Rheumatology International (2022) 42:1539–1548
https://doi.org/10.1007/s00296-022-05110-7

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Assessment of autonomic dysfunction with the COMPASS-31 and its relationship with disease activity and cardiovascular risks in patients with psoriatic arthritis

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Received: 15 September 2021 / Accepted: 3 March 2022 / Published online: 21 March 2022

Abstract

This study aimed to evaluate the autonomic dysfunction as assessed by the Composite Autonomic Symptom Score-31 (COMPASS-31) as well as its relationship with disease activity and cardiovascular risks in patients with psoriatic arthritis (PsA). This cross-sectional observational study involved 118 PsA patients (85 females, mean age 45.6 years) and 64 healthy subjects. Cardiovascular risks were recorded including body mass index (BMI), hypertension (HT), diabetes mellitus (DM), dyslipidemia, metabolic syndrome (MetS), and 10-year Framingham Risk scores (FRS) were calculated. PsA was assessed with regard to disease activity, quality of life, and function. Autonomic dysfunction was evaluated using the COMPASS-31 consisting of six subdivisions including orthostatic, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor functions. The mean disease duration was 63.3 months. The mean total COMPASS-31 score was significantly higher in PsA patients than in controls (24.4 vs 11.1; $p < 0.001$), as were all sub-domain scores. COMPASS-31 scores were significantly lower in patients with DAPSA-REM and MDA. The COMPASS-31 total score showed significant correlations with scores of pain, global assessment, fatigue, function, quality of life, DAPSA, and BASDAI ($p < 0.05$).The presence of HT, dyslipidemia, MetS, and abdominal obesity did not significantly affect the total COMPASS-31 and sub-domain scores, except for the secretomotor scores being significantly higher in patients with abdominal obesity and MetS ($p < 0.05$). COMPASS-31 scores were not significantly different across the FRS risk groups. The symptoms of autonomic dysfunction are prevalent in PsA patients. High disease activity and pain have negative effects on autonomic function, and also functional impairment, fatigue, and poor quality of life are associated with autonomic dysfunction. However, the COMPASS-31 was found to be insufficient to demonstrate a clear relationship between autonomic dysfunction and cardiovascular risk.

Keywords Psoriatic arthritis · Autonomic dysfunction · Cardiovascular disease · Metabolic syndrome · COMPASS-31

Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease covering arthritis, psoriasis, enthesitis, and spondylitis and is associated with significant inflammatory processes resulting in autonomic nervous system (ANS) dysfunction [1, 2]. Although there are still controversies, various theories have been composed concerning the pathogenesis of rheumatic disease and autonomic dysfunction. Vasculitis, amyloidosis, therapeutic side effect, autoantibodies against the autonomic nervous system or increased inflammatory cytokines may be the underlying reasons. Because of the close communication between the immune system and autonomic system through direct and indirect pathways, PsA-induced increases in cytokines and inflammatory markers may be associated with the deterioration in the cardiac autonomic nervous system. Animal studies have shown that intraperitoneal administration of TNF-alpha impairs parasympathetic activity and heart rate variability (HRV) [2–4]. In addition, the circulating level of TNF is an independent predictor of depressed HRV indicative of autonomic dysfunction. This autonomic dysfunction associated with inflammatory cytokines is also closely related to disease activity and levels of acute-phase reactants [5].

Besides central nervous and peripheral nervous system involvement, rheumatic diseases are also characterized by ANS involvement [4, 6]. Currently, the gold-standard test

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to identify autonomic dysfunction is the Ewing battery test, which objectively measures HRV and blood pressure response to orthostasis [7]. However, despite its objectivity, it is time-consuming and requires patient compliance. Recently, more easily administered questionnaires have been developed. The Composite Autonomic Symptom Scale-31 (COMPASS-31) is a self-administered, simple, and noninvasive tool for the assessment of autonomic symptoms, which has been used for ANS evaluation in patients with systemic sclerosis (SSc), familial Mediterranean fever, fibromyalgia, diabetes mellitus (DM), multiple sclerosis, polyneuropathy, and parkinsonism [8–10].

Increased cardiovascular risk and autonomic dysfunction in rheumatic diseases and the general population are not yet fully clarified, especially in rheumatic disease. In a meta-analysis, PsA was associated with an increased risk of myocardial infarction and heart failure, with a 43% increased risk of cardiovascular diseases (CVD) than the general population [11]. PsA-mediated acceleration in the atherosclerotic process related to endothelial dysfunction can partly explain this increased risk. Yet, the causes of this increased risk are still not fully elucidated [12]. One of the reasons for this increased risk may be autonomic dysfunction. Reduced HRV is a major sign of autonomic dysfunction resulting in cardiovascular events [13]. Patients with PsA have been shown to have a reduced HRV and autonomic dysfunction [4]. Cardiac autonomic neuropathy with rheumatic disease is associated with significant sudden death and a higher mortality rate from arrhythmia and myocardial infarction with sympathetic predominance and hyperactivity [14].

Although there are insufficient data on autonomic dysfunction in patients with PsA in previous studies, the relationship of autonomic dysfunction symptoms with disease parameters and significantly increased cardiovascular disease has not been investigated before. In the current study, we aimed to (1) evaluate the symptoms of autonomic dysfunction as assessed by the COMPASS-31 and their relationship with disease activity and cardiovascular risks in patients with PsA and (2) compare autonomic dysfunction symptoms with the population of the healthy one.

Methods

Study design and subjects

In this cross-sectional observational study, we prospectively enrolled 151 consecutive PsA patients who presented to the Department of Rheumatology, Marmara University, Turkey, from January 2019 to December 2019 (Fig. 1). Inclusion criteria were a diagnosis of PsA according to the CASPAR criteria [15] and age between 18 and 65 years. Exclusion criteria included comorbidities that might affect the autonomous nervous system, including DM [16] (a self-reported previous diagnosis of DM or use of hypoglycemic agents, or a fasting plasma glucose $\geq$ 126 mg/dl on at least two measurements), severe cardiovascular diseases, such as myocardial infarction, heart failure, or arrhythmia, vasculitis, alcoholism, kidney or liver dysfunction, pregnancy, lactation, ischemic stroke, malignancy, and other inflammatory diseases. The control group included 64 healthy age-, sex, and body mass index (BMI)-matched subjects who were selected among individuals accompanying patients during outpatient visits or hospital staff. The control group had the same exclusion criteria as the PsA group.

The study was approved by the institutional clinical ethics committee of the Marmara University (09.2019.041) and was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from each participant in the study.

Demographic and clinical features including age, gender, education level, marital status, comorbidities, disease duration, and medications were recorded.

Sample size

We calculated the study's sample size based on the study's primary objective. Since there was no similar study conducted in patients with PsA, in a similar study performed in systemic sclerosis, the mean COMPASS-31 score was 24.9 ± 15.5 mm, while it was 8.9 ± 8.7 mm in healthy controls, and the difference was significant ($p < 0.05$) [9]. While Type I error is 0.05 and test power is 0.95, the minimum sample size required in each group was determined as 18 by the G-Power version 3.0.10 program.

Disease activity assessments in patients with PsA

In each patient, articular involvement was assessed concerning tenderness and swelling in 68 and 66 joints, respectively. The Leeds enthesitis index (LEI) (range 0–6) was designed for PsA and had six examination points, including left and right lateral epicondyles, medial femoral condyles and Achilles' tendon insertions were used to assess enthesitis [17]. Pain and global patient assessment (PtGA) were rated on a visual analogue scale (VAS) from 0 to 100 mm [18]. The extent of skin involvement was evaluated with the Psoriasis Area and Severity Index (PASI) (range 0–72) that evaluates four body areas for surface area, erythema, induration, and desquamation [19].

The Disease Activity in Psoriatic Arthritis (DAPSA) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were used to assess disease activity for peripheral and axial disease activity, respectively. The DAPSA contains 66/68-joint evaluation, patient global VAS, patient

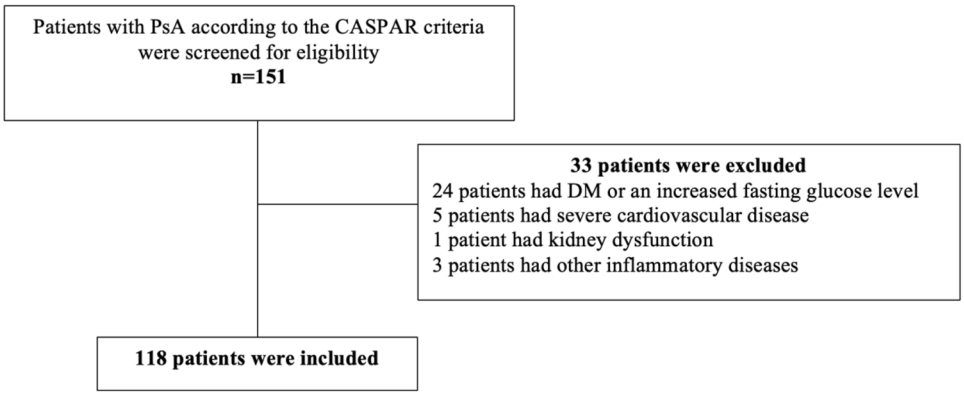

Fig. 1 Patient disposition during the study

pain VAS, and CRP (mg/dL). Cutoff points of remission were defined as a DAPSA score of ≤ 4, with higher scores indicating low disease activity (> 4–≤ 14), moderate disease activity (> 14–≤ 28), and high disease activity (> 28) [20].

Minimal Disease Activity (MDA) was defined when five of seven clinical domains [Tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, PASI ≤ 1, LEI ≤ 1, VAS-pain ≤ 15 mm, PtGA ≤ 20 mm, and the Health Assessment Questionnaire (HAQ) ≤ 0.5] were fulfilled [21]. Laboratory measurements included erythrocyte sedimentation rate (ESR) (mm/h) and C-reactive protein (CRP) (mg/L).

Assessment of cardiovascular disease (CVD) risk in patients with PsA

Anthropometric measurements (height, weight), waist circumference (WC), hip circumference (HC), and blood pressure were measured. Blood pressure was measured noninvasively with a cuff sphygmomanometer. The waist–hip ratio (WHR) was calculated as waist-to-hip circumference. Waist circumference was measured from the midpoint between the lowest rib and lateral iliac points, and HC was measured at the level of the greater trochanters. Based on the report of the Turkish population, abdominal obesity was defined as a WC ≥ 100 cm in males and ≥ 90 cm in females [22]. Body mass index was calculated by dividing the weight (in kg) by the square of the height in meters. Patients were categorized as obese if the BMI was ≥ 30 kg/m^2, based on the National Institutes of Health Expert Panel guidelines [23]. Smoking status (current, former, and never) was recorded.

Blood lipid and fasting glucose levels obtained beyond a duration of 6 months were disregarded.

Comorbidities were identified, including hypertension (HT) [24] (a history of HT or use of anti-hypertensive agents, or a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 85 mmHg), and dyslipidemia [25] (a history of dyslipidemia or use of lipid-lowering therapy, or a total cholesterol level ≥ 240 mg/dl, a low-density lipoprotein level (LDL) ≥ 160 mg/dl, a high-density lipoprotein level (HDL) ≤ 40 mg/dl, or a triglyceride level ≥ 150 mg/dl).

The metabolic syndrome (MetS) was defined as the presence of at least 3 of the five parameters, according to the American Heart Association/National Heart, Lung, and Blood Institute criteria: (1) abdominal obesity (WC > 100 cm for males and > 90 cm for females); (2) the presence of hypertension (SBP > 130 mmHg and/or DBP > 85 mmHg) or use of anti-hypertensive therapy; (3) hypertriglyceridemia (≥ 150 mg/dL) or treatment for elevated triglycerides; (4) a low HDL level (< 40 mg/dL in males and < 50 mg/dL in females) or treatment for reduced HDL; and (5) a high fasting plasma glucose level (≥ 100 mg/dL) or treatment for hyperglycemia [24].

The 10-year risk of CVD was estimated using the Framingham risk score (FRS) algorithm, which assesses the main CVD risk (coronary artery disease, stroke, peripheral arterial disease, or heart failure) by incorporating the traditional CVD risk factors (age, gender, total cholesterol, HDL, blood pressure, smoking, and DM), in which a score of < 10% indicates low, 10–19% intermediate, and ≥ 20% a high risk [26].

Assessment of autonomic dysfunction

Autonomic dysfunction was evaluated using a self-reported COMPASS-31 instrument consisting of 31 items with six domains: orthostatic intolerance (4 items), vasomotor dysfunction (3 items), secretomotor dysfunction (4 items), gastrointestinal system (GIS) dysfunction (12 items), bladder dysfunction (3 items), and pupillomotor dysfunction (5 items). The final score was a total of 0 to 100 of all weighted subscales, with higher scores indicating more severe dysfunction. The maximum weighted scores for each subdomain were as follows: 40 for orthostatic intolerance, 5 for vasomotor dysfunction, 15 for secretomotor dysfunction, 25 for GIS dysfunction, 10 for urinary dysfunction, and 5 for pupillomotor dysfunction [27]. The symptoms of autonomic

dysfunction were evaluated in both PsA patients and healthy subjects.

Patient-reported outcome measures in patients with PsA

Functional status, quality of life, and depression-anxiety were assessed using the Health Assessment Questionnaire (HAQ), the Psoriatic Arthritis Quality of Life scale (PsAQoL), and the Hospital Anxiety and Depression Scale (HADS), respectively [28–30]. A visual analogue scale for fatigue (0–10 mm) was used to rate fatigue during the previous week.

Statistical analysis

Descriptive data are presented as mean and standard deviation (±) for continuous variables and numbers and percentages (%) for categorical variables. The Kolmogorov–Smirnov test and histogram graphs were used to assess the distribution of continuous variables. The Student's *t* test was used, and for non-normal distributions, the Mann–Whitney *U* test and Kruskal–Wallis test were used. Categorical variables were compared with the chi-squared test or the Fisher's exact test where appropriate. Spearman's correlation coefficient was calculated for correlations between the COMPASS-31 scores and disease characteristics. Correlations between continuous variables were assessed with Spearman's correlation coefficient, where rho values of > 0.60, 0.40–0.60, and < 0.40 indicated strong, moderate, and weak correlations, respectively [31]. Simple linear regression analysis was performed with COMPASS-31 and disease activity scores (DAPSA, BASDAI). Data were processed using the Statistical Package for Social Sciences software (SPSS, version 22 IBM Corporation, Armonk, NY, USA). A *p* value of less than 0.05 was considered statistically significant.

Results

Demographic data

In total, 151 patients with PsA were evaluated, of whom 33 were excluded. Thus, 118 patients (33 males, 85 females) were eligible. The demographic and clinical features of PsA patients and controls are presented in Table 1. The mean age was 45.6 ± 12 years, and the mean disease duration was 63.3 ± 76.3 months in the patient group. The patient and control groups were similar in age, gender, and BMI ($p > 0.05$).

At the time of enrollment, 70 patients (59.3%) were on synthetic disease-modifying anti-rheumatic drugs (sDMARD) therapy, with methotrexate being the most common, followed by sulfasalazine and leflunomide. Fourteen patients (11.9%) received a biological DMARD (bDMARD). Of the 14 patients who received biologic therapy, nine received anti-TNF treatment, while others received IL-17 or IL12/23 inhibitors.

Scoring of autonomic dysfunctions

Patients with PsA had a significantly higher mean total COMPASS-31 score than controls (24.4 vs 11.1; $p < 0.001$). In the sub-domain analysis, PsA patients exhibited significantly higher mean scores in all domains (Table 2).

COMPASS-31 scores and clinical associations in PsA

In patients with PsA, the mean COMPASS-31 score for females was 25.9 ± 15.3 as compared with 20.4 ± 13.5 for males ($p = 0.07$). Females had higher GIS, secretomotor, and

Table 1 Demographic and clinical characteristics of PsA patients and controls

	PsA ($n = 118$)	Controls ($n = 64$)	*p*
Age, years	45.6 (12)	42.3 (27.2)	0.07*
Gender, (female/male)	85/33	37/27	0.06**
BMI, kg/m^2	28.7 (5.5)	27.2 (4.5)	0.07*
Smokers	34 (28.8%)	7 (10.9%)	0.005**
Educational level, years	9.1 (4.3)	7.7 (4.3)	*0.02**
Disease Activity Assessment			
TJC	2.7 (3.2)	–	–
SJC	0.6 (1.5)	–	–
Leeds score	1.9 (2.1)	–	–
VAS Pain	55 (27.5)	–	–
PtGA	50.5 (21.2)	–	–
PASI	2.1 (6.1)	–	–
ESR, mm/h	26.5 (18.7)	–	–
CRP, mg/L	6.3 (6.5)	–	–
DAPSA	15 (7.3)	–	–
DAPSA-REM, *n* (%)	7 (5.9%)	–	–
BASDAI	4.9 (2.3)	–	–
MDA	29 (24.6%)	–	–

Data are presented as mean (±) and *n* (%)

p value italic indicates statistical significance

BMI body mass index, *TJC* Tender Joint Count, *SJC* Swollen Joint Count, *PtGA* Patient Global Assessment, *PASI* Psoriasis Area and Severity Index, *ESR* Erythrocyte Sedimentation Rate, *CRP* C-reactive protein, *DAPSA* Disease Activity in Psoriatic Arthritis, *REM* Remission, *LDA* Low disease Activity, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *MDA* Minimal Disease Activity

*Mann–Whitney *U* test or **Chi-squared test

pupillomotor subdomain scores than males ($p=0.001$, 0.02, and 0.04, respectively).

GIS and bladder scores were significantly higher in smokers than in non-smokers [(7.8 ± 3.7) vs (5.8 ± 3.4) $p=0.008$ and (2.4 ± 1.7) vs (1.5 ± 1.7) $p=0.004$, respectively].

COMPASS-31 total scores and subdomain scores were similar in sDMARD users and non-users ($p>0.05$).

COMPASS-31 scores were significantly lower in patients with DAPSA-REM or MDA than those with non-REM or non-MDA ($p=0.004$ and <0.001, respectively). COMPASS-31 subgroup results according to REM and MDA are presented in Table 3.

The correlations between COMPASS-31 scores and disease characteristics are shown in Table 4. COMPASS-31 total score showed a strong correlation with PsAQoL (rho: 0.63, $p<0.001$), moderate correlations with pain (rho: 0.47, $p<0.001$), global assessment (rho: 0.45, $p<0.001$), fatigue (rho: 0.56, $p<0.001$), DAPSA (rho: 0.48, $p<0.001$), BASDAI (rho: 0.56, $p<0.001$), and HAQ (rho: 0.51, $p<0.001$), and weak correlations with BMI (rho: 0.2, p: 0.0.2), tender joint count (rho: 0.21, p: 0.02), and Leeds enthesitis index (rho: 0.28, p: 0.002). COMPASS-31 totals score showed no correlation with age (rho: 0.09, p: 0.6), disease duration (rho: 0.04, p: 0.63), swollen joint count (rho: 0.04, p: 0.67), PASI (rho: −0.03, p: 0.71), ESR (rho: 0.07, p: 0.45), CRP (rho: 0.09, p: 0.3), and FRS (rho: 0.14, p: 0.13) (Table 4).

The simple linear regression analysis demonstrated a statistically significant association between COMPASS-31 total and BASDAI scores (coefficient [95% CI], 0.576 [2.684, 4.576], $r^2=0.33$; $p<0.001$) and between COMPASS-31 total and DAPSA scores (coefficient [95% CI], 0.474 [0.634, 1.293], $r^2=0.22$; $p<0.001$).

Table 2 Total and sub-domain scores of COMPASS-31 in PsA and controls

COMPASS-31	PsA ($n=118$)	Controls ($n=64$)	p value*
Total score	24.4 (15)	11.1 (12.4)	***< 0.001***
Orthostatic	10.1 (10.7)	4.6 (8.3)	***0.001***
Vasomotor	0.8 (1.2)	0.2 (0.5)	***< 0.001***
Secretomotor	3.7 (3.1)	0.8 (2.1)	***< 0.001***
Gastrointestinal	6.3 (3.6)	3.1 (3.2)	***< 0.001***
Bladder	1.8 (1.7)	1.1 (1.5)	***0.001***
Pupillomotor	1.5 (1.2)	1.1 (1.2)	***0.015***

Data are presented as mean (±)

p values in bold and italics indicate statistical significance

*Mann–Whitney *U* test

COMPASS-31 and cardiovascular risk assessment in patients with PsA

The mean BMI was 28.8 ± 5.6 kg/m^2, indicating normal, overweight, and obese in 23.7%, 39%, and 37.3% of the patients. Of 112 patients with complete data, 62 (52.5%) had abdominal obesity and 22 (19.8%) had MetS. Serum lipid measurements were available in 115 patients with the following parameters given as means: total cholesterol 214.2 ± 44.7 mg/dL; LDL 133.6 ± 37.5 mg/dL; HDL 53.5 ± 11 mg/dL; and triglycerides 132.2 ± 76.5 mg/dL. Of 115 patients, 48 (41.7%) had dyslipidemia. There were 10 (8.4%) patients receiving lipid-lowering therapy and 20 (16.9%) receiving anti-hypertensive medications. The mean blood pressure was 128.3 ± 20.5/79.2 ± 13.1 mmHg.

The mean 10-year Framingham risk score was 8.1 ± 7.4% (range 0.6–30), with 69.5%, 20.3%, and 6.8% of patients having low-, moderate- and high-risk profiles, respectively.

The presence of HT, dyslipidemia, MetS and abdominal obesity did not significantly affect the total COMPASS-31 and sub-domain scores ($p>0.05$), except for the secretomotor scores being markedly higher in patients with abdominal

Table 3 Comparisons of COMPASS-31 scores in relation to disease activity

	COMPASS-31						
	Total score	Orthostatic	Vasomotor	Secretomotor	Gastrointestinal	Bladder	Pupillomotor
DAPSA-REM							
Yes	10.2 (7.6)	4 (6.9)	0.1 (0.3)	0.9 (1.1)	3.3 (1.6)	0.7 (1)	1.1 (0.8)
No	25.2 (14.9)	10.5 (10.8)	0.9 (1.2)	3.8 (3.1)	6.5 (3.6)	1.8 (1.7)	1.5 (1.2)
*p**	***0.004***	*0.114*	*0.123*	***0.011***	***0.015***	*0.104*	*0.371*
MDA							
Yes	14.8 (10.7)	4.8 (7.3)	0.4 (0.7)	2.2 (2.1)	4.5 (2.7)	1.7 (1.7)	1.1 (1.2)
No	27.5 (14.9)	11.8 (11.1)	1 (1.3)	4.1 (4.2)	6.9 (3.7)	1.8 (1.7)	1.6 (1.1)
*p**	***< 0.001***	***0.002***	***0.032***	***0.002***	***0.002***	*0.842*	***0.013***

Data are presented as mean (±)

p values in bold and italics indicate statistical significance

DAPSA Disease Activity in Psoriatic Arthritis, *REM* Remission, *MDA* Minimal Disease Activity

*Mann–Whitney *U* test

Table 4 Correlations between COMPASS-31 scores and disease characteristics

	COMPASS-31 (rho)						
	Total score	Orthostatic	Vasomotor	Secretomotor	Gastrointestinal	Bladder	Pupillomotor
Age	0.09	0.05	−0.11	0.18	0.01	***0.21****	−0.03
Disease duration	*0.04*	*0.02*	*−0.06*	***0.25****	*−0.08*	*0.17*	*0.07*
BMI	***0.2****	*0.1*	*0.01*	***0.19****	***0.19****	***0.24****	*0.15*
TJC	***0.21****	***0.19****	***0.26***	*0.17*	*0.11*	*−0.04*	*0.04*
SJC	*0.04*	*0.06*	*0.16*	*−0.11*	*−0.03*	*−0.01*	*0.02*
Leeds score	***0.28***	***0.22****	*−0.09*	***0.19****	***0.27***	*0.06*	***0.26***
VAS Pain	***0.47*****	***0.33*****	***0.27***	***0.36*****	***0.38*****	*0.08*	***0.31***
PtGA	***0.45*****	***0.3***	***0.19****	***0.35*****	***0.35*****	***0.19****	***0.26***
Fatigue	***0.56*****	***0.44*****	*0.16*	***0.36*****	***0.38*****	***0.22****	***0.35*****
PASI	*−0.03*	*−0.06*	*0.15*	*0.03*	*−0.06*	*0.06*	*−0.03*
ESR	*0.07*	*0.06*	*0.06*	*0.06*	*0.003*	*0.06*	*−0.1*
CRP	0.09	0.11	0.11	0.003	0.02	0.05	−0.15
DAPSA	**0.48*****	**0.37*****	**0.33*****	**0.33*****	**0.31****	0.1	**0.26****
BASDAI	**0.56*****	**0.43*****	**0.3****	**0.39*****	**0.42*****	0.15	**0.34*****
HAQ	**0.51*****	**0.39*****	**0.23***	**0.38*****	**0.35*****	**0.23***	**0.35*****
PSAQOL	**0.63*****	**0.48*****	**0.24***	**0.38*****	**0.45*****	**0.33*****	**0.42*****
FRS	0.14	0.07	−0.11	**0.19***	0.09	**0.37*****	−0.02

BMI body mass index, *TJC* Tender Joint Count, *SJC* Swollen Joint Count, *PtGA* Patient Global Assessment, *PASI* Psoriasis Area and Severity Index, *ESR* Erythrocyte Sedimentation Rate, *CRP* C-reactive protein, *DAPSA* Disease Activity in Psoriatic Arthritis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *HAQ* Health Assessment Questionnaire, *PSAQoL* Psoriatic Arthritis Quality of Life, *FRS* Framingham Risk Score

*$p<0.05$; **$p<0.01$; ***$p<0.001$

rho values in bold and italics indicate statistical significance

obesity and MetS ($p=0.02$ and 0.03, respectively). COMPASS-31 total and subgroup scores were not significantly different across the FRS risk groups ($p>0.05$) (Table 5).

Discussion

To the best of our knowledge, this is the first comprehensive study to evaluate autonomic dysfunction, as assessed by COMPASS-31 scores, and its relationship with cardiovascular risk in patients with PsA and its association with disease activity status and clinical features of PsA. In the current study, all COMPASS-31 scores were higher in patients with PsA than in healthy volunteers, suggesting the presence of an increased risk of autonomic dysfunction in this patient population.

So far, cardiovascular risk imposed on PsA patients has not been evaluated in the context of autonomic dysfunction. A previous study found varying degrees of autonomic dysfunction in PsA patients using the Ewing battery compared with healthy controls, with parasympathetic involvement being more common than sympathetic dysfunction [4]. The COMPASS-31 questionnaire has also been applied in various rheumatic diseases, but not in PsA, showing high scores of autonomic dysfunctions in patients with SSc and Sjögren's syndrome (SjS). Similar to our finding of 24.4 points, the COMPASS-31 score was 24.9 in SSc patients, with females having higher scores than males [9]. As expected in SjS, the mean total COMPASS-31 score was even higher with 56 points, indicating pronounced autonomic symptoms [32]. Symptoms of ANS dysfunction were widespread among patients with SjS and were associated with other disease features, particularly fatigue. Vagus nerve stimulation has also been related to the improvement of fatigue because of the inter-relationship between the autonomic nervous system and the immune system via the vagus nerve [33]. Similarly, there was a strong relationship between ANS dysfunction and fatigue in our study. In addition, autonomic dysfunction symptoms significantly impair the quality-of-life scores in PsA patients. The PsAQoL scores correlated most strongly with AD scores, particularly orthostatic, gastrointestinal and pupillomotor symptoms. While the relationship between autonomic dysfunction and quality of life has not been explored in PsA, similar results have been found in healthy subjects and many diseases. In Parkinson's patients, all types of autonomic dysfunction impaired quality of life, primarily gastrointestinal and thermoregulatory dysfunctions [34]. In

Table 5 Comparisons between COMPASS-31 scores and cardiovascular diseases

	COMPASS-31						
	Total score	Orthostatic	Vasomotor	Secretomotor	Gastrointestinal	Bladder	Pupillomotor
Hypertension							
Yes	26.3 (14.5)	10 (10.5)	0.6 (1.1)	4.6 (2.5)	7.4 (3.4)	1.6 (1.4)	1.5 (1.2)
No	24 (15.1)	10.1 (10.8)	0.9 (1.2)	3.5 (3.2)	6 (3.6)	1.8 (1.8)	1.5 (1.2)
*p**	*0.55*	*0.99*	*0.34*	*0.07*	*0.15*	*0.74*	*0.95*
Dyslipidemia							
Yes	*25.5 (13.6)*	*10.7 (10.1)*	*0.6 (1)*	*4.1 (3.3)*	*6.3 (3.9)*	*2.1 (1.9)*	*1.5 (1.2)*
No	*23.5 (15.9)*	*9.4 (11.2)*	*1.1 (1.4)*	*3.4 (4.3)*	*6.4 (3.4)*	*1.6 (1.6)*	*1.6 (1.2)*
*p**	*0.26*	*0.43*	*0.13*	*0.2*	*0.8*	*0.2*	*0.72*
Metabolic syndrome							
Yes	27.8 (14.5)	11.6 (10.3)	0.5 (0.9)	4.9 (2.9)	6.9 (4.3)	2.4 (1.9)	1.3 (1.1)
No	23.5 (14.9)	9.5 (10.7)	0.9 (1.3)	3.4 (3.1)	6.3 (3.4)	1.7 (1.6)	1.6 (1.2)
*p**	*0.18*	*0.31*	*0.22*	***0.02***	*0.56*	*0.14*	*0.33*
Abdominal obesity							
Yes	26.5 (15.2)	10.5 (10.5)	0.9 (1.2)	4.2 (3.1)	7.1 (3.7)	2.1 (1.8)	1.7 (1.1)
No	21.3 (14.2)	8.7 (10.8)	1 (1.2)	2.9 (2.9)	5.8 (3.1)	1.4 (1.4)	1.4 (1.2)
*p**	*0.05*	*0.32*	*0.59*	***0.03***	*0.06*	*0.05*	*0.12*
FRS							
Low	23.8 (15.1)	9.5 (10.8)	1.1 (1.3)	3.6 (3.1)	6.4 (3.6)	1.7 (1.8)	1.6 (1.1)
Moderate	24.3 (13.1)	10.8 (10.1)	0.5 (0.9)	3.8 (2.8)	6.1 (3.3)	1.9 (1.4)	1.1 (1.1)
High	29.3 (20.1)	11(12.2)	0.8 (1.1)	4.8 (3.3)	7.8 (4.1)	2.9 (2.1)	1.9 (1.3)
*p***	*0.78*	*0.78*	*0.21*	*0.51*	*0.41*	*0.09*	*0.09*

FRS Framingham risk score

Data are presented as mean (±)

p values in bold and italics indicate statistical significance

*Mann–Whitney *U* test, **Kruskal–Wallis test

SLE, autonomic dysfunction was significantly related to the low physical qualify of life scores with SF-12 [35].

Our findings also demonstrated that autonomic dysfunction showed significant correlations with disease activity status, with patients in REM or MDA having significantly lower COMPASS-31 scores than those with active disease. Using the Ewing battery, Syngle et al. also found significant correlations between variables of autonomic neuropathy and disease activity [5]. As a mechanism of this relationship, inflammatory markers seem to be essential mediators in both processes, namely disease activity and autonomic dysfunction, in that inflammatory markers such as IL-6 and CRP were shown to be associated with reduced HRV, a marker of the vagus nerve activity [36]. Although we could not find a close relationship between autonomic dysfunction and inflammatory parameters such as ESR and CRP, composite disease activity scores were related to autonomic dysfunction. This difference may be due to the strong relationship between pain scores used in the composite scales and autonomic dysfunction. COMPASS-31 scores were strongly correlated with pain and patient global assessment scores, but not with the objective evaluations such as swollen joints and acute phase reactants. This may be partially explained with the subjective assessment of pain and the COMPASS-31 scale. Single et al. using an objective test, showed that HR response to standing test significantly correlated with ESR and CRP levels. However, this study did not compare autonomic dysfunction and disease activity with composite scales and pain [4]. While there was no relationship between disease activity and autonomic neuropathy in lupus, kidney involvement was associated with more severe autonomic neuropathy in systemic sclerosis [37]. Although our study found no significant association in autonomic symptoms according to sDMARD treatment, a prospective study investigating the efficacy of both sDMARD and bDMARD in RA and AS has demonstrated a favourable DMARD treatment effect on autonomic neuropathy. In these observational studies, improvements in autonomic neuropathy may have resulted from the resolution of disease activity. It is also known from previous studies that DMARD therapy affects cholinergic anti-inflammatory pathways through the vagus nerve. The vagus nerve represents the main component of the parasympathetic nervous system,

and in chronic inflammatory disease, its activity reduces [5]. TNF alpha, an essential cytokine in disease activity, can cause gastric stasis through interaction with vago-vagal neurocircuitry in the brainstem [5]. Pre- and post-treatment evaluation of objective methods for autonomic dysfunction may be more beneficial to assess the impact of treatment.

Several studies reported high incidences of obesity in patients with psoriasis and PsA [38]. More than half of our patients were overweight or obese, and 19.8% had MetS. Assessment of the MetS in PsA about the cardiovascular risk is relevant, because it increases the cardiovascular risk burden and is independently associated with the severity of PsA. The prevalence of MetS in PsA patients ranges from 27 to 58% [39]. In the present study, the lower incidence of MetS may be attributed to excluding DM patients, which might have affected the lower 10-year Framingham risk score. Nonetheless, the COMPASS-31 scores were consistently higher with incremental increases in BMI. Both MetS and abdominal obesity had significant adverse effects on secretomotor function. This finding was in line with an animal study that found obesity-related decreases in salivary gland size induced by hypothalamic damage, resulting in reduced sympathetic activity [40]. Most patients were in the low-risk group in Framingham risk scores as in metabolic syndrome. This may be due to the exclusion of diabetes, severe cardiovascular disease, kidney or liver dysfunction, and stroke, affecting the autonomic nervous system.

Although Framingham's cardiovascular risk score was found to be in correlation with objective autonomic dysfunction tests [41], its relationship with COMPASS-31 has not been assessed. In the current study, Framingham's risks score was not correlated with the overall COMPASS-31 score, although the latter showed consistent increases with the Framingham risk groups. Even though altered ANS function is thought to contribute to the pathogenesis of cardiovascular disease, we found no association between cardiovascular disease and autonomic functions as assessed by COMPASS-31 [42].

Limitations

With a relatively large sample size, we sought to determine autonomic dysfunction in PsA patients compared with healthy controls and cardiovascular risk assessment. The main limitation to the study is that a COMPASS-31 scale is a subjective tool based on symptom scoring. As the objective tests are complex and costly, the COMPASS-31 scale is readily available and provides sufficient information about the components of autonomic dysfunction, at least for screening purposes. In addition, the long form of COMPASS correlates with many cardiovascular tests [43]. Another limitation was that, although patients with DM and severe cardiovascular disease were excluded because of the direct impact of DM on the autonomic nervous system [44], those with stable hypertension and hyperlipidemia were not, who accounted for less than 10%.

In conclusion, the symptoms of autonomic dysfunction are prevalent in PsA patients compared with healthy subjects. High disease activity and pain have negative effects on autonomic function, and also functional impairment, fatigue, and poor quality of life are associated with autonomic dysfunction. However, the COMPASS-31 questionnaire was insufficient to demonstrate a clear relationship between autonomic dysfunction and cardiovascular risk. Yet, the relation of MetS and abdominal obesity with secretomotor dysfunction was clear.

Author contributions All authors contributed to the study's conception, design, and data collection. HHG, DEG, SAK and MTD performed material preparation and analysis. HHG wrote the first draft of the manuscript and all authors commented on previous versions. All co-authors are fully responsible for all aspects of the study and the final manuscript in line with the IJME 4 criteria. All co-authors satisfy all four criteria (participated in study design, data collection, analysis, interpretation and writing equally), and take full responsibility for the integrity of the study and the final manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

Ethics approval All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was taken from the Marmara University Ethics Committee on 09.2019. The protocol number was 41.

Consent to participate Informed consent was obtained from all subjects before enrollment.

Consent for publication Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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