Acta Dermatovenerol Croat 2022;30(1):8-17 ORIGINAL SCIENTIFIC ARTICLE

The Association Between the Severity of Psoriasis and Obesity Based on the Analysis of Visceral Fat Index and Serum Levels of Tumor Necrosis Factor-α, Interleukin-6, and Resistin

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ABSTRACT Aim of this study was to investigate the relationship between the severity of psoriasis and obesity based on the analysis of the visceral fat index and serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and resistin. The study included 50 patients with psoriasis and 30 subjects in the control group. The measured parameters were height, weight, waist circumference, visceral fat index, and serum levels of TNF-α, IL-6, and resistin. The severity of the disease was evaluated using the psoriasis area and severity index (PASI). Visceral fat index was measured using the method of bioelectrical impedance analysis. Serum levels of TNF-α, IL-6, and resistin were correlated with visceral fat index, and the relationship of all these parameters with psoriasis severity was also analyzed. Patients with psoriasis have a significantly higher body mass index, waist circumference, and visceral fat index compared with the control group. Elevated serum levels of TNF-α, IL-6, and resistin, as well as a correlation with psoriasis severity and visceral fat index was also found in the patient group. Visceral fat index was a better indicator of the relationship between psoriasis severity and obesity than waist circumference and body mass index.

We concluded that serum levels of TNF-α, IL-6, and resistin could be useful in assessing psoriasis activity and optimizing therapeutic strategies. It is suggested that visceral fat index should be evaluated in all patients with psoriasis, especially before the decision on systemic therapy.

KEY WORDS: psoriasis, obesity, visceral fat, TNF-α, IL-6, resistin, PASI

INTRODUCTION

Psoriasis is an immune-mediated, chronic inflammatory disease of multifactorial etiology, affecting 1-3% of the world's population (1,2). Although it was described in ancient times (3), very little was known about this disease for centuries, which even resulted in the isolation of patients during the Middle Ages (4). It was not until the 19th century that psoriasis was recognized as a separate clinical entity (5), and

until recently it was considered to be limited only to the skin.

Numerous studies conducted in the past thirty years have significantly contributed to the understanding of psoriasis pathogenesis (6). Psoriasis develops primarily in people with a genetic predisposition under the influence of various endogenous and exogenous provoking factors. Clinically, it most often manifests as plaques with erythema, infiltration, and desquamation on the skin (7). Only in recent years, psoriasis has been increasingly recognized as a systemic disease in which an increased release of proinflammatory cytokines and chronic activation of the innate and acquired immune systems cause long-term damage to various tissues and organs (8). Psoriasis considerably impairs the quality of life, and the financial aspect should also not be neglected, as it also affects the working ability in addition to the high costs of psoriasis treatment.

With worsening psoriasis severity, the risk of comorbidities also increases. Obesity is among the most important comorbidities one can influence in patients with psoriasis. Given that psoriasis is a chronic disease, and obesity is one of the leading health problems today (9), the prevalence of obese patients with psoriasis can be expected to further increase. Despite great advancements in psoriasis research in recent years, which have enabled important insights into its pathogenesis and development of new targeted therapies, the mechanism of its association with obesity has not yet been fully elucidated. Although most studies show that obesity increases the risk of developing psoriasis and leads to worse long-term outcomes due to the presence of chronic inflammation (10-14), obesity may also be a consequence of psoriasis due to disturbed metabolism and impaired quality of life of individuals suffering from the disease (15). In a large prospective study from 2017, Snekvik *et al*. found that obesity and high abdominal fat mass double the risk of psoriasis (16). These results suggest that an increased amount of visceral fat may play a role in the onset as well as the worsening of the existing psoriasis.

Adipose tissue, especially visceral fat, is a metabolically active endocrine, autocrine, and paracrine organ that affects a number of metabolic processes (17-20). Adipocytes and other cells in adipose tissue secrete more than 50 bioactive molecules (21) which are involved in the regulation of homeostasis, metabolism, and inflammatory processes (17,22). Because adipocytokines can lead to a proinflammatory state in obese individuals (23), obesity can be considered a low-grade chronic systemic inflammatory disease (24).

Since there are still many unresolved questions concerning the interaction of chronic inflammation in psoriasis and obesity, the aim of this study was to investigate the association between psoriasis severity

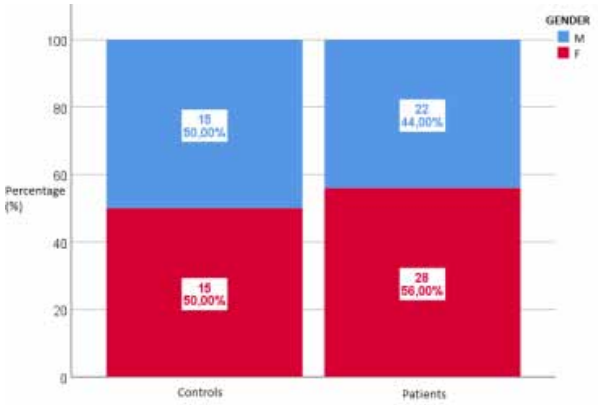

Figure 1. Sex differences between the groups (Fisher exact test, *P*=0.648).

Table 1. Socio-demographic, clinical, and anthropometric differences between the groups (Mann-Whitney U test)

		N	Min	Max	Centile			P
					25.	Median	75.	
Age (years)	Controls	30	23.00	67.00	29.75	40.50	54.00	0,210
	Patients	50	19.00	65.00	34.75	47.00	58.00	
Psoriasis lasting (years)	Controls	0						NA
	Patients	50	1.00	48.00	7.00	14.50	28.00	
PASI	Controls	0						NA
	Patients	50	1.50	36.60	8.10	10.75	15.43	
BMI	Controls	30	19.90	33.80	22.88	25.60	27.58	0.001
	Patients	50	19.30	42.60	26.00	28.20	30.45	
Waist circumference (cm)	Controls	30	65.00	105.00	78.75	88.00	95.50	0.001
	Patients	50	66.00	125.00	87.75	98.00	104.25	
Visceral fat index	Controls	30	1.00	12.00	3.75	6.00	7.00	<0,001
	Patients	50	1.00	14.00	6.00	9.00	11.25	

and obesity based on the analysis of visceral fat index and serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and resistin.

PATIENTS AND METHODS

This study was conducted from October 2017 to June 2018 at the Department of Dermatology and Venereology, University Hospital Center Zagreb and University of Zagreb School of Medicine, in collaboration with the Department of Physiology and the Center for Sports Medicine and Health Promotion at Work, School of Medicine, Andrija Stampar School of Public Health. Ethical approval was given by the Ethics Committee of the University Hospital Centre Zagreb (02/21 AG). The study was carried out according to the ethical principles of the Declaration of Helsinki.

The study included 50 patients with histopathologically verified vulgar psoriasis and 30 subjects of matching age and sex but without personal or family history of psoriasis. The criteria for exclusion were age under 18 years, pregnancy, breastfeeding, accompanying systemic inflammatory or autoimmune disease, active malignant disease, immunodeficiency, systemic immunosuppressive drugs, acute or chronic infection, ongoing systemic antibiotic therapy, pacemaker implantation, or any metal implants. The specific exclusion criteria for patients with psoriasis were taking any systemic psoriasis therapy four weeks before the trial and presence of other clinical forms of psoriasis. All the subjects signed written consent forms and were assigned an identification number in order to protect their identity.

The following parameters were measured: height, weight, waist circumference, visceral fat index, and serum levels of TNF-α, IL-6, and resistin. All the patients were clinically examined, a detailed history was taken, and the severity of the disease was evaluated

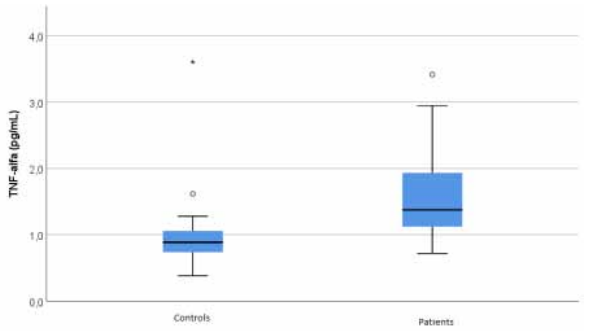

Figure 2a. TNF-α levels in serum of patients with psoriasis and matched controls (Mann Whitney U test, *P*<0.001).

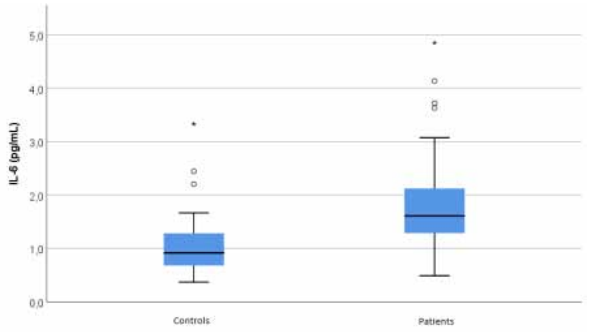

Figure 2b. IL-6 levels in serum of patients with psoriasis and matched controls (Mann Whitney U test, *P*<0.001).

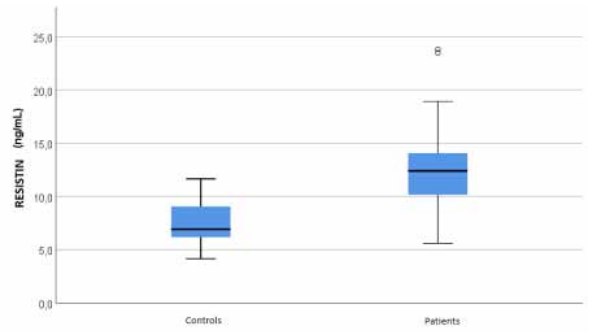

Figure 2c. Resistin levels in serum of patients with psoriasis and matched controls (Mann Whitney U test, *P*<0.001).

Table 2. Differences in serum levels of TNF-α, IL-6, and resistin between patients with psoriasis and the control group (Mann-Whitney U test)

		N	Min	Max	Centile			P
					25.	Median	75.	
TNF-α (pg/mL)	Controls	30	0.38	3.60	0.73	0.89	1.06	<0.001
	Patients	50	0.72	9.94	1.11	1.38	1.97	
IL-6 (pg/mL)	Controls	30	0.37	22.72	0.68	0.92	1.29	<0.001
	Patients	50	0.49	4.85	1.29	1.61	2.13	
RESISTIN (ng/mL)	Controls	30	4.17	11.66	6.17	6.93	9.08	<0.001
	Patients	50	5.61	23.83	10.14	12.40	14.20	

Table 3. Correlation of TNF-α, IL-6, and resistin with PASI (Spearman's correlation coefficient rho)

		PASI
TNF-α (pg/mL)	Correlation coefficient	0.735
	P	<0.001
	N	50
IL-6 (pg/mL)	Correlation coefficient	0.666
	P	<0.001
	N	50
RESISTIN (ng/mL)	Correlation coefficient	0.584
	P	<0.001
	N	50

based on the psoriasis area and severity index (PASI). In order to make the assessment objective, all the patients were evaluated by the same dermatologist.

Venous blood samples of 5 mL were obtained from the antecubital vein after an 8-hour fasting period during the early morning. The tubes were marked with the appropriate identification number, it was thus not known during the analysis whether the samples belonged to the patients or controls. The serum was separated and kept at -20 °C until the time of use. The serum levels of TNF-α, IL-6, and resistin were determined by enzyme-linked immunosorbent assay (ELISA) using commercial kits (R&D Systems, Bio-Techne Ltd., UK). Visceral fat was measured by bioelectrical impedance analysis using the Tanita product (BC-418, Tanita Corporation of America Inc., Arlington Heights, IL, USA) after at least 3 hours of fasting and rest.

Statistical analysis

Nonparametric distribution was confirmed using the Kolmogorov-Smirnov normality test, and corresponding nonparametric tests were conducted in further statistical analysis. The differences between the groups were analyzed with the Mann-Whitney U test, shown as a box and whisker plot. The differences in categorical values were assessed with the Fisher exact test. Spearman's correlation coefficient was used in the analysis of the following parameters: correlation of TNF-α, IL-6 and resistin with PASI; correlation of TNF-α, IL-6 and resistin with visceral fat index; correlation of PASI with body mass index (BMI), waist circumference, and visceral fat index. Absolute values of correlation coefficients greater than 0.600

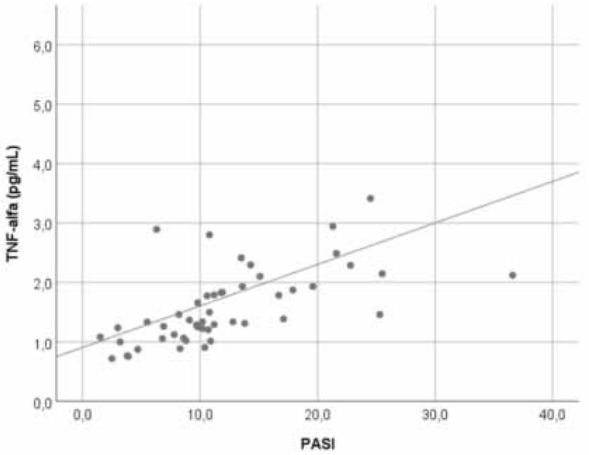

Figure 3a. Disease severity (PASI) correlated with patients' serum TNF-α levels (Spearman's correlation coefficient rho).

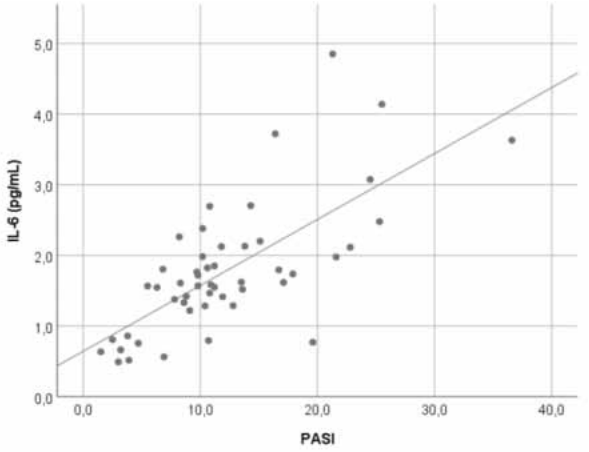

Figure 3b. Disease severity (PASI) correlated with patients' serum IL-6 levels (Spearman's correlation coefficient rho).

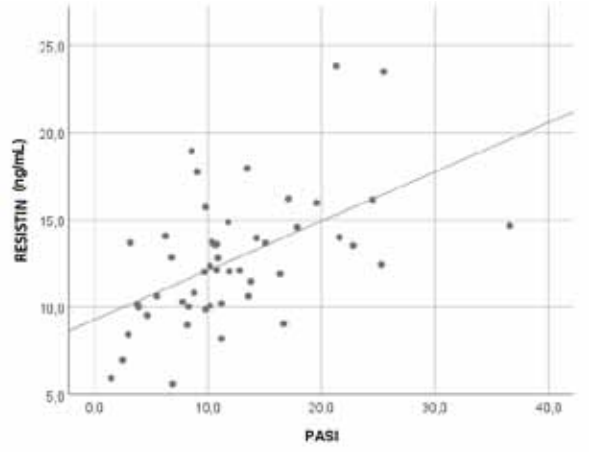

Figure 3c. Disease severity (PASI) correlated with patients' serum resistin levels (Spearman's correlation coefficient rho).

Table 4. Correlation of TNF-α, IL-6, and resistin with visceral fat index (Spearman's correlation coefficient rho)

		Control group	Patients with psoriasis
		Visceral fat index	Visceral fat index
TNF-α (pg/mL)	Correlation coefficient	0.454	0.457
	P	0.012	0.001
	N	30	50
IL-6 (pg/mL)	Correlation coefficient	0.544	0.415
	P	0.002	0.003
	N	30	50
RESISTIN (ng/mL)	Correlation coefficient	0.206	0.502
	P	0.274	<0.001
	N	30	50

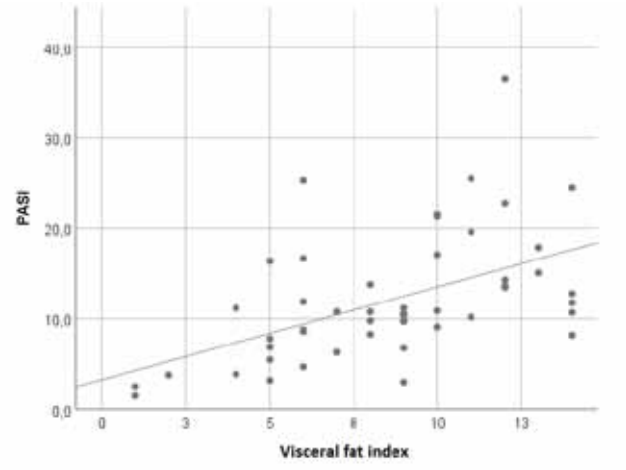

Figure 4. Correlation of psoriasis severity (PASI) and visceral fat index.

were considered strong correlations, values from 0.300 to 0.599 were considered correlations of medium strength, while values less than 0.300 were considered weak correlations, whether positive or negative. All *P* values lower than 0.05 were considered significant. Data preparation was performed using a Microsoft Office Excel computer spreadsheet. Statistical analysis was performed with IBM SPSS Statistics version 25 (IBM Corporation, NY, USA).

RESULTS

Socio-demographic, clinical, and anthropometric differences between the two groups are shown in Table 1. There were no significant differences with respect to age (*P*=0.210) and sex (Figure 1, P=0.648). Median (interquartile range) duration of psoriasis in patients was 14.5 (7.0-28.0) years. Compared with the control group, patients with psoriasis had significantly higher body mass index (*P*=0.001), waist circumference (*P*=0.001)m and visceral fat index (*P*<0.001).

Differences in serum levels of TNF-α, IL-6, and resistin are shown in Table 2 and Figures 2a, 2b, and 2c. In patients with psoriasis, serum levels of TNF-α, IL-6, and resistin were significantly higher than in the control group (*P*<0.001). PASI showed a significant positive correlation with serum levels of TNF-α (rho=0.735, *P*<0.001, Figure 3a), IL-6 (rho=0.666, P<0.001, Figure 3b), and resistin (rho=0.584, *P*<0.001, Figure 3c). Of all the measured serum parameters, TNF-α showed the strongest correlation with psoriasis severity (Table 3).

Visceral fat index showed a positive correlation with TNF-α and IL-6 both in patients with psoriasis and in matching controls. A positive correlation of visceral fat index and resistin was significant only in patients with psoriasis (Table 4). Correlation of psoriasis severity with body mass index, waist circumference, and visceral fat index is shown in Table 5. The strongest correlation of all the measured anthropo-

Table 5. Correlation of PASI with BMI, waist circumference, and visceral fat index (Spearman's correlation coefficient rho)

		PASI
BMI	Correlation coefficient	0.446
	P	0.001
	N	50
Waist circumference	Correlation coefficient	0.452
	P	0.001
	N	50
Visceral fat index	Correlation coefficient	0.560
	P	<0.001
	N	50

metric parameters was with the visceral fat index (rho=0.560, *P*<0.001, Figure 4).

DISCUSSION

This study analyzed the relationship between psoriasis and obesity in a comprehensive way, correlating various parameters that are usually investigated separately. Earlier studies have primarily been based on body mass index as a measure of obesity and have not considered visceral fat, which may be an essential factor in the inflammatory state present in obesity. In our study, visceral fat index was analyzed and correlated with serum levels of cytokines in order to objectify the systemic inflammation that accompanies both psoriasis and obesity. Serum levels of TNF-α, IL-6, and resistin were correlated with visceral fat index, and the association of all these parameters with psoriasis severity was also analyzed.

Epidemiological studies have shown that patients with psoriasis have a higher BMI compared with the general population (25). Our study confirmed that patients with psoriasis have a significantly higher BMI compared with controls (*P*=0.001) and that it significantly positively correlates with disease severity (*P*=0.001). These results are consistent with majority of studies that have investigated the association between BMI and PASI (26). Nevertheless, BMI used for classification of obesity cannot asses waist circumference, muscle mass, adipose tissue, bone structure, age, sex, race, or the amount of visceral fat. A study from 2017 has shown that even the patients with psoriasis who were not obese according to the BMI classification may have an increased total fat percentage (27). This clearly shows that BMI is not the best method for assessing obesity in patients with psoriasis, because it is the adipose tissue that plays a key role in inflammation and associated comorbidities (28,29).

A small number of studies conducted so far have measured waist circumference in patients with psoriasis (30-34). The results of our study have shown that waist circumference was significantly larger in the patient group of than in controls (*P*=0.001). Two groups of researchers sought to determine the association of waist circumference with the severity of psoriasis. Sobhan *et al*. failed to confirm this correlation (35), while the results of the study by Petridis *et al*. suggested a weak correlation between waist circumference and PASI (36). According to the results of our study, the values of waist circumference significantly correlate with psoriasis severity (*P* = 0.001).

Despite the fact that body composition may be an important factor in treatment planning (29), surprisingly few studies have evaluated visceral fat in patients with psoriasis. A study from 2016 has shown that dual x-ray absorptiometry (DXA) is a better method for assessing obesity than BMI or waist circumference, but no statistically significant differences were found between the patient and the control groups (37). Using computerized tomography (CT), two studies have demonstrated a higher percentage of visceral fat in patients with psoriasis compared with controls (38,39). Nevertheless, it is important to keep in mind that CT and other methods that use ionizing radiation also carry a number of health risks, such as the development of malignant tumors (40,41). Since the risks of using such methods to assess body composition outweigh the possible benefits, it can be concluded that their use for this purpose is not justified. Therefore, , a safe and accurate method was used to assess visceral fat in our research – bioelectrical impedance analysis (BIA).

BIA is a noninvasive method that uses a weak electrical signal and is the most suitable method for the measurement of visceral fat accumulation (42). Very few studies so far have assessed visceral fat in patients with psoriasis using BIA (34,43,44). Our study found that visceral fat index was significantly higher in patients with psoriasis than in the control group (*P*<0.001). The difference between the patients and controls was more significant with regard to visceral fat index (*P*<0.001) than in waist circumference and BMI (*P*=0.001). Our results have also shown that although psoriasis severity statistically significantly positively correlates with BMI, waist circumference, and visceral fat index, the strongest correlation was with visceral fat index (*P*<0.001). It can therefore be concluded that for patients with psoriasis it is more valuable to determine visceral fat index than BMI or waist circumference.

The association between psoriasis and increased visceral fat is a chronic inflammatory state (15) mediated by various proinflammatory mediators, particularly elevated levels of the multifunctional cytokine TNF-α (45). Most studies have found elevated serum levels of TNF-α in patients with psoriasis (46,47), which was also confirmed in our study. On the other hand, the results of the studies conducted so far investigating the correlation of TNF-α with the psoriasis severity were contradictory (18,48,49). According to the results of our study, serum TNF-α levels significantly positively correlate with PASI (*P*<0.001). Moreover, of all the measured parameters in serum, the strongest correlation with disease severity was that with TNF-α. A very small number of studies have investigated the association between TNF-α and obesity in patients with psoriasis, finding contradictory results (18,44,49). Unlike these studies that have

used exclusively BMI for obesity classification, our study used the visceral fat index for this purpose and have found a significant correlation between visceral fat index and TNF-α in both groups, with the stronger correlation in patients with psoriasis. This shows that the circulating TNF-α at least partially originates from visceral fat. Since the role of TNF-α inhibitors in the treatment of psoriasis is the elimination of TNF-α from circulation, and its secretion is increased from visceral adipose tissue in obese individuals (19,23) as also indicated by the results of our study, this group of drugs could have lower efficacy in obese patients (50-52).

Although the results of most studies show elevated levels of IL-6 in patients with psoriasis (46), its correlation with disease severity is still inconclusive (18,48,53). Our study found significantly higher levels of IL-6 in the patient group compared to controls ($P<0.001$), as well as a significant positive correlation to PASI ($P<0.001$). The association of IL-6 with obesity in patients with psoriasis has been poorly investigated and only using BMI as a measure of obesity (54). The results of several studies conducted so far have not demonstrated a correlation between IL-6 and BMI (18,53,55). The results of this study speak in favor of a strong association between IL-6 and obesity, especially in patients with psoriasis. Serum IL-6 levels were shown to significantly correlate with the visceral fat index both in patients ($P=0.003$) and the control group ($P=0.002$).

Our results of significantly increased resistin levels in patients with psoriasis compared with the control group ($P<0.001$) are in concordance with previously published studies (56). Although its correlation to PASI is still inconclusive (18,49,53), several studies have suggested that improvement of psoriasis during treatment results in a decrease in serum resistin concentration (57,58). The results of our study show a clear correlation of resistin serum levels both with PASI ($P<0.001$) and with visceral fat index ($P<0.001$) in patients with psoriasis.

According to the results of our study, TNF-α, IL-6, and resistin may serve as biomarkers in the evaluation of the clinical status of patients with psoriasis and may be indicators of disease activity. Since our study showed a significant correlation of TNF-α, IL-6, and resistin with both the psoriasis severity and the visceral fat index, these cytokines may be the link between the chronic inflammatory state in psoriasis and obesity. Their elevated systemic levels could significantly impact the treatment of obese patients with psoriasis, a group that requires an individual therapeutic approach, which is often not the case in practice. Obesity can reduce the response to systemic psoriasis treatment (50,59), and obese patients with psoriasis have a higher risk of treatment side-effects (29,50,59). Reduction of excess visceral fat could lead to a reduction of systemic inflammation mediated by proinflammatory cytokines (29,59) and improve efficacy and safety of treatment in patients with psoriasis. The results of this study have confirmed visceral fat to be an important factor that influences an increase of proinflammatory cytokines. We have found that elevated levels of TNF-α, IL-6, and resistin directly correlate with increased visceral fat in patients with psoriasis. Although less pronounced, a significant association was also present in the control group between visceral fat and cytokines TNF-α and IL-6. Our results also show that visceral fat index is a better indicator of the relationship between psoriasis and obesity than waist circumference and BMI, since it showed the strongest correlation with disease severity.

CONCLUSION

The results of our study suggest that visceral fat, using BIA as a safe method of measurement, should be assessed in every patient with psoriasis, especially before initiating systemic therapy. Individuals who are not considered obese according to the BMI classification should also be included, as they too may have increased visceral fat. This could have an impact on preventing the development of obesity-related comorbidities as well as improving the treatment strategy even of those patients who were not previously considered to be in a risk group. The limitations of this study were the relatively small number of subjects and the inability to determine the sources of cytokines measured in serum. Therefore, further research is needed to elucidate the mechanism of action and role of each of the measured serum parameters in patients with psoriasis, as well as clinical studies that would analyze the visceral fat in a larger number of subjects. If our results are confirmed, visceral fat measurement and reduction of excess body weight should certainly be introduced in the treatment guidelines of patients with psoriasis.

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