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No Association between Vitiligo and Obesity: A Case-Control Study

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Significance of the Study

- In this study, vitiligo did not appear to be associated with a high body mass index, in contrast to most other autoimmune diseases. This lack of an association could be due to a high expression of p53 and a high concentration of transforming growth factor-β in vitiligo patients. Hence, in these patients, vitiligo could not lead to obesity.

Keywords
Vitiligo · Obesity · Case-control study · Body mass index

Abstract

Objective: The purpose of this study was to investigate the relationship between vitiligo and body mass index (BMI) to assess the possible association between vitiligo and obesity. ***Subjects and Methods:*** This was a case-control study on a total of 400 participants, i.e., 200 patients with vitiligo and 200 healthy volunteers. Medical assessments were performed by dermatologists using the modified Vitiligo European Task Force form. The height and weight of all of the participants were measured and used to calculate the BMI. Data were analyzed using multivariate logistic regression models. Adjustment for age and gender was carried out preliminarily in the case-control analysis, whereas a forward stepwise selection algorithm was used to assess which independent factors were associated with a BMI ≥30 or a BMI ≤18.5. ***Results:*** Comparison of the vitiligo and control groups revealed the absence of a significant association. The multivariate analysis of factors associated with a high BMI (≥30) in vitiligo patients showed a significant association between a high BMI and a sudden onset of vitiligo ($p = 0.021$; OR = 3.83; 95% CI 1.22–11.99) and the presence of inflammation and pruritus ($p = 0.031$; OR = 3.26; 95% CI 1.11–9.57). No significant association was observed in the analysis of factors associated with a low BMI (≤18.5) in vitiligo patients. ***Conclusion:*** In this study, vitiligo did not appear to be associated with a high BMI; obesity might not be a risk factor for vitiligo, in contrast to most autoimmune diseases which are significantly associated with obesity.

Introduction

Vitiligo is an acquired, depigmenting skin disorder characterized by the appearance of well-delineated, white macules on the skin due to the selective disappearance of

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functional melanocytes in the epidermis [1]. Vitiligo affects people of all ages and both sexes equally, with a prevalence of approximately 0.5% of the world population [2]. Currently, vitiligo is considered a multifactorial disease with the specific involvement of autoimmunity, and thus vitiligo is regarded mainly as an autoimmune dermatosis [3, 4].

The association between many autoimmune or inflammatory diseases and obesity had been demonstrated [5, 6]. Rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, systemic sclerosis, psoriasis, and autoimmune thyroid diseases are some of the disorders linked to obesity and they can also be associated with vitiligo [5–9].

In obese people, fat cells produce high levels of leptin, a cytokine-like hormone that mediates the autocrine production of a wide variety of mediators including the proinflammatory cytokines tumor necrosis factor-α and interleukin-6 which contribute to creating a chronic inflammatory state capable of increasing the risk of autoimmune diseases [10–13].

In vitiligo, a significantly high expression of proinflammatory cytokines has been reported in lesional and perilesional skin. These are thought to be essential regulators of melanocyte dysfunction and death. Contradictory results have been observed at a systemic level [14–17]. Recently, elevated serum interleukin-17A, transforming growth factor-β1, and interleukin-21 levels have been identified at a systemic level in vitiligo patients [18].

Karadag et al. [19] showed that patients with vitiligo have a higher insulin resistance, a higher LDL/HDL ratio, and a higher systolic blood pressure. A recent report provided information on the reduction of some cardiovascular risk factors in patients with vitiligo. However, the relationship between vitiligo and cardiovascular disease is not yet clear and no association between vitiligo and obesity has ever been documented in a case-control study [20].

The purpose of this study was to investigate the relationship between vitiligo and body mass index (BMI) to assess the possible association between vitiligo and obesity.

Subjects and Methods

A case-control study was performed at our specialized vitiligo outpatient service in Florence, Italy, during a 3-year period (March 2012 to March 2015). A total of 400 Caucasian participants were included in this study, i.e., 200 patients with vitiligo and 200 healthy volunteers. Of the 200 vitiligo patients, 92 were males and 108 females, with ages ranging between 14 and 75 years. In doubtful cases, a histological examination was performed to confirm the diagnosis. This study was conducted according to the principles of the Declaration of Helsinki, and written informed consent was obtained from each patient for retrospective data collection. The medical assessment involved natural and Wood's light examinations consistent with the modified Vitiligo European Task Force form [21]. Based on the Vitiligo European Task Force, a patient's palm corresponding to 1% of body surface area was used to calculate the total vitiligo extension [22]. Exclusion criteria were segmental vitiligo, doubtful diagnosis of vitiligo with no histological evidence, and no written informed consent.

The control group included 200 healthy volunteers (92 males and 108 females, aged between 17 and 76 years, with no history of dermatological or systemic disease and who were age and sex matched to the vitiligo patients.

The height and weight of all of the participants were measured and used to calculate the BMI (weight in kg divided by height in m squared [kg/m^2]). All of the participants were measured for height and weight and the BMI was calculated. BMI was taken as an index of obesity (BMI ≥30 was the obesity marker and BMI ≤18.5 was the underweight marker) and analyzed its possible relationship with the following clinical features of vitiligo: age at onset, vitiligo onset, modality of onset, growth of lesions, disease activity, total disease extension, Koebner's phenomenon, and inflammation/pruritus.

A personal history of cardiovascular disease, cancer, autoimmune disease (discoid lupus erythematosus, alopecia areata, autoimmune thyroiditis and/or gastritis, celiac disease, type 1 diabetes, Addison's disease, and scleroderma) and psoriasis were all evaluated. In addition, corticosteroid therapy, immunosuppressive therapy, and smoking habit were assessed. All of these data were obtained from paper and computerized medical records.

Statistical Analysis

Data were analyzed using multivariate logistic regression models. Adjustment for age (in quintiles) and gender was carried out preliminarily in the case-control analysis, whereas a forward stepwise selection algorithm was then used to assess which independent factors were associated with a BMI ≥30 or a BMI ≤18.5. The effect of selected factors was expressed in terms of OR with 95% CI and p values. $p < 0.05$ was considered statistically significant.

Results

The general data for the cases and controls are summarized in Appendix 1. The mean (±SD) and median age of the patients was 43.7 ± 16 and 45 years, respectively, and that of the controls was 44.3 ± 16.1 and 48.0 years, respectively. Comparison of the vitiligo and control groups revealed the absence of a significant association (Table 1). A crude analysis of the factors associated with a high BMI (≥30, obese) in vitiligo patients had a highlighted significant association between a high BMI and sudden onset of vitiligo (appearance of all of the patches present at the time of the visit in <1 month) ($p = 0.028$), the presence of in-

flammation and pruritus in vitiligo lesions ($p = 0.037$), and a personal history of cardiovascular disease ($p = 0.003$) (Table 2). Multivariate analysis revealed a significant association between a high BMI and sudden onset of vitiligo ($p = 0.021$; OR = 3.83; 95% CI 1.22–11.99) and the presence of inflammation and pruritus in vitiligo lesions ($p = 0.031$; OR = 3.26; 95% CI 1.11–9.57).

No significant association was observed in the analysis of factors associated with a low BMI (≤18.5) in vitiligo patients (Table 3).

Discussion

In this study, the high BMI was significantly associated with the sudden onset of vitiligo, inflammation, and pruritus. Obesity is a proinflammatory condition in which hypertrophic adipocytes and adipose tissue-resident cells contribute to increase circulating levels of proinflammatory cytokines [23]. Leptin plays a pivotal role that can reduce the function and expansion of regulatory T cells and thereby amplifies inflammatory processes through the recruitment of CD8+ Th1 lymphocytes, mast cells, and macrophages and stimulates the release of proinflammatory cytokines and interleukin-2 [6]. Therefore, this chronic low-grade systemic inflammation can explain the association between a high BMI and the presence of inflammation/pruritus in vitiligo macules and possibly also the sudden onset of the disease.

However, vitiligo did not seem to be associated with a high BMI, in contrast to most autoimmune diseases which are significantly associated with obesity [6]. Increasing evidence suggests that the p53 tumor suppressor protein which also has important regulatory functions in cell growth/differentiation and metabolism is overexpressed in both lesional and nonlesional epidermis of patients with vitiligo [24–26]. A recent in vivo study showed that p53 exerts a suppressive effect on white adipocyte differentiation in both mouse and human cells, suggesting that this protein has a potential protective effect against diet-induced obesity [27]. The same study highlighted how p53 is implicated in proper brown adipose tissue differentiation which seemingly is protective against obesity [27]. Thus, it is conceivable that in vitiligo patients p53 is overexpressed in adipose tissue as well as in the skin, explaining our results at least in part.

An additional explanation of our results may be that in vitiligo there is a high systemic concentration of transforming growth factor-β, which is known to be a potent

Table 1. Case-control analysis

	Vitiligo ($n = 200$)		Control ($n = 200$)		p value
	n	%	n	%	
Age, years	43.7	16.1	44.4	16.2	
<35	65	32.5	61	30.5	0.544
35–49	53	26.5	63	31.5	
50+	82	41.0	76	38.0	
Sex					
Female	108	54.0	108	54.0	1
Male	92	46.0	92	46.0	
BMI	23.8	3.5	23.6	4.3	
≤18.5	29	14.5	33	16.5	0.667
18.6–29.9	153	76.5	154	77.0	
≥30.0	18	9.0	13	6.5	
Type of vitiligo onset					
Early (age <18 years)	49	24.6	–	–	–
Late (>18 years)	150	75.4	–	–	
Speed of vitiligo onset					
Sudden	83	42.3	–	–	–
Gradual	113	57.7	–	–	
Growth of vitiligo lesions					
Absent	12	6.1	–	–	–
Slow	145	73.6	–	–	
Rapid	40	20.3	–	–	
Inflammation/pruritus					
No	147	75.4	–	–	–
Yes	48	24.6	–	–	
Total vitiligo extension, %	7.6	16.7			
<1.0	50	29.1	–	–	–
1.0–4.9	71	41.3	–	–	
≥5.0	51	29.7	–	–	
Disease activity					
Active	104	53.6	–	–	–
Borderline	34	17.5	–	–	
Stable	56	28.9	–	–	
Koebner's phenomenon					
No	99	51.6	–	–	–
Yes	93	48.4	–	–	
Personal history of cardiovascular disease					
No	176	88.0	164	82.0	0.193
Yes	24	12.0	36	18.0	
Personal history of cancer					
No	191	96.0	184	92.0	0.295
Yes	8	4.0	16	8.0	
Personal history of autoimmune disease					
No	165	82.5	194	97.0	0.101
Yes	35	17.5	6	3.0	
Personal history of psoriasis					
No	190	95.0	189	94.5	0.823
Yes	10	5.0	11	5.5	
Smoker					
No	108	60.0	142	71.0	0.224
Yes	72	40.0	58	29.0	
Corticosteroid therapy					
No	198	99.0	195	97.5	0.449
Yes	2	1.0	5	2.5	
Immunosuppressive therapy					
No	200	100.0	197	98.5	0.248
Yes	0	0.0	3	1.5	

Table 2. Crude analysis of factors associated with a high BMI (≥30) in vitiligo patients

	N	BMI ≥30		*p* value
		n	%	
Age				
<35 years	126	4	3.2	0.055
35–49 years	116	10	8.6	
50+ years	158	17	10.8	
Sex				
Female	216	11	5.1	0.031
Male	184	20	10.9	
Type of vitiligo onset				
Early (age <18 years)	49	2	4.1	0.251
Late (age >18 years)	150	16	10.7	
Speed of vitiligo onset				
Sudden	83	12	14.5	0.028
Gradual	113	6	5.3	
Growth of vitiligo lesions				
Absent	12	0	0.0	0.746
Slow	145	15	10.3	
Rapid	40	3	7.5	
Inflammation/pruritus				
No	147	9	6.1	0.037
Yes	48	8	16.7	
Total vitiligo extension				
<1.0%	50	4	8.0	1
1.0–4.9%	71	6	8.5	
≥5.0%	51	5	9.8	
Disease activity				
Active	104	11	10.6	0.456
Borderline	34	1	2.9	
Stable	56	5	8.9	
Koebner's phenomenon				
No	99	9	9.1	0.695
Yes	93	7	7.5	
Personal history of cardiovascular disease				
No	340	20	5.9	0.003
Yes	60	11	18.3	
Personal history of cancer				
No	375	30	8.0	0.240
Yes	24	0	0.0	
Personal history of autoimmune disease				
No	359	30	8.4	0.348
Yes	41	1	2.4	
Personal history of psoriasis				
No	379	29	7.7	0.673
Yes	21	2	9.5	
Smoker				
No	250	16	6.4	0.210
Yes	130	13	10.0	
Corticosteroid therapy				
No	393	31	7.9	1
Yes	7	0	0.0	
Immunosuppressive therapy				
No	397	30	7.6	0.215
Yes	3	1	33.3	

Table 3. Analysis of factors associated with a low BMI (≤18.5) in vitiligo patients

	N	BMI <20		*p* value
		n	%	
Age				
<35 years	126	29	23.0	<0.001
35–49 years	116	23	19.8	
50+ years	158	10	6.3	
Sex				
Female	216	49	22.7	<0.001
Male	184	13	7.1	
Type of vitiligo onset				
Early (age <18 years)	49	12	24.5	0.023
Late (age >18 years)	150	17	11.3	
Speed of vitiligo onset				
Sudden	83	11	13.3	0.602
Gradual	113	18	15.9	
Growth of vitiligo lesions				
Absent	12	2	16.7	0.639
Slow	145	23	15.9	
Rapid	40	4	10.0	
Inflammation/pruritus				
No	147	25	17.0	0.143
Yes	48	4	8.3	
Total vitiligo extension				
<1.0%	50	8	16.0	0.254
1.0–4.9%	71	13	18.3	
≥5.0%	51	4	7.8	
Disease activity				
Active	104	16	15.4	0.843
Borderline	34	4	11.8	
Stable	56	9	16.1	
Koebner phenomenon				
No	99	13	13.1	0.556
Yes	93	15	16.1	
Personal history of cardiovascular disease				
No	340	59	17.4	0.015
Yes	60	3	5.0	
Personal history of cancer				
No	375	59	15.7	1
Yes	24	3	12.5	
Personal history of autoimmune disease				
No	359	54	15.0	0.454
Yes	41	8	19.5	
Personal history of psoriasis				
No	379	59	15.6	1
Yes	21	3	14.3	
Smoker				
No	250	40	16.0	0.969
Yes	130	21	16.2	
Corticosteroid therapy				
No	393	60	15.3	0.297
Yes	7	2	28.6	
Immunosuppressive therapy				
No	397	62	15.6	1
Yes	3	0	0.0	

inhibitor of white adipose tissue differentiation [18, 28, 29].

Thus, it is conceivable that the high expression of p53 and the high concentration of transforming growth factor-β can contribute to the absence of obesity in our patients, as opposed to other autoimmune diseases.

A possible limitation of this study was noninvestigation of p53 and transforming growth factor-β, which could have affected the findings.

Conclusion

In this study, in contrast with most autoimmune diseases which are significantly associated with obesity, vitiligo did not appear to be related to a high BMI. Therefore, neither a high BMI nor obesity represents a feature of vitiligo in these patients and this seems to be an unusual autoimmune disease.

Appendix 1

General characteristics of the case and control groups.

Characteristic	Vitiligo (n = 200)	Control (n = 200)
Gender		
Female	108	108
Male	92	92
Age range	14–75	17–76
Type of onset of vitiligo		
Early (age <18 years)	49 (24.6%)	
Late (age >18 years)	150 (75.4%)	
Speed of vitiligo onset		
Sudden	83 (42.3%)	
Gradual	113 (57.7%)	
Growth of vitiligo lesions		
Absent	12 (6.1%)	
Slow	145 (73.6%)	
Rapid	40 (20.3%)	
Inflammation/pruritus		
No	147 (75.4%)	
Yes	48 (24.6%)	
Disease activity		
Active	104 (53.6%)	
Borderline	34 (17.5%)	
Stable	56 (28.9%)	
Total vitiligo extension		
<1%	50 (29.1%)	
1–4.9%	71 (41.3%)	
≥5%	51 (29.7%)	
Koebner's phenomenon		
No	99 (51.6%)	
Yes	93 (48.4%)	
Personal history of cardiovascular disease		
No	176 (88.0%)	164 (82.0%)
Yes	24 (12.0%)	36 (18.0%)
Personal history of autoimmune disease		
No	165 (82.5%)	194 (97.0%)
Yes	35 (17.5%)	6 (3.0%)
Personal history of cancer		
No	191 (96.0%)	184 (92.0%)
Si	8 (4.0%)	16 (8.0%)
Personal history of psoriasis		
No	190 (95.0%)	189 (94.5%)
Yes	10 (5.0%)	11 (5.5%)
Corticosteroid therapy		
No	198 (99.0%)	195 (97.5%)
Yes	2 (1.0%)	5 (2.5%)
Immunosuppressive therapy		
No	200 (100.0%)	197 (98.5%)
Yes	0 (0.0%)	3 (1.5%)

References

1 Ezzedine K, Eleftheriadou V, Whitton M, et al: Vitiligo. Lancet 2015;386:74–84.
2 Conti R, Colucci R, Arunachalam M, et al: Hair and scalp disorders in a Tuscan pediatric dermatological outpatient clinic: a clinical and epidemiological evaluation. Med Princ Pract 2016;25:67–71.
3 Ongenae K, Van Geel N, Naeyaert JM: Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Res 2003;16:90–100.
4 Colucci R, Dragoni F, Moretti S: Oxidative stress and immune system in vitiligo and thyroid diseases. Oxid Med Cell Longev 2015; 2015:631927.
5 Al-Herz A, Al-Awadhi A, Saleh K, et al: Low prevalence of modules in rheumatoid arthritis patients in Kuwait: a description and a comparison of patients from the Kuwait Registry for Rheumatic Diseases. Med Princ Pract 2017;26:152–156.
6 Procaccini C, Carbone F, Galgani M, et al: Obesity and susceptibility to autoimmune diseases. Expert Rev Clin Immunol 2011;7: 287–294.
7 Versini M, Jeandel PY, Rosenthal E, et al: Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev 2014;13: 981–1000.
8 Winsz-Szczotka K, Kuznik-Trocha K, Komosinska-Vassev K, et al: Relationship between adiponectin, leptin, IGF-1 and total lipid peroxides plasma concentrations in patients with systemic sclerosis: possible role in disease development. Int J Rheum Dis 2016;19:706–714.
9 Arunachalam M, Dragoni F, Colucci R, et al: Non-segmental vitiligo and psoriasis comorbidity – a case-control study in Italian patients. J Eur Acad Dermatol Venereol 2014; 28:433–437.
10 Bulló M, García-Lorda P, Megias I, et al: Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. Obes Res 2003;11:525–531.
11 Procaccini C, Pucino V, Mantzoros CS, et al: Leptin in autoimmune diseases. Metabolism 2015;64:92–104.
12 Fidan-Yaylali G, Yaylali YT, Erdogan Ç, et al: The association between central adiposity and autonomic dysfunction in obesity. Med Princ Pract 2016;25:442–448.
13 Bagir GS, Bakiner OS, Bozkirli E, et al: Body mass index below obesity threshold implies similar cardiovascular risk among various polycystic ovary syndrome phenotypes. Med Princ Pract 2016;25:61–66.
14 Camara-Lemarroy CR, Salas-Alanis JC: The role of tumor necrosis factor-α in the pathogenesis of vitiligo. Am J Clin Dermatol 2013; 14:343–350.
15 Moretti S, Spallanzani A, Amato L, et al: New insights into the pathogenesis of vitiligo: Imbalance of epidermal cytokines at sites of lesions. Pigment Cell Res 2002;15:87–92.
16 Singh S, Singh U, Pandey SS: Serum concentration of IL-6, IL-2, TNF-α, and IFNγ in vitiligo patients. Indian J Dermatol 2012;57:12–14.
17 Yu HS, Chang KL, Yu CL, et al: Alterations in IL-6, IL-8, GM-CSF, TNF-alpha, and IFN-gamma release by peripheral mononuclear cells in patients with active vitiligo. J Invest Dermatol 1997;108:527–529.
18 Zhou L, Shi YL, Li K, et al: Increased circulating Th17 cells and elevated serum levels of TGF-beta and IL-21 are correlated with human non-segmental vitiligo development. Pigment Cell Melanoma Res 2015;28:324–329.
19 Karadag AS, Tutal E, Ertugrul DT: Insulin resistance is increased in patients with vitiligo. Acta Derm Venereol 2011;9:541–544.
20 Rodríguez-Martín M, de Paz NM, Mehtani P, et al: Patients with vitiligo present fewer cardiovascular risk factors: results from a case-control study. J Eur Acad Dermatol Venereol 2013;27:124–125.
21 Moretti S, Arunachalam M, Colucci R, et al: Autoimmune markers in vitiligo patients appear correlated with obsession and phobia. J Eur Acad Dermatol Venereol 2012;26:861–867.
22 Taïeb A, Picardo M; VETF Members: The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment Cell Res 2007;20:27–35.
23 Makki K, Froguel P, Wolowczuk I: Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm 2013;2013:139239.
24 Vousden KH, Prives C: Blinded by the light: the growing complexity of p53. Cell 2009;137: 413–431.
25 Schallreuter KU, Behrens-Williams S, Khaliq TP, et al: Increased epidermal functioning wild-type p53 expression in vitiligo. Exp Dermatol 2003;12:268–277.
26 Salem MM, Shalbaf M, Gibbons NC, et al: Enhanced DNA binding capacity on up-regulated epidermal wild-type p53 in vitiligo by H2O2-mediated oxidation: a possible repair mechanism for DNA damage. FASEB J 2009; 23:3790–3807.
27 Molchadsky A, Ezra O, Amendola PG, et al: p53 is required for brown adipogenic differentiation and has a protective role against diet-induced obesity. Cell Death Differ 2013;20: 774–783.
28 Choy L, Derynck R: Transforming growth factor-beta inhibits adipocyte differentiation by Smad3 interacting with CCAAT/enhancer-binding protein (C/EBP) and repressing C/EBP transactivation function. J Biol Chem 2003;278:9609–9619.
29 Ali AT, Hochfeld WE, Myburgh R, et al: Adipocyte and adipogenesis. Eur J Cell Biol 2013; 92:229–236.