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Original Article

Effects of Disease Duration on The Cardiovascular Autonomic Function in Patients With Psoriasis

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Abstract

Background: Psoriasis is a chronic systemic inflammatory disorder of unknown etiology which is associated with increased risk of cardiovascular diseases. However, the effects of psoriasis on the autonomic nervous system modulating cardiovascular functions have not yet been adequately addressed. In the present study, we aimed to evaluate the cardiovascular autonomic function with regard to duration of the disease in patients with psoriasis.

Materials and methods: 28 male psoriasis patients and 30 controls were enrolled in the present study. Based on duration of the psoriasis they were grouped in to new psoriasis (n-16) (Less than one year) and old psoriasis (n-12) patients (More than one year) group. Autonomic function tests (AFT) and short term HRV was performed in both psoriasis group and control group.

Results: In short term HRV, Time and frequency domain parameters were significantly reduced in new and old psoriasis patients as compared with controls, evidenced by the significantly low SDNN, RMSSD, SDSD, NN50 and pNN50. In autonomic reactivity test (table:2) DBP in sympathetic reactivity in IHG (7.87±2.72 vs 10.20±3.67) was significantly decreased in old patients compared to new patients and control subjects. Resting heart rate, Valsalva maneuver, and 30:15 ratio in lying to standing test for parasympathetic reactivity showed significant ($P<0.05$) variation in old patients compared to controls.

Conclusion: In recently diagnosed patients with psoriasis there appears to be only compromised parasympathetic activity and in patients with chronic psoriasis both parasympathetic and sympathetic systems are compromised.

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Introduction

Psoriasis is a chronic systemic inflammatory disorder of unknown etiology and appears to result from a complex interplay between genetics, environment, skin barrier disruption, and immune dysfunction (1,

2). Apart from the skin psoriasis is also associated with scalp, nails, and occasionally the joints (3). Recently pro inflammatory markers like tumor necrosis factor-5 (TNF-5), IL-12, IL-23, and IL-17 have been shown to play major roles in the development of the immune response in psoriasis (4). Chronic inflammation makes the body susceptible to various diseases where the inflammatory markers have a major role in the pathogenesis of various cardiovascular diseases e.g. Atherosclerosis, coronary artery disease (CAD), and stroke (5-7). Several studies have documented the direct association between psoriasis and cardiovascular disorder related morbidity and mortality (8-10). Imbalance of the autonomic cardiovascular (CV) regulation system towards the sympathetic arm strongly correlates with an increased CV risk in the general population (11). There have been studies incriminating dysautonomia as one of the most important yet ignored causes of cardiovascular diseases in psoriatic patients (12). The pathophysiology however remains unclear as the studies show contradictory results. There are some studies suggesting autonomic imbalance with a shift towards the sympathetic arm (13), there are others suggesting an involvement of only the parasympathetic system and a few suggesting that no such involvement of either of the systems occurs in psoriasis (14). Due to this paucity of knowledge regarding the status of the autonomic function in the psoriasis patients, we hypothesized that the contradictory results could be related to the effect of the course and duration of the disease on the autonomic nervous system. Hence in our study we made an attempt to assess the autonomic status in patients with psoriasis in the early stage of the disease as recently diagnosed and in patients with chronic psoriasis with a purpose to achieve an idea about the effect of the course of the disease on the autonomic nervous system.

Materials and Methods

Subjects:

The present case control study was conducted in 28 psoriasis male patients and 30 (healthy male) controls. Based on duration of the disease they were grouped in to new psoriasis (n-16) (Less than one year) and old psoriasis (n-12) patients group (more than one year). Age matched healthy male subjects acted as controls and psoriasis patients were referred from psoriasis clinic in dermatology department in SRMC & RI by the dermatologists after careful examination of the skin lesions using the Psoriasis Area and Severity Index (PASI) (15). The PASI score ranged from 1 to 39 among the psoriasis patients and higher PASI scores indicate more severe psoriasis. The project was approved by the institutional ethical committee (IEC) and written informed consent was obtained from all the subjects after explaining the nature of the project and experiments. Psoriasis patients were excluded from the study if they had any of the following conditions: diabetes mellitus, thyroid disorders, vitamin B12 deficiency, any form of anemia, patients on neuro-protective and antihypertensive drugs, cardiac failure, cardiac arrhythmia, known case of smoking, psychosomatic and neurological (Parkinsonism, ataxia etc.) disorders. All the subjects were found to be in a stable condition.

Assessments:

Autonomic function test was carried out in the autonomic lab in the Department of Physiology in SRMC & RI. Cardiovascular autonomic dysfunction was diagnosed by applying cardiovascular reflex tests according to Ewing (16) using CANWIN cardiac autonomic neuropathy analyzer. For Short term HRV, Vario_Win HR (PC based HRV analysis) was used. All tests were performed under standardized conditions, in climate-controlled rooms (temperature-23°C), in the morning.

Heart rate variability assessment:

Before HRV data recording, all subjects were instructed to maintain their normal sleep pattern, not ingest beverages with caffeine or alcohol, and not perform physical exercise 12 hours before the assessment. This test was conducted in morning after 2 hrs of light breakfast. Subjects were encouraged to void urine before commencement of the recording. After 15 minutes of supine rest on a couch, ECG was recorded for 5 minutes with

controlled breathing. For recording of short-term HRV, recommendation of the Task Force on HRV was followed (17). Time domain and frequency domain parameters were analyzed in this study. In the time domain, the *standard deviation of the NN interval* (SDNN), the square root of the mean squared differences of successive NN intervals *(RMSSD)*, the number of interval differences of successive NN intervals greater than 50 ms *(NN50)*, and the proportion derived by dividing NN50 by the total number of NN intervals *(pNN50)* were used. In frequency domain power spectral density (PSD) analysis in non-parametric method (fast Fourier transform) were used. They were low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.40 Hz) in square milliseconds (ms^2) as well as normalized units (LF nu and HF nu, respectively), and LF/HF ratio . Poincare plot parameters SD 1, SD 2 and SD 1/SD 2 ratio also included.

Autonomic function test:

a. Parasympathetic Reactivity Tests.

1. Resting heart rate: 5 min continuous ECG was recorded in supine position after ten min of rest and from the ECG recording heart rate was evaluated.

2. Deep breathing test (DBT): It is the ratio of longest R-R interval during expiration to the shortest R-R interval during inspiration. The subject breathes deeply (6 breath/min) and steadily at six breaths per minute and the E: I ratio was calculated.

3. 30:15 ratios: It is the ratio of R-R interval corresponding to the 30th and 15th heart beat upon standing from supine position.

4. Valsalva maneuver: subjects are asked to blow into a special tube to maintain a column of mercury at 40 mmHg for 15 s. ECG is recorded during the resting period and during the subsequent 40 heart beats after the maneuver.

b. Sympathetic Reactivity Tests.

1. Blood pressure (BP) response to standing: Participants were asked to stand up for 3 min after a 10 min resting period in a supine position. The systolic and diastolic blood pressure (SBP and DBP), in supine rest, immediately after standing and 2 min after active standing, were determined to define postural change in blood pressure to evaluate orthostatic intolerance. A decline in diastolic blood pressure by more than 10 mmHg is considered abnormal.

2. Isometric hand grip (IHG) exercise: After recording resting BP, IHG exercise was done with Hand Grip Dynamometer (INCO, Ambala, India). The subjects were asked to hold the dynamometer in dominant hand and pull the grip with maximal power. Three successive trials were performed; the highest value of three trials was taken as maximum voluntary contraction (MVC). Following this, handgrip was maintained steadily by the subject at 30% of MVC for 3 min. During this maneuver, both SBP & DBP were recorded every 1 min on the non-exercising arm in sitting position. The maximum rise in DBP was taken as an index of response to hand gripand it should normally be higher than 15 mmHg.

Results

Table I shows the baseline clinical characteristics of psoriasis and control groups. Regarding age, height, weight and body mass index, there was no significant difference between the 3 groups. The mean duration of disease in chronic psoriasis was 5.40±3.72 years and mean PASI score of patients was 13.58±7.41 in acute and 7.80±4.28 in the chronic psoriasis group.

In HRV, the time domain parameters (Fig. 1) were significantly low in new and old psoriasis patients as compared with controls, evidenced by the significantly low SDNN, RMSSD,NN50 and pNN50. In frequency domain (Fig. 2), HF (n.u) value was significantly low in old and new psoriasis patients, whereas LF (n.u) value was significantly high in old psoriasis and new patients as compared with controls. LF/HF ratio was significantly high in both groups of psoriasis patients as compared to controls. There was no significant difference in the time and frequency domain parameters between the new and the old

TABLE I: Baseline clinical characteristics of the psoriasis and control groups.

Variables	*Controln-30*	*New Patientsn-16*	*Old Patientsn-12*
Age (yr)	34.80±6.52	37.28±8.84	39.76±5.60
Height (cm)	146.78±12.90	142.79±11.85	150.36±8.92
Weight (kg)	54.81±13.20	58.60±7.28	55.80±6.48
BMI (Kg/cm^2)	25.33±3.65	28.76±4.62	24.44±3.93
Disease duration (yrs)	NA	< 1	5.40±3.72
PASI score	NA	13.58±7.41	7.80±4.28

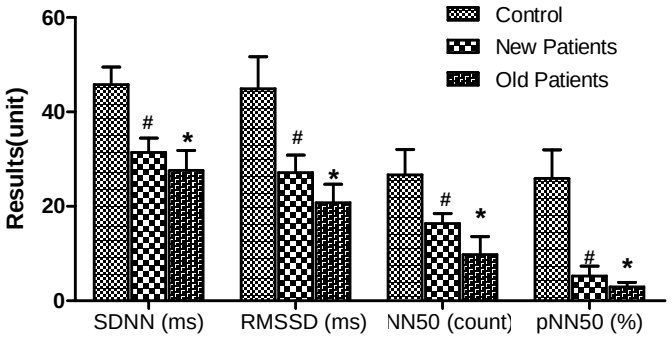

Fig. 1: Time domain parameters of Short term HRV in psoriasis and control groups.

RMSSD, square root of the mean squared differences between adjacent normal RR intervals; SDNN, standard deviation of all normal RR intervals;, SDSD, standard deviation of successive differences between adjoining normal cycles, N50 the number of interval differences of successive NN intervals greater than 50 ms, and pNN50 the proportion derived by dividing NN50 by the total numberof NN intervals.

Control vs New psoriasis, * Control vs Old Psoriasis.

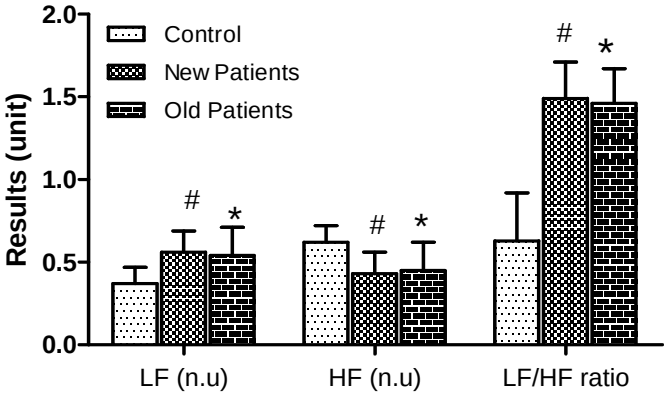

Fig. 2: Frequency domain parameters of Short term HRV in psoriasis and control groups.

LF- low frequency; HF-high frequency; LF/HF ratio, ms- milliseconds; nu- normalizedunits.

Control vs New psoriasis, * Control vs Old Psoriasis.

psoriasis patients. In Poincare plot (Fig. 3) SD1 was significantly reduced in both new and old psoriasis, whereas SD2 was only reduced in old psoriasis.

In the test for autonomic reactivity (Table II), the change in DBP as a measure of sympathetic reactivity during IHG (7.87±2.72 vs 10.20±3.67) was significantly low in old patients compared to new patients and controls. Though the DBP change on

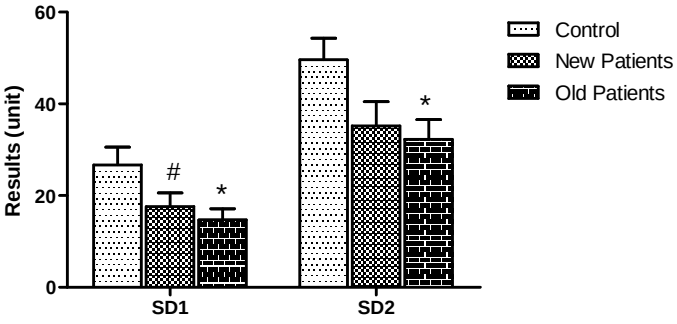

Fig. 3: Poincare plot parameters of Short term HRV in psoriasis and control groups.

Control vs New psoriasis, * Control vs Old psoriasis.

TABLE II: Autonomic function test in psoriasis and control group.

AFT variables	*Controln-30*	*New Patientsn-16*	*Old Patientsn-12*	*P value*
HR (bpm)	69.24±12.64	78.92±10.76	73.56±9.84*	0.05
Deep Breathing Test (DBT)	1.39±0.25	1.52±0.79	1.09±0.39	0.215
30:15 ratio	1.35±0.28	1.33±0.26	1.00±0.60*	0.04
Valsalva maneuver	1.81±0.32	1.55±0.33	1.19±0.17*	0.04
Isometric hand grip (IHG) delta change in DBP (mmHg)	16.30±4.53	10.20±3.67	7.87±2.72**$	0.026
Change in DBP response to standing (mmHg)	8.42±1.68	6.30±0.86	5.46±1.38*	0.04

*Control vs old psoriasis, $ New patients vs Old patients *P<0.05, **P<0.01.

immediate standing (5.46±1.38 vs 6.30±0.86) was significantly lower (P<0.05) in old psoriasis than new psoriasis patients and controls, the change falls within the normal range.

HR, valsalva maneuver and 30:15 ratio in lying to standing test for parasympathetic reactivity showed significant (P<0.05) variation in old patients than controls. Though there was a decrease in DBT test in old psoriasis patients compared to control subjects, it was not statistically significant (P=0.215).

Discussion

The present study demonstrated the extent of autonomic dysfunction in psoriasis with respect to the duration of the disease. In recently diagnosed patients of psoriasis there appears to be a compromise of only the parasympathetic activity and in patients of chronic psoriasis there is involvement of both the parasympathetic as well as the sympathetic system.

Psoriasis patients who were diagnosed recently i.e. duration of the disease being one year or less without clinically overt features of autonomic dysfunction showed compromised parasympathetic activity at rest as evidenced by the low HF values during HRV. The parasympathetic reactivity however remained intact as assessed by the Valsalva ratio and the E:I ratio from deep breathing test. Patients with history of psoriasis for duration of more than 1 year showed compromised parasympathetic activity as well as reactivity evidenced by the low HF, Valsalva ratio and E:I ratio and compromised sympathetic reactivity evidenced by IHG test and BP response to standing. The cause has been attributed to the inflammatory mediators such as tumour necrosis factor-5 (TNF-5), IL-1, IL-12, IL-23, and IL-17. (4)TNF- 5 has been reported to be associated with reduced HRV indices causing autonomic imbalance (An inverse correlation between TNF alpha serum levels and heart rate variability in patients with heart failure, Valentina et al 2013, Journal of cardiology). It has been reported in patients with psoriasis, that increased pro-inflammatory cytokines inhibit the sympathetic nervous system at the site of inflammation and increase sympathetic tones in sites without inflammation (18). These inflammatory mediators act independently of conventional cardio vascular risk factor which promotes atherosclerosis (19). Impairment in the autonomic function leads to increased cardiovascular disease risk in the psoriasis patients (20,21). Several studies have shown that in patients with psoriasis there is increased incidence of cardiovascular diseases as well as an increased cardiovascular risk factors such as, diabetes, hypertension and dyslipidaemia (22-24). Increased arterial stiffness is associated with atherosclerosis in patients with psoriasis has been found in various studies (25, 26).

Psoriasis is a chronic inflammatory skin disease and initially thought of as being primarily a skin disease, but with understanding of the immune patho-genesis and genetics of the disease it has been accepted as a systemic inflammatory condition (1, 2).

The status of the Autonomic function in psoriasis has been evaluated previously but the results are controversial. Recently, Haligur et al., found that dysfunction of sympathetic system in the psoriasis by sympathetic skin response (SSR) and R-R interval variation (RRIV) (12). Pancar Yuksel E. et al., 2014 using heart rate recovery index (HRRI) is an indicator of autonomic nervous system function and has found that the impairment of parasympathetic system in psoriasis patients (25). But Biçer et al., found that there is no involvement of the autonomic dysfunction in the psoriasis patients in 24 hrs Holter recording for heart rate variability (HRV) and turbulence analysis (14). The possible reason for the varied results might be due to the heterogeneity in the severity and duration of the disease among the patients. In our study, we have compared patients who were recently diagnosed as well as the ones with disease of longer duration with the normal subjects and found that the autonomic function was differently compromised in the two groups of patient. Recently diagnosed patients have only parasympathetic involvement, whereas chronic patients have both sympathetic and parasympathetic compromise. But in the above mentioned studies the disease duration was not taken into consideration and a heterogeneous group of psoriasis patients were recruited as well as only one method was used to

assess the autonomic function. We had used both activity as well reactivity tests to assess the autonomic status in the patients of psoriasis.

The differing results in the newly diagnosed and the chronic patients could be attributed to the level of inflammatory markers and their association with the disease duration. This preliminary study opens up an opportunity to make further research in patients with psoriasis and autonomic dysfunction including the immune status and its contribution to autonomic dysfunction.

Conclusion

In conclusion, duration of disease seems to influence autonomic dysfunction in patients with psoriasis. Involvement of the parasympathetic system occurs in early phase of the disease and with increasing duration of the disease the sympathetic system also gets compromised. The cause of this progressive involvement could be due to the psoriasis related alteration in the cardiovascular function and/ or inflammatorybiomarkers in the patients with psoriasis, however this requires further investigation.

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