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Title: Correlation of metabolic syndrome with serum omentin-1 and visfatin levels and disease severity in psoriasis and psoriatic arthritis

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Correlation of metabolic syndrome with serum omentin-1 and visfatin levels and disease severity in psoriasis and psoriatic arthritis

ABSTRACT

Psoriasis and psoriatic arthritis (PsA) have been linked to metabolic syndrome (MS). The impact of adipokines on psoriasis, PsA, and MS pathogenesis has recently received investigative attention.

A total of 80 subjects with psoriasis, 40 subjects with PsA, and 60 healthy controls were enrolled. Serum omentin and visfatin levels were measured, and MS presence was determined. PASI and DAS28 were used to measure disease severity for psoriasis and PsA, respectively.

The prevalence of MS was determined to be 49% in psoriasis, 48% in PsA, and 28% in control groups. Rates were similar in psoriasis and PsA groups and was significantly greater when compared to control (p=0.028). Diastolic blood pressure and waist circumference were significantly greater in the psoriasis group. Although the presence of MS positively correlated with age and disease duration in the psoriasis group, no significant relationships with PASI and DAS28 were found. Among all groups combined, there was no significant relationship with omentin and visfatin levels. In the psoriasis group, omentin and visfatin levels were greater in those with MS compared to those without MS.

The relationships between omentin and visfatin levels with MS in patients with psoriasis and PsA has not yet been fully elucidated. These results suggest that elevated omentin and visfatin levels seen in psoriasis may be linked to MS rather than psoriasis itself. Additional research is needed to investigate the utility of these measurements as indicators of MS in patients with psoriasis.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects 2-3% of the general population. Although its etiology and pathogenesis are not yet fully understood, it is considered to be a polygenic, multi-systemic, immune-mediated (Th1, Th17, and Th22) disease with triggering factors that include medications, trauma, and infection.[1] Psoriasis can negatively affect physical and psychosocial well-being of patients. It may also be accompanied by psoriatic arthritis (PsA), which can vary in terms of severity and which joints are involved.[2] More recently, psoriasis has been associated with systemic inflammation as a result of the circulation of upregulated cytokines, which has been thought to contribute to many comorbidities, such as metabolic syndrome (MS), insulin resistance, type II diabetes, hypertension, dyslipidemia, obesity, and atherosclerosis.[3]

Research has demonstrated that the prevalence of MS is 30-50% in psoriasis[4] and 40-50% in PsA.[5] This has been reported to have a strong effect on disease severity; however, the pathogenesis has not yet been completely elucidated. Cytokines produced by lymphocytes and keratinocytes, which are activated by Th1 and Th17 cells, and adipokines produced by adipose tissue have been thought to play a role. In addition, obesity and smoking are believed to increase disease severity and prevalence of MS.[6]

Adipokines produced from visceral fat tissue can cause increases in metabolic and cardiovascular problems as a result of abdominal lipoidosis. Adipokines that have an effect on immune regulation, vascular functioning, and adipocyte metabolism play a key role in the pathogenesis of MS and are also a risk factor for the development of psoriasis.[7]

Omentin is an adipokine that is released from white fat tissue consisting of 313 amino acids, and it has a storage-specific feature. It increases the insulin-stimulated glucose reuptake in human adipocytes, and low concentrations have been found in obese patients. Additionally, the omentin gene area has been connected to type II diabetes.[8] Omentin levels can be significantly lower in psoriasis patients and can negatively correlate with psoriasis area and

severity index (PASI).[9] A 2018 meta-analysis states that omentin may have anti-inflammatory effects on psoriasis, but more research is required in order to prove this.[10] In the only study carried out on patients with PsA, omentin levels were reported to be greater than patients with psoriasis and healthy controls, but no significant relationship with PsA severity was reported.[11]

Visfatin is another adipokine, whose glucose-diminishing effect has been noted as a result of its connection to insulin receptors in fat tissue, which increase in obesity, type II diabetes, MS, and cardiovascular disease.[12] In the meta-analysis, visfatin demonstrated relationship with increased IL-1β, IL-6, and TNF-α, which are pro-inflammatory cytokines for psoriasis; however, this study showed no statistically significant difference in visfatin levels of patients with psoriasis and healthy controls.[10] In a study of just patients with PsA, visfatin levels were found to be elevated, but more research is still needed.[13]

The objectives of this study were to measure omentin and visfatin levels in patients with psoriasis or PsA and correlate these levels with disease severity and duration. We also looked into the relationships between these adipokines and MS in order to fill gaps in the literature.

MATERIALS AND METHODS

Study Population

The study consisted of 80 subjects with psoriasis vulgaris, 40 subjects with PsA according to CASPAR14 criteria, and 60 healthy subjects who were consulted for cosmetic reasons to serve as controls. All subjects were enrolled in the dermatology and rheumatology departments at Istanbul Medeniyet University. The study protocol was approved by the University Clinic Research Board of Ethics. The study was recorded in Clinical Trials with the number of NCT03932110.

Inclusion Criteria

Subjects were included if they were at least 18 years of age and were diagnosed with psoriasis or PsA, unless they were to be in the control group. Subjects had to agree to participate for the duration of the study.

Exclusion Criteria

Subjects were excluded if they were younger than 18 years of age; pregnant or breastfeeding; received systemic treatment for psoriasis or PsA within the past 1 month; diagnosed with malignancy or infection; and had an autoimmune or rheumatologic disease diagnosis besides psoriasis and PsA. None of the subjects used systemic medications. The control group was selected in reference to the psoriasis and PsA groups in terms of age and gender.

Clinical Parameters

Subject characteristics, including age, gender, disease duration, presence of diabetes or hypertension, and smoking status, were recorded. Their height, weight, wait circumference, and blood pressure were measured. Waist circumference was measured at the point between the lower border of chest cage and iliac crest. Body mass index (BMI) was calculated, and participants were categorized: Normal weight (BMI 18-25 kg/m^2), overweight (BMI 26-30 kg/m^2), or obese (BMI > 30 kg/m^2).

Laboratory Parameters

Venous blood samples were collected after a 10-12-hour fasting period from all subjects for biochemical analyses. Blood samples were centrifuged and then stored at -80 degrees Celsius. All blood samples were checked for omentin-1, visfatin, triglyceride, high-density lipoproteins (HDL), insulin, and fasting glucose levels at the same time. Serum omentin-1 (Human omentin ELISA Kit, Elabscience, WuHan, PRC) and visfatin (Human visfatin ELISA Kit, Elabscience, WuHan, PRC) levels were measured using enzyme-linked immunosorbent assays (ELISA). It was checked whether there was a difference between the patient and control groups in terms of omentin and visfatin levels. The effect of MS and disease severity on this was examined. The presence of insulin resistance was calculated using the homeostatic model of insulin resistance (HOMA-IR) method (fasting glucose (mg/dl) x insulin resistance (uU/ml) / 405), and results greater than 2.7 were considered as insulin resistant.

Evaluation of Disease Activity

Psoriasis severity was calculated using PASI.[15] Subjects were categorized: Mild (0-5), moderate (6-10), or severe (>10). Disease Activity Score 28 (DAS28) was used to determine PsA severity. According to DAS28, subjects were categorized: Remission (<2.3), mild (2.3-2.7), moderate (2.8-4.1), or severe (>4.1). Of the 40 subjects, two had isolated DIF uptake and two had only axial uptake, so DAS28 was calculated for the remaining 36 subjects. Subjects were assessed according to disease severity, omentin and visfatin levels, presence of MS, and BMI.

Definition of Metabolic Syndrome

The presence of MS was determined according to relevant criteria by AHA/NHLBI 2005 (revised ATP III criteria).[6] This criteria defines the presence of MS if three of the following features are present: 1) Waistline ≥ 102 for men and ≥ 88 for women; 2) Fasting triglycerides ≥ 150 mg/dL or receiving medication for increased triglyceride; 3) HDL cholesterol (HDL-C) < 40 mg/dL for men and < 50 mg/dL for women or receiving medication for decreased HDL-C; 4) Blood pressure ≥ 130 mmHg systolic blood pressure (SBP) or ≥ 85 mmHg diastolic blood pressure (DBP) or receiving antihypertensive medication; and 5) Fasting glucose ≥ 100 mg/dL or receiving treatment for hyperglycemia. The prevalence of MS was measured between groups. The relationship between omentin and visfatin levels and disease severity was evaluated by subdividing groups according to presence of MS.

Statistical Analysis

Statistical analysis was completed by using independent t-test, Mann-Whitney U test, Kruskal Wallis test, Chi-square test, and Pearson correlation. $P < 0.05$ was accepted as statistically significant.

RESULTS

A total of 180 subjects participated in the study, which included 80 with psoriasis, 40 with PsA, and 60 as control. There were no significant differences between psoriasis and PsA groups with control in terms of age, BMI, wait circumference, and HOMA-IR. In the psoriasis

group, there were more people with diabetes, hypertension, and positive smoking status compared to control. The mean PASI was 10.15 in the psoriasis group and 4.25 in the PsA group. The mean DAS28 was 2.27 in the PsA group. (Table 1)

The prevalence of MS was 49% (n=39) in the psoriasis group, 48% (n=19) in the PsA group, and 28% (n=17) in the control group. The prevalence of MS was similar in psoriasis and PsA groups and was significantly greater compared to control (p=0.028). Waist circumference (p=0.001) and DBP (p=0.03) were significantly greater in the psoriasis group (Table 2); however, no other differences were significant for other parameters.

The PASI of those with MS in the psoriasis group was two times greater than those without MS, but this was not significant (p=0.065). There was no significant relationship between MS and DAS28 in the PsA group. For the psoriasis group, the prevalence of MS was significantly greater when subjects were over 40 years of age (p=0.001) and when disease duration was longer (p=0.005). No significant relationships between PASI and DAS28 with BMI were observed.

There were no significant differences between psoriasis, PsA, and control groups in terms of omentin (p=0.273) and visfatin levels (p=0.164) (Table 3). There were no significant relationships between omentin and visfatin levels with PASI and DAS28. When all subjects combined with and without MS were compared, there was no significant difference between omentin (p=0.097) and visfatin levels (p=0.718). However, when the psoriasis group was evaluated separately, omentin (p=0.009) and visfatin (p=0.038) levels were significantly greater in those with MS compared to those without MS. In contrast, no significant difference was found within PsA and control groups.

DISCUSSION

The presence of MS represents a recent problem for today's patients and one that seemingly will not end anytime soon. MS can accompany many illnesses and can cause significant health problems. Additional research investigating the relationships between various skin diseases and MS is needed. Although many illnesses can accompany MS, such as

hidradenitis suppurativa, lichen planus, lupus erythematosus, chronic urticaria, and atopic dermatitis, the most studied and well-known is psoriasis.

One of the objectives of our study was to investigate the prevalence of MS in patients with psoriasis and PsA and then compare this to an unaffected population. In Turkey, MS was reported in 22% of adults.[17] The overall rate of MS has been shown to be 30-50% in psoriasis and 40-50% in PsA. In a meta-analysis of 1,450,188 subjects from 35 studies, which included 46,714 patients with psoriasis, the risk of MS for patients with psoriasis was 2.14 times greater than control.[18] Table 4 summarizes the relevant research.[19-27] In our study, the rate of MS was 49% in psoriasis, 48% in PsA, and 28% in controls, which is consistent with previous studies.

Various parameters associated with MS, such as waist circumference, triglycerides, HDL, blood pressure, and fasting glucose, were evaluated in different studies (Table 4). In one of the studies, hyperglycemia, hypertriglyceridemia, and low HDL were significantly greater in patients with psoriasis compared to control.[20] In patients with PsA, waist circumference was significantly greater than control.[19] In a comparative study of patients with psoriasis and PsA, hypertension and hyperglycemia were both significantly greater in PsA compared to psoriasis, while other parameters showed no difference.[23] In our study, DBP and waist circumference were significantly greater in those with psoriasis compared to control. However, SBP, HDL-C, triglycerides, and glucose levels showed no significant differences among groups. When the PsA and psoriasis groups were compared, no significant differences were observed with various parameters.

In previous studies, psoriasis patients with MS were older and had longer disease duration. Patients with psoriasis were more often obese than controls, but these studies found no relationship between MS and PASI.[20,27,28] Studies including patients with PsA demonstrated that those with MS usually developed psoriasis and PsA later on and also developed PsA following psoriasis earlier.[24,29] Our study supported that the prevalence of MS occurred in older patients, who were over 40 years of age, and in those who had longer disease duration. Although PASI was found to be greater in psoriasis patients who had MS compared to those who did not, the difference was not statistically significant. In patients with PsA, MS and disease duration or DAS28 showed no significant difference.

The importance of white fat tissue and the adipokine profile in psoriasis, PsA, and MS pathogenesis has been investigated. There have been several studies on the effects of adiponectin, leptin, resistin, retinol binding protein-4, visfatin, and omentin on lipid and glucose metabolism, insulin resistance, and inflammatory and anti-inflammatory effects on psoriasis.[30] In patients with psoriasis, leptin and resistin were elevated[31,32], adiponectin was decreased[32], and retinol binding protein-4 was unchanged[33].

In a recent study, serum omentin was significantly decreased in patients with psoriasis, and lower omentin levels were also expressed in psoriatic plaques compared to normal skin.[34] A negative correlation was observed between omentin level and PASI. Conversely, serum visfatin level was demonstrated to be significantly greater in patients with psoriasis, and there was a positive correlation between visfatin and PASI.[7,35]

In the only study looking at omentin in patients with PsA, omentin levels were significantly greater in those with PsA compared to psoriasis and control groups; however, this did not correlate with PsA severity.[11] In the two studies looking at visfatin in PsA, serum visfatin level was significantly greater than control patients in one, and the other showed no difference between patients with PsA and psoriasis.[13]

Our study, which included 80 subjects with psoriasis and 40 with PsA, showed no significant difference in omentin and visfatin levels between groups. Likewise, no significant correlation was found between omentin and visfatin levels and PASI and DAS28. However, when subjects were examined separately, omentin and visfatin levels were greater in subjects with psoriasis and MS compared to those without MS. Our findings suggest that perhaps elevated omentin and visfatin levels seen in psoriasis may be linked to MS rather than psoriasis itself. However, additional large-scale studies are needed to confirm these findings since our study is limited by the small number of subjects in each group. These studies should also examine other adipokines besides omentin and visfatin in order to provide a complete picture on the role of adipokines in MS, psoriasis, and PsA.

CONCLUSION

More information on the relationship between MS and omentin and visfatin levels in psoriasis and PsA is needed. Our study adds information on the study of adipokines. There was no significant relationship overall with MS and omentin and visfatin levels. When subjects were examined separately, omentin and visfatin levels were greater in subjects with psoriasis and MS compared to those without MS. Whether patients had MS or not did not affect omentin and visfatin levels in PsA and control groups. These results suggest that elevated omentin and visfatin levels seen in psoriasis may be linked to MS rather than psoriasis itself. Additional research is needed to investigate the utility of these measurements as indicators of MS in patients with psoriasis.

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Data Availability Statement

Data available on request from the authors

TABLES

	Psoriasis (n=80)	PsA (n=40)	Control (n=60)	P-Value
Age (years)	44.5 ± 24.5	49.0 ± 26.8	44.0 ± 25.2	0.130
Gender (F; M)	40; 40	26; 14	30; 30	
Body weight (kg)	82.1 ± 23.0	78.0 ± 23.0	75.9 ± 22.0	
BMI (kg/m²)	29.3 ± 6.5	28.7 ± 6.1	27.3 ± 5.2	0.334
Waist circumference (cm)	98.4 ± 34	95.5 ± 22.0	88.0 ± 21.0	0.165
PASI	10.2 ± 9.9	4.9 ± 4.8		
Duration of psoriasis (years)	13.8 ± 13.0	17.0 ± 15.2		
Duration of PsA (years)		8.2 ± 7.2		
DAS28		2.3 ± 0.7		
Hypertension (Y; N)	27; 53	8; 32	7; 53	
Diabetes mellitus (Y; N)	22; 58	8; 32	8; 52	
HOMA-IR	5.9 ± 4.2	3.8 ± 2.0	3.3 ± 1.4	
Smoking status (Y; N)	44; 36	12; 28	17; 43	

Table 1. Demographics and clinical characteristics. (BMI: Body mass index; PASI: Psoriasis area and severity index; DAS28: Disease activity score 28; HOMA-IR: Homeostatic model of insulin resistance).

	Psoriasis (n=80)	PsA (n=40)	Control (n=60)	P-Value
Metabolic syndrome (n; %)	39; 49%	19; 48%	17; 28%	**0.028**
Mean diastolic blood pressure (mmHG)	87.46	80.95	78.53	**0.030**
Mean systolic blood pressure (mmHG)	138.52	129.47	130.06	0.165

Mean HDL cholesterol (mg/dl)	40.30	44.16	42.41	0.393
Mean triglycerides (mg/dl)	186.48	191.74	231.12	0.458
Mean glucose (mg/dl)	125.53	119.89	113.53	0.612
Mean waist circumference (cm)	108	102	96	**0.001**

Table 2. Prevalence of metabolic syndrome and its components. (HDL: High density lipoprotein).

	Omentin-1 (mean ng/ml ± SD)	**Visfatin (mean ng/ml ± SD)**
Psoriasis (n=80)	12.96 ± 10.99	8.31 ± 8.76
PsA (n=40)	15.66 ± 14.36	8.03 ± 6.85
Control (n=60)	18.25 ± 17.03	10.82 ± 10.97
Total (n=180)	15.32 ± 13.79	9.08 ± 9.18
P-Value	0.273	0.164

Table 3. Relationship of psoriasis, PsA and control groups with omentin-1 and visfatin levels.

	Psoriasis % (n) of MS	**PsA % (n) of MS**	**Control % (n) of MS**	**Waist circumference (F > 88 cm; M > 102 cm)**	**Hypertension (> 130/85 mmHg)**	**Triglycerides (> 150 mg/dl)**	**HDL-C (F < 50; M < 40 mg/dl)**	**Glucose (> 100 mg/dl)**	**PASI**	**PsA severity**
Gui et al.	14.3 (859)		10 (1,71	NO	NO	YES	YES	YES	NO	

2017[20]			8)							
Zindancı et al. 2011[21]	53 (115)		39 (140)	NO	YES	NO	NO	YES	NO	
Milcic et al. 2016[22]	45.1 (244)		19.6 (163)	YES	YES	YES	NO	NO	NO	
Feld et al. 2018[19]		54.8 (74)	36.6 (82)	YES	YES	YES	NO	NO		NO
Eder et al. 2012[23]	27.1 (155)	36.5 (203)		NO	YES	NO	NO	YES		
Caso et al. 2018[24]	40.48 (42)	13.16 (38)		NO	YES	YES	NO	NO	NO	NO
Salunke et al. 2017[25]	38.95 (95)		21.05 (95)	YES	YES	YES	YES	NO	NO	
Ferdinando et al. 2017[26]	49.4 (97)		35 (97)	YES	YES	NO	YES	YES	NO	
Akçalı et al. 2013[27]	50 (50)		25 (40)	NO	YES	NO	NO	NO	NO	
This study	49 (80)	48 (40)	28 (60)	YES	YES	YES	YES	YES	YES	YES

Table 4. Studies on metabolic syndrome in psoriasis and PsA patients. (HDL: High density lipoprotein cholesterol; PASI: Psoriasis area and severity index).

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