Body Composition Evaluated by Bioelectrical Impedance Analysis in Patients With Pemphigus Vulgaris

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Research Article

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Abstract

Background:

Pemphigus is a rare autoimmune disease affecting the skin and mucosa. Metabolic dysfunctions are shown to be associated with this disorder. The pemphigus disease area index (PDAI) score has been used as an accurate tool to assess the severity of pemphigus. This study aimed to evaluate the association between nutritional, metabolic indexes and Phase angle (PhA) in patients with pemphigus vulgaris (PV) and severity of disease based on the PDAI index.

Methods:

In this regard, 103 pemphigus patients and 125 healthy cases who were matched regarding their sex, age and body mass index were chosen.

Results:

Our results showed that there was a significant correlation between phase angle and sarcopenic index in patients with PV. Moreover, steroid dose had a significant correlation with sarcopenia index; while had no correlation with visceral fat area (VFA), BMI, volume load, percent body fat (PBF), and PhA. The volume load was lower but phase angle and sarcopenic index were higher in males, and females had a significantly higher BMI. Moreover, PBF and VFA were significantly higher in females compared to males. Besides, patients treated with rituximab had lower PBF and higher sarcopenic index and volume loads compared to patients receiving other adjuvant treatments. In comparison to healthy controls, PV patients had a significantly higher VFA and PBF.

Conclusion:

Conclusively, patients with PV had a significantly higher VFA and PBF compared to healthy objects. Moreover, sarcopenic index was related to steroid dose and history of rituximab treatment.

1. Introduction

Pemphigus vulgaris (PV) is a potentially life-threating autoimmune blistering disease that is characterized by autoantibodies targeting keratinocytes and resulting in acantholysis.[1] PV can affect both the skin by producing anti-desmoglein-1(anti-Dsg1) and the mucosa due to the production of anti-Dsg3.[1,2] In 2008, international pemphigus committee developed the pemphigus disease area index (PDAI) score to evaluate the extent of mucous lesions and skin severity damage.[3] Recent evidence suggests that metabolic imbalance is more commonly involved in chronic skin disorders such as psoriasis, lichen planus, and pemphigus. Chronic inflammatory diseases and their underlying mechanisms cause metabolic abnormalities.[4] Although glucocorticosteroid in high dose is the first treatment given for pemphigus, it may cause severe side effects which lead to set off risk factors for metabolic syndrome,[1,2,

[5] and also contributes into development of atherosclerotic cardiovascular disease.[5] It has been documented that corticosteroids increase the total cholesterol and triglyceride serum level in patients with pemphigus. Thus, dyslipidemia may be observed among patients with pemphigus.[5]

Bioelectrical impedance analysis (BIA) is a useful, non-invasive, and relatively inexpensive diagnostic tool for checking parameters such as body fat percentage, hydration (intracellular, extracellular, total) and electrolyte content of the body which are essential for the overall health.[6, 7] Phase Angle (PhA) is a reliable indicator of health that is measured by BIA and is used extensively in health care. PhA demonstrates the integrity of the cell membrane, the water distribution between intracellular and extracellular spaces and the prediction of cell mass. It is associated with cellularity, cell size and also depends on tissue hydration. It has been shown that PhA reduction is correlated with cell death and reflects the cell membrane degradation.[6–8] In healthy people, PhA is affected by age, sex, and body mass index (BMI). Due to specific parameters of the disease and inflammation, PhA in metabolic syndrome condition is usually lower than normal. In various studies, PhA has been proposed as a prognostic mortality factor in chronic diseases such as malignancy, diabetes, and obesity.[6,7] The recent study in psoriatic patients has shown that PhA levels alternation is related to the severity of the disease and metabolic syndrome.[9]

Considering the previous studies in this field, this study aimed to investigate the extent of nutritional and metabolic indexes including percent body fat (PBF), visceral fat area (VFA) and sarcopenia as well as PhA in patients with PV, and evaluate their association with the severity of the disease based on the PDAI index.

2. Materials And Methods

Patients

This cross-sectional study was performed on 103 patients with PV and 125 healthy subjects who referred to … dermatology clinic in …, … in 2017-2018. All the patients were fully enlightened about the study objectives, methods and signed an informed written consent. The diagnosis of PV was made based on skin biopsy and direct immunofluorescence test. Patients with medical history of chronic disease, malignancy, and chemotherapy in the last five years were excluded from this study.

Clinical assessments

The following demographic data were recorded for each patient: age, sex, age of disease onset, illness duration, and alcohol consumption. Physicians scored the severity of the disease by using the PDAI index. Patients' PBF and VFA were measured and also sarcopenia index was assessed in all patients. All experiments were carried out at the … Hospital laboratory.

Afterwards, anthropometric indicators including height, weight, waist circumference (WC) were measured without shoes and light indoor clothing by an experienced nurse.

BIA was performed with the use of an RJL instrument (model 101; RJL Systems, Mt Clemens, MI), which applies an 800-μA current at the frequency of 50 KHz. The measurements were performed under a strict standardization of the procedure, according to the National Institutes of Health.[1]

Statistical method:

The Kolmogorov-Smirnov test and Q-Q plot evaluated the normal distribution of quantitative data. To describe data, we used, mean, standard deviation, median, and range. To evaluate the difference among groups in the baseline, we used analysis of variance (ANOVA), Kruskal-Wallis test and Chi-Square test. Within each group we used a linear mixed model, to assess the changes. To compare the results in different, follow-ups adjusted for the baseline values, we used Analysis of Covariance (ANCOVA). Multiple comparisons considered by the Sidak method. All statistical analysis performed by SPSS software (IBM Corp. Released 2017. IBM SPSS statistics for windows, version 25.0, Armonk, NY: IBM Corp.). All the tests are two-sided and the p-value less than 0.05 considered statistically significant.

3. Results

The sample size in this study consisted of 103 pemphigus patients and 125 healthy individuals who were matched regarding their sex (p-value = 0.87), age (p-value = 0.67) and BMI (p-value = 0.07). The healthy cases had a mean age of 48 ± 12.8. The mean of age for cases was 48.7 ± 12.9 (Range: 18-77, Median 51). The average duration of disease was 46.7 ± 49.5 months (Range: 1-200 months).

3.1. Evaluation of Indexes in Pemphigus patients

In addition to routine corticosteroid therapy, the applied adjuvant treatments in pemphigus patients were as the following: 46.6% (48 individuals) received Rituximab and 14.6% (15 individuals) Mycophenolate Mofetil, 4.9% (5 individuals) Methotrexate, 2.9% (3 individuals) Azathioprine and 31.2% (32 individuals) were treated with no other adjuvant drugs. The mean cumulative dose for steroids was recorded as 14.6 ± 16 gr.

Evaluating other target indexes, our results showed that pemphigus patients had a PDAI of 6.86 ± 11, desmoglein 1 of 76.1 ± 83 and desmoglein 3 of 111.5 ± 82. Phase angle, PBF and VFA were recorded as 5.72 ± 0.81, 38.36 ± 10, 147.32 ± 54, respectively. At last, it was indicated that the patients had a sarcopenic index of 7.63 ± 3.9.

Evaluation of the correlations between PDAI, steroid cumulative doses, phase angle and sarcopenic index in all patients revealed that there was only a significant correlation between phase angle and sarcopenic index (Spearman rho = 0.689, P<0.001). Moreover, studying the correlation between steroid dose and

other assessed factors, it was revealed that steroid dose had a significant correlation with PDAI (Spearman rho = (-) 0.408, P<0.001), desmoglein 1 (Spearman rho = (-) 0.335, P=0.001) and desmoglein 3 (Spearman rho = (-) 0.199, P=0.044) and sarcopenia index (Spearman rho = (-) 0.214, P=0.030); while steroid dose had no correlation with VFA, BMI, volume load, PBF, cumulative steroid dose or phase angle (P>0.05).

Based on our finding there was no significant correlation between gender and type of adjuvant therapy and duration of treatment in this study (P>0.05). Cumulative doses of steroids were similar between both genders (P=0.34), the volume load was significantly lower in males (P=0.03), phase angle and sarcopenic index were both significantly higher in males compared to females (P<0.001) and females had a significantly higher BMI (P=0.017). However, there was no significant difference in PDAI, desmoglein 1 and 3, and age between sexes (P>0.05). Moreover, PBF and VFA were significantly higher in females compared to males (P<0.001) (Table 1).

Table 1
Comparison of indexes between different sexes and treatment durations

Index	Gender			Time		
	female	male	P-value*	More than 6 Months	Less than 6 Months	P-value*
cumulative dose	13.85 (±15.32)	16.15 (±17.69)	0.347	17.14 (±16.63)	2.65 (±1.95)	**<0.001**
Phase angle	5.04 (±0.68)	5.75 (±0.85)	**<0.001**	5.28 (±0.84)	5.22 (±0.64)	0.862
Sarcopenic Index	6.82 (±1.14)	9.28 (±6.42)	**<0.001**	7.74 (±4.32)	7.11 (±0.68)	0.670
Volume load	0.065 (±0.56)	-0.08 (±0.55)	**0.035**	-0.01 (±0.59)	0.14 (±0.35)	0.527
PDAI	7.59 (±13.25)	5.38 (±7.65)	0.895	4.68 (±9.36)	17.17 (±15.90)	**0.001**
desmoglein 1	75.35 (±83.47)	77.62 (±84.47)	0.860	66.74 (±78.8)	120.32 (±92.37)	**0.013**
desmoglein 3	107.09 (±82.45)	120.7 (±84.01)	0.438	96.28 (±80.81)	183.84 (±46.46)	**<0.001**
BMI	28.59 (±4.69)	26.28 (±4.63)	**0.017**	27.76 (±4.93)	28.15 (±4.08)	0.460
age	47.84 (±12.89)	48.53 (±13.35)	0.551	48.66 (±12.99)	45.28 (±12.92)	0.368
PBF	43.44 (±6.41)	28.05 (±8.55)	**<0.001**	38.02 (±10.52)	39.97 (±8.55)	0.561
VFA	167.36 (±43.14)	106.66 (±53.16)	**<0.001**	145.82 (±55.73)	154.43 (±49.58)	0.633

PDAI, pemphigus disease area index; BMI, body mass index; PBF, percent body fat; VFA, visceral fat area

Patients who were treated for less than six months had a significantly higher PDAI (P = 0.001), desmoglein 1 (P=0.013) and desmoglein 3 (P<0.001) and a significantly lower cumulative dose of steroids (P<0.001) compared to those treated for more than 6 months (Table 1). Moreover, there was significant reverse Spearman´s correlation between age and Phase angle (r = -0.399, P<0.001), sarcopenic Index (r= -0.263, P=0.007), cumulative steroid dose (r= -0.266, P=0.007) and volume load (r= -0.218, P=0.027).

In order to assess the effect of adjuvant treatments, there was a significant difference between patients receiving rituximab, other adjuvant therapies and no adjuvant therapy regarding age (P=0.002), PDAI

(P=0.011) and cumulative steroid dose (P=0.018). In addition, our results indicated that patients treated with rituximab received a significantly lower cumulative dose of steroids (P=0.002), and their age (P=0.002) and PBF (P=0.04) were significantly lower, while they had a significantly higher sarcopenic index (P=0.02) and higher volume loads (P=0.04) compared to patients receiving other adjuvant treatments. However, there was no significant difference regarding phase angle, PDAI, desmoglein 1 and 3, VFA and BMI (P>0.05).

Finally data revealed that there was a significant Spearman´s correlation between phase angle and sarcopenic index (r= 0.689, P<0.001), PBF (r= - 0.411, P<0.001), and VFA (r =-0.283, P=0.004). Further, PBF had significant reverse relation with sarcopenic index (r= -0.307, P=0.002) in pemphigus patients.

3.2. Comparison of pemphigus patients to control group

The differences of indexes between the case and control groups were also evaluated in this study. Based on the obtained results from student's t test, except for the VFA (P=0.021) and PBF(P=0.031), there was no significant difference between case and control groups in other indexes. In this regard, the results revealed that compared to healthy controls, PV patients had a significantly higher VFA (147.32 vs 131.06) and PBF (38.36 vs 35.63). Further details on the comparison of PV cases and healthy participants is demonstrated in Table 2. Moreover, patients who were affected by PV below one year duration (N=40) were also compared with healthy controls. Interestingly, similar results were obtained where there was only a significant difference between these patients and the control group regarding their VFA (153.54 vs 131, P = 0.017) and PBF (39.42 vs 35.63, P = 0.022).

Table 2
Comparison of Indexes between Pemphigus vulgaris patients and healthy subjects

Index	group	Mean	Std. Deviation	P-value
age	control	48.79	12.86	0.674
	case	48.07	12.98	
BMI	control	26.74	4.42	0.077
	case	27.83	4.77	
Phase angle	control	5.27	0.83	0.958
	case	5.27	0.81	
Sarcopenic index	control	7.16	1.21	0.488
	case	7.28	1.29	
VFA	control	131.06	50.8	**0.021**
	case	147.32	54.57	
BCM	control	29.79	6.07	0.957
	case	29.74	7.28	
ECW	control	13.08	2.61	0.987
	case	13.09	2.93	
ICW	control	20.80	4.24	0.842
	case	20.68	5.03	
TBW	control	33.89	6.81	0.859
	case	33.71	8.00	
PBF	control	35.63	8.76	**0.031**
	case	38.36	10.19	

BMI, body mass index; VFA, visceral fat area; BCM, body cell mass; ECM, extracellular mass; ICW, intracellular mass; TBW, total body water; PBF, percent body fat;

4. Discussion

The results of this case–control study report that there is no significant relationship between pemphigus and its severity and PhA, as the general indicator of cell membrane integrity. In comparison to healthy controls, PV patients had a significantly higher VFA and PBF. Our results showed that there was a significant reverse correlation between PhA and sarcopenic index in patients with PV. Moreover, steroid

dose had a significant correlation with sarcopenia index; while had no correlation with VFA, BMI, volume load, PBF, and PhA. The volume load was lower but PhA and sarcopenic index were higher in males, and females had a significantly higher BMI. Moreover, PBF and VFA were significantly higher in females compared to males. Besides, patients treated with rituximab had lower PBF and higher sarcopenic index and volume loads compared to patients receiving other adjuvant treatments.

PV is considered as an autoimmune disorder which dramatically reduces the quality of life. The preliminary experiences worldwide demonstrated rituximab a promising therapeutic option for patients with autoimmune disease.[2] In 2007, Joly et al. reported rituximab as an effective treatment for severe types of pemphigus. However, it has been suggested that due to potential side effects, its use should be limited to intervals of several months.[3] Our results revealed that rituximab reduced the needed cumulative doses of steroids in PV patients and resulted in significant difference in their clinical outcomes. The combined use of steroids with adjuvant therapies is a well-known therapy for PV, which is usually well tolerated and is generally believed to be more effective than steroid alone, both in terms of mortality and remission.[4] In harmony with this, our results showed that administration of co-adjuvants reduces the necessary cumulative steroid doses needed for PV patients which could potentially prevent further adverse effects by steroids as well as improving therapeutic results.

Pemphigus treatment has been a challenge and merely depends on experts who have abundant experience in this regard. The identification of proper means for assessing the severity and prognosis of the disease is a crucial query for PV clinical management. Currently, the autoimmune bullous skin disorder intensity score (ABSIS) and PDAI have been validated as scoring systems for this disease.[5] Rosenbach et al. reported that PDAI is more desirable to be performed by physicians compared to ABSIS.[6] There is evidence indicating that skin disease severity in pemphigus is relatively more related to Dsg1, while Dsg3 antibodies are involved in mucosal PV.[7] The PDAI score system includes three component associated with the skin, scalp and mucous membranes, so it had been confirmed that PDAI has high validity in grading the severity of PV.[5,6] However, more accurate objective instruments are needed to assess the disease's severity.

According to the literature, metabolic syndrome is related to the increased severity of psoriasis which is an immune-mediated skin disease.[8] Besides, it has been reported that metabolic syndrome correlated with PV.[9–10] In addition, glucocorticoids are the first treatment given for PV which the side effects of these drugs mainly lead to metabolic syndrome.[11] PhA is reversely associated with the clinical severity and the quality of life in psoriatic patients; and it represents a major prognostic value for the diagnosis of metabolic syndrome in psoriatic patients.[12] In harmony with this, evidence indicates that PhA is also inversely related to muscle mass and could be a proper biomarker to diagnose elderly patients at risk of sarcopenia.[13] In line with the phase angle reference values stratified by age, sex, and BMI,[14] higher values of PhA are expected among men because the PhA increases together with the muscle mass and the body cell mass. Furthermore, the PhA tends to decrease with age, as a function of the reduction of muscle mass and the influence of the alterations in the ICW/ECW ratio associated with aging.[12]

In different diseases such as Diffuse Large B-Cell Lymphoma (DLBCL) that are associated with sarcopenia, administration of rituximab has been shown to have potential therapeutic effects on the sarcopenia as well, if complete response occurs.[15–16] In the current study, patients treated with rituximab required lower cumulative dose of steroids while they had higher sarcopenia index and muscle mass, too. Considering previous studies, higher sarcopenia index could have occurred due to the patients' response to rituximab treatment. In addition, corticosteroids are known to cause muscle atrophy,[17] which means the lower cumulative doses of corticosteroids could have played a crucial role in PV patients' sarcopenia. However, further follow up is necessary to differentiate between these effects and provide a more accurate description.

On the other hand, there are some reports indicate that metabolic syndrome is a high-risk consequence of the sarcopenia especially in the patient with sarcopenic obesity.[18–20] Our study demonstrates that there is no correlation between the severity of pemphigus based on PDAI with PhA. Also, the administration of the high doses of the corticosteroid drug had direct association with PDAI in pemphigus patients, while it had a reverse association with sarcopenia index and there was no significant association of PhA, PBF, and VFA with steroid dose. Considering the reverse association of steroid dose and sarcopenia index and its direct correlation with PDAI, and the direct association between PhA and sarcopenia index, it could be concluded that PDAI has an indirect reverse relationship with PhA.

Taken together, our findings demonstrated that the severity of PV has not any association with the PhA. Moreover, patients with PV had a significantly higher VFA and PBF compared to healthy objects. Furthermore, sarcopenic index was related to steroid dose and history of rituximab treatment.

Abbreviations

PDAI; pemphigus disease area index

PhA; Phase angle

PV; pemphigus vulgaris

BIA; Bioelectrical impedance analysis

WC; waist circumference

BMI; body mass index

VFA; visceral fat area

BCM; body cell mass

ECM; extracellular mass

ICW; intracellular mass

TBW; total body water

PBF; percent body fat

Declarations

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all patients signed a consent to participate form before BIA

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data available on request from authors.

Authors contributions:

Maryam nasimi: conception and design, revising the manuscript, Given final approval

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Mohammad Taghi Najafi: conception and design, revising the manuscript, given final approval

Amir Teymourpour: analyse of data.

Nasim Tootoonchi: drafting the manuscript, analysis and interpretation of data.

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