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Exploring the Role of Adipose Tissue Dysregulation in Vitiligo Pathogenesis: A Body Composition Analysis

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Vitiligo is a commonly acquired pigmentary disease characterized by the progressive destruction of melanocytes. The role of adipose tissue in vitiligo remains unclear. To investigate the role of adipose tissue in the pathogenesis of vitiligo, 50 patients newly diagnosed with vitiligo and 40 age- and sex-matched healthy controls were enrolled, and fat mass and distribution using dual-energy X-ray absorptiometry (DXA) and serum adipokine levels using enzyme-linked immunosorbent assay were assessed. The trunk and whole-body fat mass and the trunk/limb fat mass ratio were significantly higher in patients with vitiligo. Higher leptin and resistin levels and lower adiponectin levels were observed. Positive correlation of the trunk fat mass index with vitiligo area scoring index scores ($r = 0.38$, $p = 0.0071$) was found. Additionally, plasma adiponectin levels were negatively correlated with vitiligo disease activity scores ($r = -0.307$, $p < 0.05$). Receiver operating characteristic curve analysis showed that the percentage of limb lean tissue mass, trunk/limb fat mass ratio, and serum adipokine levels achieved a high area under the curve score for distinguishing patients with vitiligo from healthy controls. In conclusion, the incidence of central obesity and adipokine dysregulation was higher in patients with vitiligo. The potential role of adipose tissue in the pathogenesis of vitiligo should be emphasized.

Key words: adipokines; adipose tissue; body composition analysis; dual-energy X-ray absorptiometry; vitiligo.

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SIGNIFICANCE

Vitiligo is a commonly acquired pigmentary disease characterized by the progressive destruction of melanocytes. The association between metabolic disorders and vitiligo has attracted increasing attention. However, the role of adipose tissue in vitiligo remains unclear. To investigate this, this study measured regional and whole-body fat mass and distribution using dual-energy X-ray absorptiometry (DXA) and serum adipokine levels among patients and healthy controls. This study found the incidence of central obesity and adipokine dysregulation was higher in patients with vitiligo. The potential role of adipose tissue in the pathogenesis of vitiligo should be emphasized.

Vitiligo is a commonly acquired pigmentary disease characterized by progressive melanocyte destruction resulting from the abnormal activation of CD8+ T cells (1, 2), which affects approximately 0.5% to 2.0% of the world's population and can occur at any age (3, 4). The pathogenesis of vitiligo is related to the dysfunction of cytotoxic CD8+ T cells, oxidative stress, inflammation, metabolic abnormalities, and phenolic compounds exposure (5–8). Due to the difficulty of vitiligo treatment, it causes a serious physical and mental burden to patients, although new targeted therapies have emerged in recent years (9). Greater knowledge and increased attention to vitiligo have led to greater focus on its associated systemic factors. Previous studies have reported a higher incidence of metabolic derangement in patients with vitiligo than in healthy controls (10–12). Growing evidence suggests that dysregulated metabolism of lipids and polyunsaturated fatty acids plays a crucial role in vitiligo (9–12).

Recently, the role of adipose tissue in the pathogenesis of vitiligo has received increasing attention. A higher level of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin (IL)-6 secreted by adipose tissue was found in patients with vitiligo (13). The number of melanocytes and degree of melanogenesis were reduced in adipose tissue (14). These results suggest a possible crosstalk between melanocytes and adipocytes. The adipose tissue synthesizes and secretes adipokines, which are associated with the dysregulation of immune processes and lead to inflammatory consequences (15). Adiponectin is an essential adipokine, which elicits an anti-inflammatory effect by decreasing vascular inflammation, inhibiting pro-inflammatory cytokines such as TNF-α, IL-6, IL-1, and IL-17, and increasing IL-10, an anti-inflammatory cytokine (16–19). Leptin and resistin increase the production of pro-inflammatory cytokines and chemokines (16). Adipokines reportedly play important roles in the development of inflammatory skin diseases (20–22). However, their role in the pathoge-

nesis of vitiligo remains unclear and requires further investigation.

To date, no study has investigated the correlation between fat mass (FM) and vitiligo, while a few studies have explored the relationship between vitiligo and obesity (23, 24), with inconsistent results. Dual-energy X-ray absorptiometry (DXA) is a highly accurate, quantitative, and extensively used technique for assessing body composition (25). Measures of body composition by DXA can more comprehensively assess FM and distribution than by standard anthropometrics such as body mass index (BMI) and waist circumference.

This study aimed to investigate the role of adipose tissue in the pathogenesis of vitiligo by assessing FM and distribution using DXA and serum adipokine levels in patients with vitiligo compared with controls.

MATERIALS AND METHODS

Study participants

We enrolled 50 newly diagnosed and untreated patients with vitiligo at the Dermatology Department of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China between February 2023 and September 2023. The experimental group consisted of adult patients diagnosed with vitiligo through auxiliary and/or histopathological examinations. Patients with other skin diseases, active autoimmune diseases, metabolic diseases, and malignancies, as well as pregnant and breastfeeding women, were excluded from the study. Inclusion and exclusion of the study population is in accordance with the flowchart in **Fig. 1**. Advertisements were used to recruit 40 sex- and age-matched healthy controls. None of the healthy participants had a personal medical background of skin or autoimmune disorders or any prior interventions that could potentially impact the inflammatory response. Dermatologists conducted direct assessments and documented epidemiological information such as sex, age, disease duration, BMI, and clinical manifestations.

Prior to the commencement of the study, written informed consent was obtained from the patients and healthy controls. The study was meticulously planned and conducted in compliance with the ethical guidelines outlined in the Declaration of Helsinki of 1964 and its later amendments and was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Number: 2023-436).

Blood sample collection

Peripheral blood samples were collected from patients with vitiligo and healthy controls to obtain serum. The serum concentrations of adiponectin (leptin, resistin, adiponectin) and pro-inflammatory cytokines and chemokines (IL-17, chemokine C-X-C ligand 10 [CXCL10], TNF-α, and interferon [IFN]-γ) were determined using enzyme-linked immunosorbent assay following the manufacturer's protocol.

Assessment of vitiligo disease activity/severity

The vitiligo disease activity (VIDA) score was used to assess disease activity (26). The vitiligo area scoring index (VASI) score was used as an index for disease severity (27). Both VIDA and VASI scores were independently evaluated by 2 experts, and the final scores were averaged among the experts.

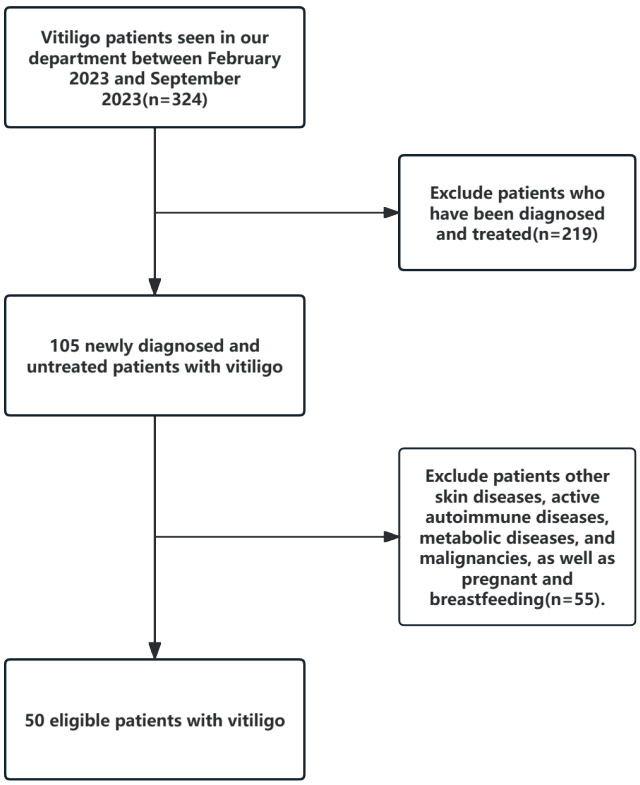

Fig. 1. Flowchart for inclusion of study participants.

DXA scan

The patterns of body composition of each participant were measured using a DXA scanner (Hologic Discovery software version APEX 4.5.3). Participants were asked to remove all metal accessories and place themselves in a supine position for measurement. Scan images were analysed using the Hologic Discovery software version APEX 4.5.3 (Hologic Discovery A; Hologic Inc, Bedford, MA, USA). FM, lean tissue mass (LTM) calculated by subtracting FM from the soft tissue mass, which can be regarded as muscle mass, and bone mineral content (BMC) of the upper limbs (UL), lower limbs (LL), appendicular region (A), trunk, and whole body were detected using the DXA scanner. The FM index (FMI, kg/m^2) and LTM index (LTMI, kg/m^2) were defined as the FM or LTM measured by DXA normalized by height squared. The regional and whole-body FM/weight (wt) (%) and LTM/wt (%) were determined by dividing the FM and LTM of each region by weight. The percentages of body FM (%FM) and body LTM (%LTM) were calculated by dividing the regional and whole-body FM and LTM by the regional and whole-body mass. The distributions of FM and LTM were assessed using the trunk/limb FM ratio (Trunk/Limb FMR) and the limb/trunk LTM ratio (Limb/Trunk LTMR).

Statistical analyses

R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis. Normality was assessed using the Shapiro–Wilk test. Data are presented as the mean (standard deviation). Quantitative data are represented by normal and median values, as well as the lower and upper quartiles. Categorical data are expressed as relative frequency in the form of a percentage. To examine the patterns of body composition among the different groups, a *t*-test was used on a separate sample for data that followed a normal distribution. When an equal variance was not assumed, an alternatively corrected *t*-test was used. The Wilcoxon test was

Table I. Epidemiological and clinical characteristics of patients with vitiligo and healthy controls

Variables	Vitiligo ($n=50$)	Control ($n=40$)	p-value
Epidemiological characteristics			
Sex, male, *n* (%)	20 (40)	18 (45)	0.793
Age (years), mean (SD)			
Age at blood sampling (years)	39.22 (14.17)	35.23 (13.27)	0.175
Age of disease onset (years)	35.92 (15.95)		
BMI (kg/m^2), mean (SD)	22.93 (3.19)	22.62 (2.34)	0.603
Disease duration (months), mean (SD)	54.77 (116.63)		
VASI score, mean (SD)	1.74 (2.42)		
VIDA score, mean (SD)	2.26 (1.37)		
Body hair whitening, *n* (%)			
No	43 (86)		
Yes	7 (14)		
Halo nevus, *n* (%)			
No	48 (96)		
Yes	2 (4)		
Koebner phenomenon, *n* (%)			
No	48 (96)		
Yes	2 (4)		
Serum cytokines			
CXCL10 (pg/mL), mean (median, IQR)	183.94 [154.58, 206.07]	139.79 [123.61, 160.73]	<0.001
TNF-α (pg/mL), mean (SD)	39.57 (11.01)	23.07 (10.89)	<0.001
IL-17 (pg/mL), mean (median, IQR)	282.22 [234.17, 315.36]	193.34 [161.21, 214.91]	<0.001
IFN-γ (pg/mL), mean (median, IQR)	450.52 [366.56, 564.64]	527.07 [452.24, 597.79]	0.010

BMI: body mass index; CXCL: chemokine C-X-C ligand; IL: interleukin; INF: interferon; IQR: interquartile range; SD: standard deviation; TNF: tumour necrosis factor; VASI: Vitiligo Area Scoring Index; VIDA: vitiligo disease activity score.

used for data that did not follow a normal distribution. Pearson's correlation and Spearman's correlation were used to analyse the correlation between normal and non-normal data, respectively. Receiver operating characteristic (ROC) curve analysis was performed to investigate the sensitivity and specificity of DXA patterns and serum adipokines as biomarkers.

RESULTS

Clinical and demographic features of patients with vitiligo

A cohort of 50 patients diagnosed with newly acquired and untreated vitiligo, as well as 40 age- and sex-matched controls, were included in the study. The epidemiological characteristics of the patients with vitiligo and healthy controls are outlined in **Table I**. Among the participants, 32 (64%) patients with vitiligo and 36 (90%) controls exhibited a BMI within the normal range of 18.5–24.9 kg/m^2. Among 50 patients with vitiligo, 7 (14%) exhibited body hair whitening, 2 (4%) had halo nevus, and 2 (4%) had the Koebner phenomenon. No significant differences in age, sex, or BMI were observed between patients with vitiligo and healthy controls. Serum CXCL10 and IFN-γ have been confirmed as novel biomarkers for evaluating the activity of vitiligo, while serum IL-17 and TNF-α have been suggested as being released from adipose tissue and are associated with the activity of vitiligo.[2,15] In our study, the serum CXCL10, IL-17, TNF-α, and IFN-γ levels were significantly higher in patients with vitiligo than in healthy controls.

Whole-body composition by DXA

Measurements of body composition obtained using DXA in patients with vitiligo and their corresponding controls are presented in **Table II**. Our study revealed a noteworthy augmentation in FM of both the trunk regions and the whole body among patients diagnosed with vitiligo compared with healthy controls, which manifested as an increase in trunk FMI, trunk FM/wt, trunk %FM, and total FM. The FM-related indices of the UL, LL, and appendicular regions did not change significantly. The trunk and limb FMR of patients with vitiligo was significantly increased ($p<0.001$). Additionally, compared with healthy controls, our study revealed a reduction in LTM/wt, limb %LTM, and trunk %LTM in the LL of patients with vitiligo. However, no significant changes in the LTMI or other LTM-related indices were observed. In addition, we explored the relationships between statistically significant indicators and clinical parameters. Among patients with vitiligo, we found a positive trend between trunk FMI and VASI scores ($r=0.38$, $p=0.0071$) (**Fig. 2**A), suggesting that the severity of vitiligo is associated with trunk FM.

Levels of plasma adipokines

Serum leptin and resistin concentrations were significantly higher in patients with vitiligo than in healthy controls (**Fig. 3**A–B). Additionally, there was a statistically significant difference in adiponectin levels between patients with vitiligo and matched controls (Fig. 3C). Furthermore, within the vitiligo groups, we observed a positive correlation of the levels of leptin with the levels of TNF-a and IL-17 ($r=0.371$, $p<0.01$; $r=0.35$, $p<0.05$) (Fig. 2B–C). Additionally, our study revealed a negative correlation between plasma adiponectin levels and VIDA scores ($r=-0.307$, $p<0.05$) (Fig. 2D). Correlation analysis between the levels of adipokines and disease-related indices showed that higher levels of leptin

Table II. Analysis of body composition of patients with vitiligo

Factor	Vitiligo ($n = 50$)	Control ($n = 40$)
FM (kg)		
UL	2.46 (1.45–3.46)	2.01 (1.48–2.55)
LL	5.90 (4.05–7.75)	5.76 (4.27–7.25)
AFM	8.35 (5.59–11.12)	7.77 (5.83–9.72)
Trunk	**9.19 (5.79–12.60)****	7.10 (5.34–8.87)
Total	**18.59 (12.79–24.40)****	15.72 (12.52–18.91)
LTM (kg)		
UL	**4.65 (3.01–6.28)***	3.90 (2.68–5.12)
LL	13.19 (9.99–16.38)	12.92 (9.81–16.04)
AFM	17.83 (13.34–22.33)	16.83 (12.58–21.07)
Trunk	**21.48 (16.83–26.13)***	19.55 (15.98–23.12)
Total	42.64 (33.46–55.81)	39.36 (31.42–47.31)
FMI (kg/m^2)		
UL	0.81 (0.67–1.03)	0.76 (0.63–0.96)
LL	2.02 (1.58–2.47)	2.24 (1.87–2.47)
AFMI	2.85 (2.37–3.59)	3.01 (2.5–3.48)
Trunk	**3.07 (2.51–4.16)***	2.8 (2.23–3.43)
Total	6.5 (5.53–7.73)	6.24 (5.46–7.06)
LTMI (kg/m^2)		
UL	1.59 (1.35–1.87)	1.43 (1.25–1.68)
LL	4.7 (4.2–5.41)	4.8 (4.5–5.39)
ALTMI	6.22 (5.66–7.09)	6.25 (5.81–6.92)
Trunk	7.52 (7–8.48)	7.42 (7.18–8.16)
Total	15.09 (13.93–16.92)	15 (14.36–16.23)
FM/wt (%)		
UL	3.77 (2.96–4.49)	3.5 (3.01–4.15)
LL	9.39 (2.44)	10.15 (2.41)
AFM/wt	13.25 (3.45)	13.68 (3.09)
Trunk	**14.62 (11.92–16.59)****	12.58 (10.24–14.22)
Total	29.37 (6.07)	27.6 (5.28)
LTM/wt (%)		
UL	6.64 (6.18–8.2)	6.37 (5.87–7.34)
LL	**21.16 (19.62–22.28)****	22.38 (20.78–23.65)
ALTM/wt	28.08 (3.75)	29.11 (3.37)
Trunk	33.31 (31.77–35.84)	34.35 (32.65–35.34)
Total	67.3 (5.72)	68.47 (4.98)
%FM		
UL	33.64 (9.56)	33.17 (8.01)
LL	31.86 (4.52)	29.91 (6.31)
Limbs	**45.76 (41.7–47.9)****	58.49 (36.84–63.51)
Trunk	**29.41 (7.02)****	25.99 (5.19)
Total	29.37 (6.08)	27.6 (5.28)
%LTM		
UL	62.48 (9.28)	62.47 (7.85)
LL	65.66 (61.75–72.74)	65.47 (62.63–70.68)
Limbs	**41.78 (40.24–43.55)****	64.93 (61.25–69.6)
Trunk	**68.58 (64.74–74.1)***	71.59 (68.38–75.51)
Total	67.29 (5.71)	68.47 (4.98)
Trunk/Limbs FMR	**1.13 (0.80–1.45)****	0.92 (0.72–1.13)
Limbs/Trunk LTMR	0.83 (0.78–0.89)	0.84 (0.8–0.91)

Bold type indicates statistical significance. *$p < 0.05$, **$p < 0.01$; statistically significant difference from the normal control. Data are presented as mean (standard deviation) for normal data and median (lower quartile–upper quartile) for non-normal data. AFMI: appendicular fat mass index; ALTMI: appendicular lean tissue mass index; AFM/wt: appendicular fat mass normalized to weight; ALTM/wt: appendicular lean tissue mass normalized to weight; %FM: percentage fat mass; FMI: fat mass index; FM/wt: fat mass normalized to weight; Limb/Trunk LTMR: Limbs/Trunk lean tissue mass ratio; LL: lower limbs; %LTM: percentage lean tissue mass; LTMI: lean tissue mass index; LTM/wt: lean tissue mass normalized to weight; Trunk/Limbs FMR: Trunk/Limbs fat mass ratio; UL: upper limbs.

indicated higher levels of pro-inflammatory cytokines, whereas lower levels of adiponectin indicated higher levels of vitiligo activity.

ROC curve analysis

ROC curve analysis was performed to identify the diagnostic value of significantly altered DXA indicators and serum adipokines for discriminating patients with vitiligo from healthy controls. These results demonstrate the sound diagnostic abilities of these DXA indicators (**Fig. 4**). Among the DXA indicators examined, limb %LTM demonstrated the highest reliability, as evidenced by an area under the ROC curve (AUC) of 0.998 (95% confidence interval [CI]: 0.994–1), with a sensitivity of 97.5% and specificity of 100%. Additionally, the trunk–limb FMR exhibited the second-best index, with an AUC of 0.971 (95% CI: 0.943–0.998), sensitivity of 97.5%, and specificity of 86%. Subsequently, our analysis revealed significant diagnostic values of serum leptin, resistin, and adiponectin, as indicated by AUC values of 0.818, 0.815, and 0.84, respectively (**Fig. 5**).

DISCUSSION

Emerging evidence emphasizes that enlarged adipocytes and infiltrating immune cells secrete multiple molecules, including adipokines such as leptin and adiponectin, and a set of cytokines/chemokines, leading to chronic systemic inflammation and triggering the development of various chronic diseases (28–30). However, their role in the pathogenesis of vitiligo remains unclear. In this study, a significant increase in the FM of the trunk regions and the whole body was observed in patients with vitiligo, indicating a higher prevalence of central obesity among individuals diagnosed with vitiligo than in the control group. Notably, previous studies have found a different relationship between obesity and vitiligo, although most studies indicated that patients with vitiligo have a higher incidence of obesity (23, 24, 31–33). A recently published meta-analysis demonstrated a significant association between vitiligo and obesity (32). Several studies have revealed no significant correlation between vitiligo and BMI or waistline (23, 33); however, Lauria et al. (34) demonstrated no difference in classifying obesity between BMI and waistline, with both indicators showing low consistency with the body FM evaluated by DXA technology. Additionally, previous studies suggested that BMI and waistline, as comprehensive indicators, may not accurately reflect the body composition when compared with DXA (35–37). Studies that systematically evaluate FM, fat distribution, and serum adipokines in patients with vitiligo and healthy controls are lacking.

DXA is widely used to estimate different body components and shows strong consistency with CT and MRI measures (25). DXA is considered better at evaluating FM and distribution than standard anthropometric indicators such as BMI and waist circumference (38). Consistent with previous research, no significant relationship was found between BMI and vitiligo in this study; however, a significant increase in the FM of the trunk regions and the whole body in patients with vitiligo was discovered using DXA scanning. Our study suggests that the incidence of central obesity is higher in patients with vitiligo. Additionally, a positive correlation between trunk FMI and VASI scores was observed, indicating that trunk FM may reflect the severity of vitiligo. Under the ROC

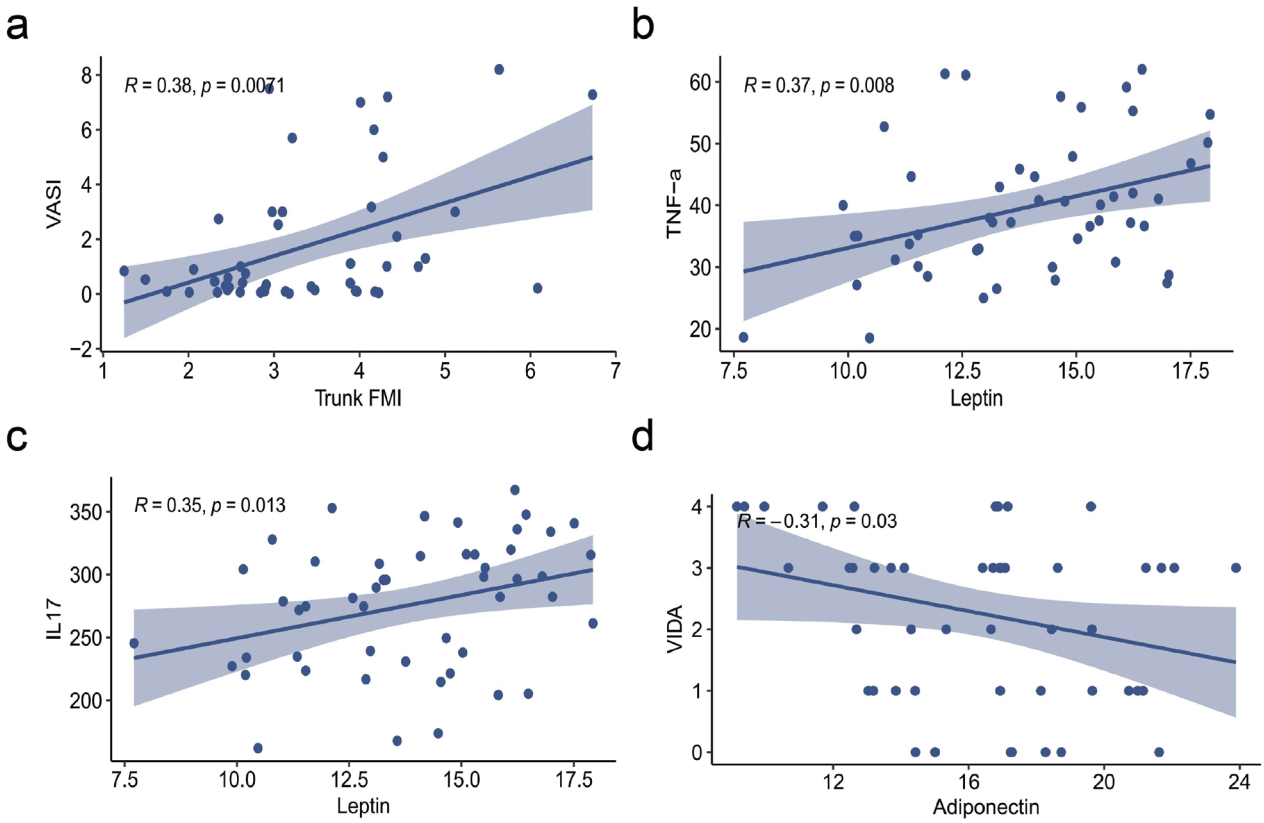

Fig. 2. Correlation of significantly altered dual-energy X-ray absorptiometry (DXA) indicators and serum adipokines with clinical parameters and serum cytokines. (A) Correlation of trunk fat mass index (FMI) and vitiligo area scoring index (VASI) scores. (B–C) Correlation of serum level of leptin and interleukin (IL)17. (D) Correlation of serum level of adiponectin and vitiligo disease activity (VIDA) scores. TNF: tumour necrosis factor.

curve analysis, we found that A%LTM and the trunk/limb FMR can effectively distinguish between patients with vitiligo and healthy controls; the AUC values were all higher than 80%. These results demonstrate a potential relationship between FM, fat distribution, and vitiligo.

To further determine the possible role of adipose tissue dysregulation in the pathogenesis of vitiligo, we assessed the serum levels of adipokines and pro-inflammatory cytokines secreted by adipocytes. Previous studies have suggested that adiponectin inhibits Th0 cell differentiation into Th1 and Th17 cells, as well as inhibiting the secretion of IL-6, IL-8, IL-17, IL-22, TNF-α, and IFN-γ from T lymphocytes, but its role in the development of vitiligo remains unclear (38–40). We found that adiponectin levels were notably reduced in patients with vitiligo and that serum adiponectin levels had a negative relationship with the VIDA score. Additionally, ROC curve analysis indicated that serum adipokines could be used as potential biomarkers for distinguishing patients with vitiligo from healthy controls. These results provide evidence that serum adiponectin is associated with the development of vitiligo. Resistin has been reported to stimulate B lymphocytes to secrete other pro-inflammatory factors that stimulate T-cell recruitment to the skin (39,

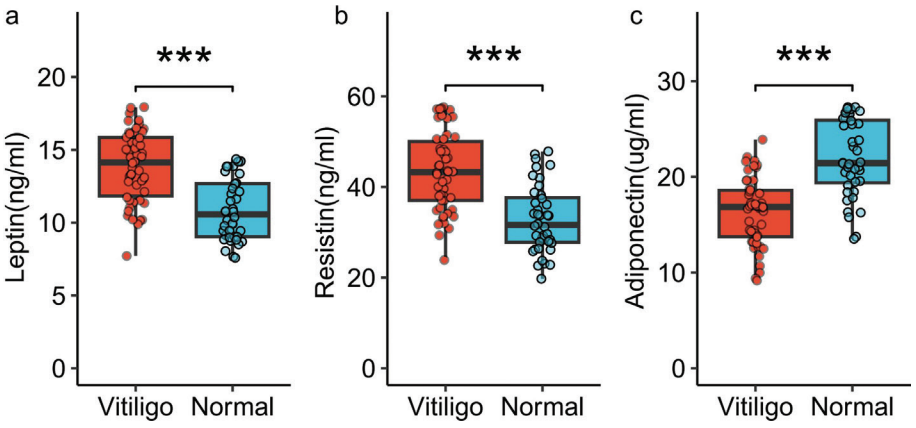

Fig. 3. Serum levels of adipokines in patients with vitiligo and healthy controls. Serum levels of (A) leptin, (B), resistin, and (C) adiponectin in patients with vitiligo and healthy controls.

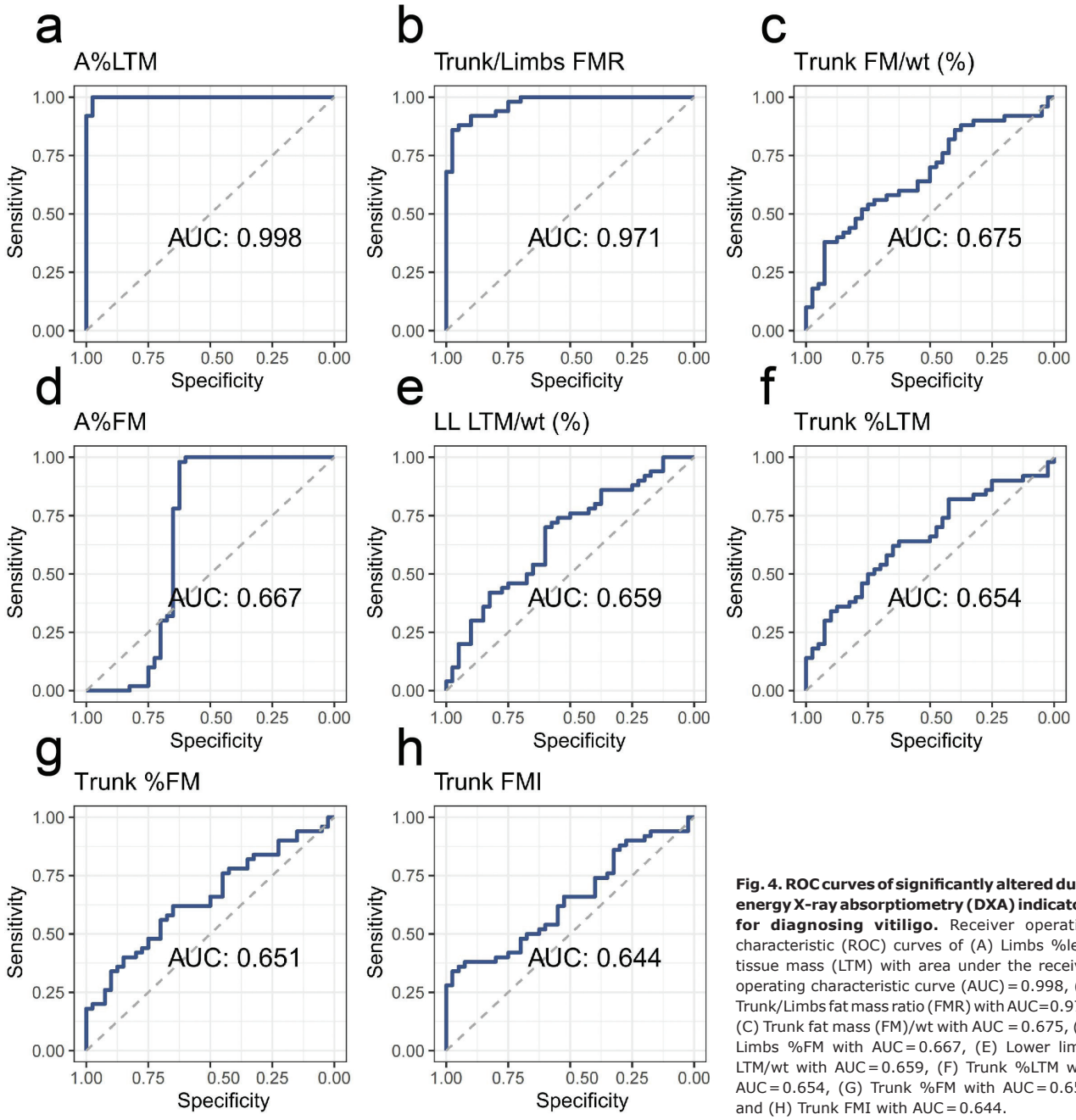

Fig. 4. ROC curves of significantly altered dual-energy X-ray absorptiometry (DXA) indicators for diagnosing vitiligo. Receiver operating characteristic (ROC) curves of (A) Limbs %lean tissue mass (LTM) with area under the receiver operating characteristic curve (AUC) = 0.998, (B) Trunk/Limbs fat mass ratio (FMR) with AUC=0.971, (C) Trunk fat mass (FM)/wt with AUC = 0.675, (D) Limbs %FM with AUC = 0.667, (E) Lower limbs LTM/wt with AUC = 0.659, (F) Trunk %LTM with AUC = 0.654, (G) Trunk %FM with AUC = 0.651, and (H) Trunk FMI with AUC = 0.644.

41) and reduce the population of Foxp3+ Treg cells in psoriasis. Our study reveals that the levels of resistin were increased in patients with vitiligo, suggesting a potential role of resistin in the pathogenesis of vitiligo. Serum leptin levels were consistent with those reported in a previous study (12, 33, 42). Wu et al. (12) found that leptin could stimulate CD8+ T cells to secrete more functional cytokines (IFN-γ, perforin, and granzyme B) in vitiligo, providing evidence that adipocytes may play a crucial role in the development of vitiligo through secreting adipokines. In our study, we found that the levels of leptin were increased and had a positive relationship with TNF-α and IL-17 levels, which validates the potential association of serum leptin with chronic inflammatory status in vitiligo. These results confirm the potential role of adipokines in vitiligo, which may participate in the pathogenesis of vitiligo by regulating cytokines.

Based on these findings, we speculate that adipose tissue may participate in the pathogenesis of vitiligo by increasing FM and secreting adipokines and pro-inflammatory cytokines; however, its specific mechanism requires further exploration.

Limitations

The limitations of the study should be considered when interpreting the results. First, the cohort size was rela-

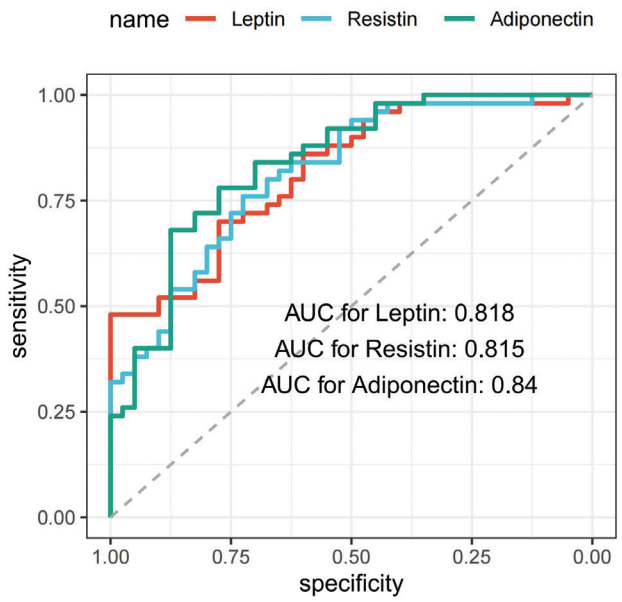

Fig. 5. Receiver operating characteristic (ROC) curve analysis of leptin, resistin, and adiponectin for discriminating patients with vitiligo from healthy controls. The red, blue, and green curves represent the ROC curve of leptin, resistin, and adiponectin, respectively. AUC: area under the receiver operating characteristic curve.

tively small, and this single-centre study enrolled only Chinese participants. In addition, causal inferences could not be made based on the results of this single-centre retrospective study. Hence, a prospective multicentre cohort and validation study are necessary to verify these biomarkers.

Conclusion

This study reveals that compared with the healthy control group, patients with vitiligo had a higher incidence of central obesity and higher patterns of differences in DXA and serum adipokines. Furthermore, the potential role of the adipose tissue in the pathogenesis of vitiligo should be emphasized. Our findings suggest the value of further study of the patterns of DXA and serum adipokines for the early diagnosis and monitoring of disease activity/severity of vitiligo.

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The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Number: 2023-436) and was conducted in compliance with the ethical guidelines outlined in the Declaration of Helsinki of 1964 and its later amendments. Written informed consent was obtained from the patients and healthy controls.

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to declare.

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