities such as oxidative stress and inflammation.[7] FABP4, mainly found in macrophages and adipocytes, has been shown to have a role in atherosclerosis and insulin resistance pathogenesis.[8]

Vascular adhesion protein 1 (VAP-1), a protein encoded by *AOC3* (amine oxidase copper-containing 3) gene, is an endothelial adhesion molecule with amine oxidase

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activity.[9] VAP-1's enzymatic activity is highly sensitive to semicarbazide (SCZ) inhibition; thus, it belongs to the SCZ-sensitive amine oxidase (SSAO) family. The involvement of VAP-1/SSAO in vascular illnesses is growing, mostly as a result of stimulation of leukocyte trafficking in inflammation and vascular injury.[10] In the arterial wall, VAP-1/SSAO produces hydrogen peroxide, aldehyde, and ammonium which contribute to advanced glycation end product production, lipid peroxidation, and protein cross-linking, which all activate endothelial cells and induce VAP-1 expression.[11]

Chitinase-3-like protein 1 (CHI3L1 or YKL-40) is a member of the mammalian chitinases family, which also includes 18-glycosyl hydrolases.[12] It is difficult to determine how YKL-40, obesity, morbid obesity, cardiovascular diseases (CVD), and MS are related. A serum triglyceride rise of 34% and a two-fold increase in ischemic stroke events incidence are linked to increased YKL-40 levels.[13]

High-sensitive C-reactive protein (hs-CRP) is a more sensitive version of CRP.[14] Previous research demonstrated that elevated hs-CRP levels are linked to MS and its various components.[15]

The connection between vitiligo and MS is being debated.[1] Many inflammatory cytokines, factors, and mediators involved in vitiligo have been linked to metabolic complications.[3] We tried to unravel the possible link between MS and vitiligo and assess the usefulness of some inflammatory biomarkers such as vaspin, FABP4, VAP-1, YKL-40, and hs-CRP in predicting the risk of MS in vitiligo patients.

Materials and Methods

Study population

The current case-control study involved 100 non-segmental vitiligo patients attending the dermatology clinic in Benha University Hospitals between December 2021 and June 2022, whose diagnosis was confirmed by Wood's light examination, and 100 age, sex, and body mass index (BMI)-matched apparently healthy control volunteers. The study was approved by the local ethics committee in accordance with the Declaration of Helsinki. All participants gave informed consent.

Any patient suffering from diabetes mellitus, thyroid dysfunction, polycystic ovary syndrome, and systemic inflammatory diseases such as psoriasis, alopecia, gallbladder disease, hypertension, liver or renal illness, heart disease, or cancer were excluded. Vitiligo patients on topical corticosteroids in the past three months and/or on systemic corticosteroids, other immunosuppressants, or medications that influence insulin metabolism in the past 6 months were excluded. Pregnant or breastfeeding women, smokers, and subjects with a BMI >30 kg/m^2 were excluded.

Methods

After a full medical history was taken, general and dermatological examinations were performed. The Vitiligo Area Severity Index (VASI) and Vitiligo Disease Activity (VIDA) scores were used to estimate disease severity and activity, respectively.[16,17] MS was screened in all participants using the current (2005) National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, updated by the American Heart Association/National Heart, Lung, and Blood Institute (NHLBI), that defined MS by the presence of three of the following criteria: abdominal circumference ≥102 cm in men and ≥88 cm in women, triglycerides (TG) ≥150 mg/dL, high-density lipoprotein cholesterol (HDL-c) <40 mg/dL in men and <50 mg/dL in women, blood pressure ≥130/85 mm Hg, fasting blood glucose (FBG) ≥100 mg/dL.[18] BMI >25 kg/m^2 was considered overweight and BMI ≥30 kg/m^2 was considered obesity as per the WHO definition.

Waist circumference (WC) was measured in centimetres using a non-extendable measuring tape placed at the umbilicus level. Quetelet's Index (weight in kilograms/height in metre^2) was used to calculate BMI. Blood pressure was measured in a sitting position once the patient was comfortable, and the average of three readings was taken as the actual readings.

Laboratory investigations

All participants were asked to consume a regular diet and avoid strenuous exercise during the 24 hours prior to blood sampling. After 12 hours of fasting, venous blood was taken in serum-separating vacutainer tubes. Serum levels of FBG were estimated after 8 hours of fasting. Total cholesterol (TC), TG, and HDL-c levels were measured by Biosystem A15 autoanalyzer (Biosystem, Spain). Friedwald's equation was used to calculate the level of low-density lipoprotein cholesterol (LDL-c) [LDL-c = TC - (TG/5 + HDL-c)]. This equation is applied if serum TG is <400 mg/dL. TC >220 mg/dL and/or TG >150 mg/dL were considered hyperlipidemia.[19]

Double-antibody sandwich enzyme-linked immunosorbent assays (ELISA) were used according to the manufacturer's instructions to assess serum levels of vaspin, FABP4, VAP-1, and YKL-40 (Cat #: 201-12-0922, 201-12-2037, 201-12-5450, and 201-12-2064, SunRedBio, China). To detect CRP levels below 0.3 mg/dL, hs-CRP was measured using Cardio Phase hs-CRP (Siemens Healthineers, Germany).

Statistical analysis

The obtained data were analyzed using SPSS Version 25.0. Chi-square (X^2) test was used to evaluate the relation between qualitative variables expressed as number and frequency. Parametric quantitative variables were

expressed as mean and standard deviation (SD) and tested by Student's t-test. Non-parametric quantitative variables were expressed as median and range and tested by Mann-Whitney U test. The correlation between quantitative variables was tested by Spearman correlation (*r*) analysis. The receiver operating characteristic (ROC) curve was used for determining the sensitivity and specificity of studied biomarkers, where the area under the ROC curve (AUC) defines the test accuracy. The biomarker is having excellent performance when the AUC ranges from 0.9 to 1, good between 0.8-0.9, fair between 0.7-0.8, poor between 0.6-0.7, and the test is failed when AUC is between 0.5 and 0.6.[20] A *P* value < 0.05 at a 95% confidence interval (CI) was considered significant.

Results

The mean age of 100 vitiligo patients who participated in the current study was 32.7 ± 13.0 years. They were 30 males and 70 females with a mean BMI of 26.4 ± 2.8 kg/m^2. Age, gender, and BMI-matched 100 healthy subjects were included as a control. Among vitiligo patients, the disease duration ranged from 1 month to 39 years (median 3 years), the VIDA score ranged from -1 to 4 (median 2) and the VASI score ranged from 0.1 to 94 (median 2).

Blood pressure (systolic and diastolic), FBG, TC, TG, HDL-c, and LDL-c levels were significantly higher in patients than controls ($P < 0.05$ each), while, WC did not differ significantly between studied groups (*P* value 0.643). Hyperlipidemia and MS were significantly observed in vitiligo patients compared to healthy controls ($P < 0.001$ each). Basic demographic, anthropometric, and disease characteristics of the studied subjects were presented in Table 1.

Among the tested inflammatory biomarkers, serum levels of FABP4, VAP-1, YKL-40, and hs-CRP were significantly higher, and serum vaspin was significantly lower in vitiligo patients than in the control group ($P < 0.001$ each) [Table 1].

The ROC curve analysis was conducted to assess the performance of the studied biomarkers in discriminating vitiligo patients from controls and to discriminate between vitiligo patients with and without MS. Serum FABP4, VAP-1, and YKL-40 were found to be tested with excellent accuracy, while vaspin had fair accuracy in discriminating between vitiligo patients and healthy subjects. Their AUCs, best cut-off values, and performance characteristics are shown in Table 2. Serum FABP4 and YKL40 showed excellent AUCs, while serum vaspin and VAP-1 showed good and fair AUCs, respectively, for discriminating between MS and non-MS among vitiligo patients. Their AUCs, best cut-off values, and performance characteristics are presented in Table 2.

We observed significant positive correlations between FABP4, VAP-1, and YKL-40 with disease severity (VASI score), vitiligo activity (VIDA score), serum FBG, TC, TG, and LDL-c levels ($P < 0.05$ each) and a significant negative correlation with HDL-c ($P < 0.05$). The three biomarkers also showed significant positive correlations with each other's levels. There were significant negative correlations between serum vaspin level and VASI score, VIDA score, serum FBG, TC, TG, and LDL-c levels ($P < 0.05$ each) and a significant positive correlation with HDL-c ($P < 0.05$). Serum vaspin levels showed significant negative

Table 1: Baseline parameters and serum levels of studied biomarkers in vitiligo patients and control group

Variables	Control *n*=100	Vitiligo patients *n*=100	*P*
Gender			
Males	35 (35%)	30 (30%)	0.63
Females	65 (65%)	70 (70%)	
Age (years)	36.4±5.6 (28-47)	32.7±13.0 (18-60)	0.146
BMI (kg/m^2)	25.1±1.9	26.4±2.8	0.264
WC (cm)	92.9±10.3	93.7±13.5	0.643
SBP (mmHg)	115.5±11.9	120±15.7	0.024
DBP (mmHg)	70.6±8.7	79.6±15	<0.001
TC (mg/dL)	173.7±23.8	197.4±43.5	0.007
TG (mg/dL)	114.6±17.5	137.4±39.6	0.004
HDL-c (mg/dL)	57.3±4.7	51.5±6.3	<0.001
LDL-c (mg/dL)	95.8±27	118.4±31.2	0.009
FBG (mg/dL)	103.2±17.6	115.1±19.4	<0.001
Hyperlipidemia	10 (10%)	36 (36%)	<0.001
MS	2 (2%)	22 (22%)	<0.001
Duration (years)	-	Mean - 5.9±6.35 Median - 3 (0.1-39)	-
VASI score	-	Mean - 3.83±3.44 Median - 2 (0.1-94)	-
VIDA Score	-	Mean - 2.35±1.74 Median – 2 (-1.0 to 4)	-
FABP4 (ng/mL)	2.80 (1.03-5.01)	11.34 (3.00-14.77)	<0.001
VAP-1 (pg/mL)	1.21 (0.51-1.48)	2.83 (1.27-3.69)	<0.001
YKL-40 (ng/mL)	0.7 (0.2-0.9)	1.2 (0.7-1.8)	<0.001
Vaspin (pg/mL)	2.1 (1.1-3.7)	1.6 (0.6-6.5)	<0.001
hs-CRP (mg/dL)	5.88 (5.12-6.15)	6.79 (6.22-7.20)	<0.001

Data represented as number (frequency), mean ± SD, or median (range). $P \leq 0.05$ is considered significant. BMI=Body mass index, WC=Waist circumference, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, TC=Total cholesterol, TG=Triglycerides, HDL-c=High-density lipoprotein cholesterol, LDL-c=Low-density lipoprotein cholesterol, FBG=Fasting blood glucose, MS=Metabolic syndrome, VASI=Vitiligo area scoring index, VIDA=Vitiligo disease activity score, FABP4=Fatty acid binding protein 4, VAP-1=Vascular adhesion protein 1, YKL-40=Chitinase-3-like protein 1, vaspin=Visceral adipose tissue-derived serine protease inhibitor, and hs-CRP=High-sensitivity C-reactive protein

correlation with other inflammatory biomarkers ($P < 0.05$ each) [Table 3].

Serum FABP4, VAP-1, and YKL- 40 levels were significantly higher and serum vaspin level was significantly lower in vitiligo patients than controls regardless of their age or BMI when patients and controls were stratified according to median BMI (25 kg/m^2) and median age (35 years) [Figures 1 and 2].

Discussion

Metabolic disturbances are common in vitiligo patients being vitiligo is a cutaneous disease with systemic manifestations.[1] In the current study, MS components were observed in 22% of vitiligo patients and 2% of the control group ($P < 0.001$). Also, Karadag *et al*.[21] advocated such a link; however, this link was refuted by Pietrzak *et al*.[1] who stated that vitiligo patients had improved lipid profiles than the control group.

Current findings indicate a significant rise in lipid profile markers except for HDL-c levels in vitiligo patients compared to control subjects, similar to previous studies.[22] On the other hand, Rodriguez-Martin *et al*.[23] study showed that vitiligo patients had higher serum HDL-c levels and lower serum TG, which they attributed to higher levels of superoxide dismutase and glutathione peroxidase in patients with active vitiligo, and this enzymatic base could be the reason why vitiligo sufferers are less prone to dyslipidemia.

To our knowledge, with the exception of hs-CRP, studies evaluating the importance of vaspin, FABP4, VAP-1, and

Table 2: ROC analysis to assess the validity of the studied serum biomarkers

	FABP4	VAP-1	YKL-40	Vaspin
Discriminating between vitiligo patients and healthy controls				
AUC (95% CI)	0.991 (0.973-1)	0.969 (0.935-1)	0.972 (0.943-1)	0.742 (0.632-0.851)
Cut-off	5.04 ng/mL	1.55 pg/mL	0.95 ng/mL	1.75 pg/mL
Sensitivity	98%	91.8%	86%	68%
Specificity	100%	100%	100%	80%
PPV	98%	91.8%	86%	85%
NPV	100%	100%	100%	60%
Accuracy	98.8%	94.9%	91.3%	72.5%
Discriminating between MS and non-MS among vitiligo patients				
AUC (95% CI)	0.918 (0.846-0.964)	0.741 (0.643-0.823)	0.907 (0.832-0.956)	0.893 (0.815-0.946)
Cut-off	12.5 ng/mL	3.0 pg/mL	1.2 ng/mL	≤1.1 pg/mL
Sensitivity	100%	86.4%	100%	81.8%
Specificity	83.1%	74%	72.7%	76.6%
PPV	62.8%	48.7%	51.1%	50.0%
NPV	100.0%	95.0%	100.0%	93.6%
Accuracy	86.9%	76.8%	78.8%	77.8%

AUC=Area under receiver operating characteristic (ROC) curve, CI=Confidence interval, PPV=Positive predictive value, NPV=Negative predictive value, MS=Metabolic syndrome, FABP4=Fatty acid binding protein 4, VAP-1=Vascular adhesion protein 1, YKL-40=Chitinase-3-like protein 1, and vaspin=Visceral adipose tissue-derived serine protease inhibitor

Table 3: Correlations of serum biomarkers with some studied parameters in the vitiligo patients

Variables	FABP4		VAP-1		YKL-40		Vaspin	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
VASI Score	0.996	<0.001	0.451	0.001	0.989	<0.001	−0.296	0.037
VIDA Score	0.465	0.001	0.323	0.022	0.377	0.017	−0.297	0.036
FBG	0.613	<0.001	0.684	<0.001	0.718	<0.001	−0. 072	0.681
TC	0.995	<0.001	0.411	0.003	0.987	<0.001	−0.623	<0.001
TG	0.981	<0.001	0.455	0.001	0.970	<0.001	−0.569	<0.001
HDL-c	-0.978	<0.001	−0.380	0.007	−0.966	<0.001	0.802	<0.001
LDL-c	0.995	<0.001	0.428	0.002	0.987	<0.001	−0.612	<0.001
hs-CRP	0.021	0.887	0.043	0.769	−0.026	0.858	0.019	0.894
FABP4			0.437	0.002	0.991	<0.001	−0.803	<0.001
VAP-1					0.436	0.002	−0.343	0.015
YKL-40							−0.703	<0.001

$P \leq 0.05$ is considered significant, *r*: Spearman correlation coefficient. VASI=Vitiligo area scoring index, VIDA=Vitiligo disease activity score, FBG=Fasting blood glucose, TC=Total cholesterol, TG=Triglycerides, HDL-c=High-density lipoprotein cholesterol, LDL-c=Low-density lipoprotein cholesterol, FABP4=Fatty acid binding protein 4, VAP-1=Vascular adhesion protein 1, YKL-40=Chitinase-3-like protein 1, vaspin=Visceral adipose tissue-derived serine protease inhibitor, and hs-CRP=High-sensitivity C-reactive protein

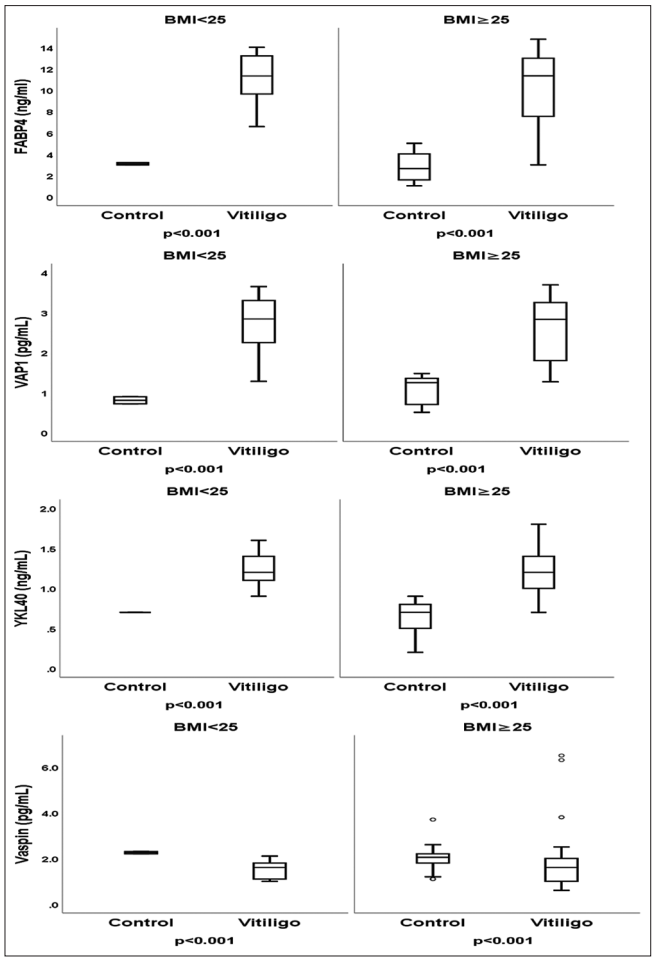

Figure 1: Boxplot comparing vitiligo patients and healthy controls with regard to body mass index. Participants were stratified according to the median BMI of all studied subjects (BMI median: 25 kg/m²)

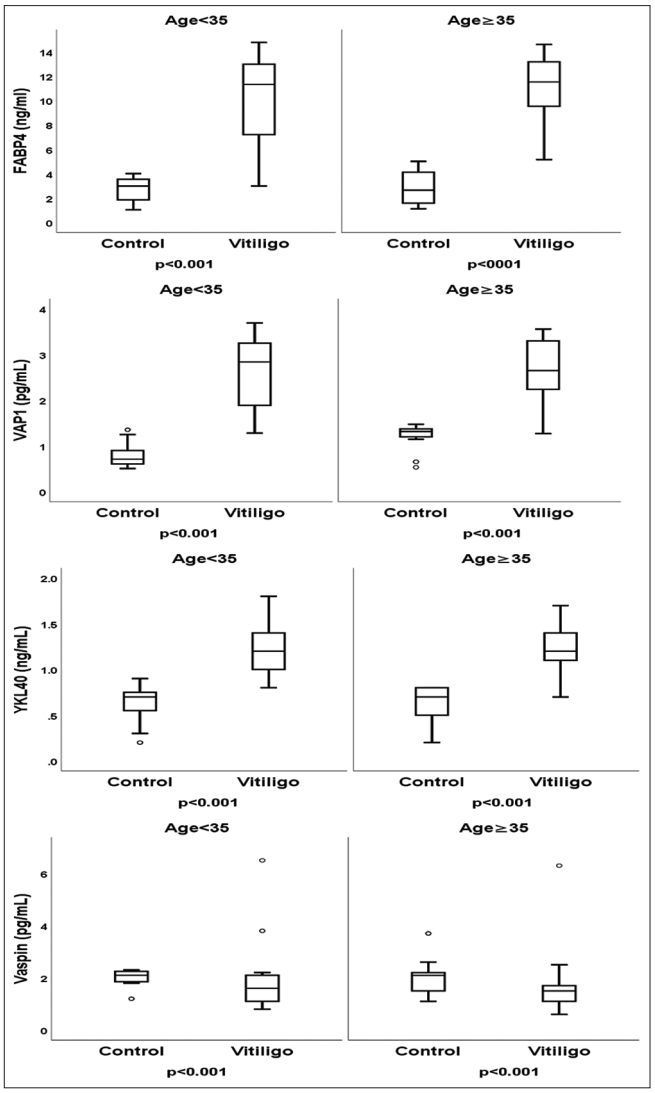

Figure 2: Boxplot comparing vitiligo patients and healthy controls with regard to age. Participants were stratified according to the median age of all studied subjects (age median: 35 years)

YKL-40 in vitiligo, and their relationship with MS in vitiligo patients are very limited. Our studied patients had greater levels of hs-CRP than control subjects, which was consistent with and supported by previous studies about the importance of hs-CRP in the clinical evaluation of vitiligo.[24]

In the investigated vitiligo patients, serum FABP4 levels were notably higher than in controls ($P < 0.001$) and positively correlated with lipid profile parameters except HDL-c levels, which was in agreement with previous findings.[25]

Makowski *et al*.[26] reported that FABP4 controls cholesterol trafficking in macrophages and is a critical regulator of the ATP-binding cassette A1 (ABCA1) pathway. ABCA1 controls intracellular cholesterol efflux, which may increase triglyceride catabolism, transfer to HDL-c, and thus influence HDL-c biogenesis. So, we could deduce that the FABP4 pro-inflammatory marker may be linked to vitiligo and its associated MS.

In our study, serum YKL-40 level was significantly higher in vitiligo patients than in controls (P < 0.001). Despite the fact that the importance of YKL-40 in the immune response has been documented in numerous studies, its role in vitiligo has yet to be fully investigated. This increase in YKL-40 levels could be linked to the disease's inflammatory phase, as vitiligo patients may have systemic inflammation. In this study, YKL-40 showed significant positive correlations with lipid profile parameters except for HDL-c, which was in accordance with previous findings.[13]

Our patients had significantly higher levels of serum VAP-1 than controls. VAP-1 is an adhesion molecule that mediates leukocyte trafficking and is involved in the pathogenesis of autoimmune diseases.[27] We found VAP-1 serum levels significantly positively correlated with TC, TG, and LDL-c; this finding is perhaps attributed to the fact that VAP-1 substrates were able to induce adipose conversion and inhibit lipolysis in the 3t3-L1 mouse cell line by producing hydrogen peroxide.[28]

In the current study, serum vaspin levels were significantly lower in vitiligo patients in comparison to control subjects. According to Phalitakul *et al*.,[29] vaspin has anti-inflammatory properties by suppressing tumour necrosis factor-induced intercellular adhesion molecule-1 expression, reactive oxygen species production, nuclear factor kappa B activation, reducing cytokine-driven inflammation in 3t3-L1 adipocytes, and attenuating the pro-inflammatory cytokine response caused by IL-1 in isolated adipocytes. Because of these anti-inflammatory properties, it is possible that lower vaspin levels are caused by an increase in pro-inflammatory cytokines in vitiligo. Regarding the relation between vaspin and the studied inflammatory markers, in support of vaspin's anti-inflammatory properties, our findings revealed a significant inverse correlation between this adipokine and other studied biomarkers. Recent research confirms that inflammation contributes to the aetiology of vitiligo and its comorbidities.[2] Janus kinase inhibitors, such as ruxolitinib, baricitinib, and tofacitinib, are effective in the treatment of vitiligo and related disorders by inhibiting the inflammatory interferon-chemokine signaling axis.[30]

If the existence of a metabolic disturbance in vitiligo is proven, the development of atherosclerosis and other CVD can be expected, which will change the way vitiligo patients are managed in the future. Simvastatin, a potent statin that prevents the production of cholesterol in the liver, may have the potential to protect vitiligo patients against oxidative stress and cytokine-mediated consequences and should be further investigated.

Conclusions

Metabolic syndrome components were more prevalent among vitiligo patients than healthy controls. The current findings could be attributed to vitiligo patients' ongoing abnormal metabolic processes. Additionally, we observed that the studied inflammatory biomarkers might induce disease development, and an imbalance between these pro- and anti-inflammatory adipocytokines may be a causative factor for MS in vitiligo. As a result, we recommend routine investigation of metabolic syndrome in vitiligo patients, and it should be regarded as an independent significant contributing factor for cardio-metabolic risk worth considering in vitiligo management. However, additional molecular, functional, and clinical large-scale studies are required.

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Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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