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ORIGINAL ARTICLE

PREVALENCE OF PULMONARY FUNCTION DEFECTS IN PSORIASIS PATIENTS RECEIVING METHOTREXATE IN A TERTIARY CARE HOSPITAL IN TAMIL NADU, INDIA

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ABSTRACT: Methotrexate is an anti-metabolite widely used in malignancy, rheumatoid arthritis and refractory cases of psoriasis.[1] The value of low dose methotrexate is well established.[2-4] There are evidences of pulmonary function defects in patients on long term low dose methotrexate in rheumatoid arthritis patients. Because methotrexate is frequently used in patients suffering from conditions such as RA, dermatomyositis or sarcoidosis, which can be associated with interstitial lung disease, determining the exact role of methotrexate in the development of pulmonary complications in these patients seems to be difficult. Therefore, we conducted a cross-sectional study to analyse the findings found on chest x-rays, high resolution computed tomography (HRCT) and pulmonary function tests (PFT) in a cohort of patients without previous recognized interstitial lung disease who were taking methotrexate as a treatment for psoriatic arthritis, a condition not associated with pleuro pulmonary disease. **RESULTS:** In this study 154 patients from the outpatient department of psoriasis clinic of dermatology department of government general hospital, Chennai who were receiving methotrexate for psoriasis were screened. Out of which 30 patients who were eligible as per inclusion criteria were included in the study. In this study 9 patients showed normal radiology and pulmonary function test. 21 patients had pulmonary function abnormalities. In this study there were 13(43%) patients with restrictive pulmonary function defect. Belzenegui.[14] et al reported 2 cases with mild restriction among 27 patients in a similar study. There were 10(33%) patients with diffusion defect in this study. Belzenegui et al reported 2 cases among 27 patients in a similar study. There were 5(16%) patients with small airway disease as suggested by decrease in mean mid expiratory flow. Belzenegui et al reported 5 cases among 27 patients in a similar study. There were 3(3%) patients with radiological lesions, 1 had bronchiectasis and 2 had interstitial fibrosis. Patients with Co-morbidities like bronchial asthma (n=3), rheumatic heart diseases (n=1), hypertension (n=1), diabetes mellitus (n=1) and habits like smoking (n=7) did not have radiological features of methotrexate induced pulmonary fibrosis. There was no case of acute pneumonitis during the study period. Average duration of respiratory symptoms in suspected patients was more than 1 month. The study is comparable with the previous studies with prevalence rate for methotrexate induced pulmonary fibrosis nearing 2% of 154 patients receiving methotrexate from dermatology outpatient department. Diffusion capacity was an useful aid in all 3 patients with methotrexate induced pulmonary toxicity. **CONCLUSION:** There were 3(10%) patients with radiological evidence of methotrexate induced pulmonary fibrosis. There were 10(33%) patients with restrictive pulmonary function defect without radiological evidence of methotrexate induced pulmonary fibrosis. There were 7(23%) patients with diffusion defect in this study without radiological evidence of methotrexate induced pulmonary fibrosis. Of these 7 patients, 5 patients had spirometric defect in the form of restriction. There were 14(47%) patients with symptoms, no radiological abnormality and no spirometric abnormalities. Of the above 14 patients, 2 patients (6.6%)

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had diffusion defect. Prevalence of pulmonary function abnormalities in this study matches similar studies elsewhere. DLco could be an early predictor of pulmonary function impairment in psoriasis patients on long term methotrexate. Regular follow up of patients who are taking methotrexate on along term basis with spirometry and dlco may be an effective tool in early identification and treatment of pulmonary complications in these patients.

KEYWORDS: Methotrexate, Psoriasis, V, Pulmonary Function Test, Spirometry, DL co, Pulmonary fibrosis.

INTRODUCTION: Methotrexate is an anti-metabolite widely used in malignancy, rheumatoid arthritis and refractory cases of psoriasis.[1] The value of low dose methotrexate is well established.[2-4] Most patients are able to tolerate low dose methotrexate with generally sustained efficacy.[5] The main pulmonary side effect of methotrexate is interstitial pneumonitis. Its incidence has been found to be about 7 to 8%, in studies in which methotrexate at antineoplastic doses was used, in combination with other cytotoxic agents.[6] There are evidences of pulmonary function defects in patients on long term low dose methotrexate in rheumatoid arthritis patients. Acute methotrexate induced pneumonitis has also been reported after low-dose therapy (<20mg/wk) for rheumatoid arthritis.[7-12] Pulmonary function test of methotrexate pneumonitis patients show restrictive pattern with impairment in diffusion capacity of carbon monoxide. It is known that in patients receiving other cytotoxic drugs such as bleomycin, abnormalities in pulmonary function can be detected before the patients become symptomatic. Because methotrexate is frequently used in patients suffering from conditions such as RA, dermatomyositis or sarcoidosis, which can be associated with interstitial lung disease, determining the exact role of methotrexate in the development of pulmonary complications in these patients seems to be difficult. Therefore, we conducted a cross-sectional study to analyse the findings found on chest x-rays, high resolution computed tomography (HRCT) and pulmonary function tests (PFT) in a cohort of patients without previous recognized interstitial lung disease who were taking methotrexate as a treatment for psoriatic arthritis, a condition not associated with pleuro pulmonary disease.

AIM OF THE STUDY: To know the prevalence of pulmonary toxicity and derangements in pulmonary function in psoriasis patients taking Methotrexate on long term basis through DLco, spirometry and radiological evaluation.

MATERIALS AND METHODS: Population Studied: This is a cross sectional study done by Institute of Thoracic Medicine, Chetpet and Government general hospital, Chennai. The study patients were from Department of Dermatology, Government General Hospital, Chennai.

INCLUSION CRITERIA:

1. Psoriasis patients have taken more than 3 months of methotrexate with respiratory complaints.
2. Age group above 14 years.
3. Patients who were willing for the study and gave informed consent for the study.
4. Both sexes.

EXCLUSION CRITERIA: Not able to perform PFT Patients treated for pulmonary tuberculosis in the past Patients known to have restrictive lung diseases due to other known causes like collagen vascular diseases.

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METHODS: All eligible Psoriasis patients who are on methotrexate therapy for more than 3 months (Cumulative dosage exceeding 150mg) were subjected to detailed history taking, clinical examination, complete haemogram, liver function test, renal function test, spirometry, diffusion capacity of carbon monoxide and radiological examination including x-ray chest and HRCT Chest (Read by 2 independent readers).The data were tabulated and analysed.

ATS RECOMMENDATION FOR PERFORMING SPIROMETRY: Procedures for recording spirometry were done as per ATS recommendation that include; Checking the spirometer calibration, Explanation of the test to subject, Preparation of the subject including asking about smoking, recent illness, medication use and measurement of weight and height. The subject were then instructed and demonstrated about the test including correct posture with head slightly elevated, rapid and complete inhalation and exhalation with maximal force. After assuming the correct posture nose clip was attached and mouthpiece was placed in mouth with close lips around the mouthpiece. Patient was instructed to inhale completely and rapidly with a pause of one second at Total Lung Capacity and then to exhale maximally until no more air can be expelled while maintaining an upright posture.

Repeated instructions were given. Minimum of three manoeuvres were repeated; no more than eight are usually required. The variables recorded included FVC, FEV_1 and FEV_1/FVC ratio. Three technically satisfactory measurements were obtained in which FVC was reproducible within 300ml. The subject's FVC was defined as the maximal FVC which was determined before the DLCO test, as recommended by the ATS.

ATS RECOMMENDATION FOR PERFORMING DLCO: DLCO measurements were performed in compliance with the American Thoracic Society (ATS) guidelines. DLCO was measured using a single-breath technique. The DLCO was routinely adjusted for haemoglobin if the value was outside the normal range. Measurements of DLCO were made with a Collins automated system using a gas mixture that contained 0.3% Methane tracer gas and 0.3% carbon monoxide. The breath holding time was 10 seconds and the washout volume was 0.75 L. Each subject's height and weight were measured.

The participants were seated, wearing nose clips, and performed at least two DLCO manoeuvers separated by more than 4 minutes. The mean DLCO value from two manoeuvers that matched within 3 ml/min/mm Hg was reported.

Before the test was performed, each subject was instructed about all of the required manoeuvers. After the subject had adapted to the mouthpiece of the test apparatus, four or five tidal volumes were recorded to determine a regular end expiratory baseline. The subject was then asked to exhale as far as possible, to the point till maximal exhalation had been reached (Residual volume RV); making a rapid, maximal inhalation within 2 to 2.5 seconds to VC continuing to hold the breath for 10 seconds while relaxing against a closed glottis and exhaling rapidly. If after two attempts an acceptable measurement could not be made, the procedure was then abandoned.

The values were interpreted as follows: DLCO and DLCOHb: Normal (>80% predicted) Mild diffusion defect (65-80%), Moderate diffusion defect (45-65%) and severe diffusion defect (<45%). FVC: Normal (>80% predicted), Mild Reduction (60-80%), Moderate Reduction(40-60%), Severe Reduction (<40%).

SEARLES AND MCKENDRY CRITERIA.[13]

Diagnostic Criteria: Acute onset of breathlessness. Fever (>38 C). Tachypnoea (>or=28 breaths/ minute) with nonproductive cough. Radiographic infiltrates of interstitial or alveolar infiltrates.

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WBCs <or =15, 000.Negative blood or sputum culture for pathogenic organisms. Pulmonary function tests showing restrictive pattern with low diffusion capacity. PaO2 <55mmhg in room air. Biopsy, histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of pathogenic organism.

PRESENCE OF METHOTREXATE PNEUMONITIS:

- Definite: at least 6.
- Probable: at least 5.
- Possible: at least 4.

MODIFIED SEARLES AND MCKENDRY CRITERIA:

Major Criteria:

1. Hypersensitivity pneumonitis by histopathology without evidence of pathogenic organism.
2. Radiological evidence of pulmonary interstitial or alveolar infiltrates.
3. Blood cultures (if febrile) and initial sputum cultures (if sputum is produced) negative for pathogenic organisms.

MINOR CRITERIA:

1. Shortness of breath <8 weeks.
2. Non-productive cough.
3. O_2 saturation <90% at the time of initial evaluation on room air.
4. DLco <or=70% predicted for the age.
5. Leukocyte count <or=15000/mm^3.

A definite case had to meet major criterion 1 (Pathologic evidence) or criteria 2 (Radiologic evidence or an abnormal chest radiograph) and 3 (Negative cultures) plus three of the five minor criteria (Shortness of breath, nonproductive cough, O_2 saturation ≤90%, DLCO [Diffusing capacity of the lung for carbon monoxide] ≤70%, and leukocyte count ≤15000 cells/mm^3). Patients were said to have met major criterion 3 if they were afebrile and did not produce sputum, even if no blood or sputum cultures were done. In some patients, bronchoalveolar lavage fluid was cultured to rule out infectious causes of disease. Probable case-patients had to meet major criteria 2 and 3 plus two of the five minor criteria. No other case-patients were considered to have methotrexate-induced lung injury. Modified searles and mckendry criteria is used in this study to confirm the diagnosis of methotrexate induced pneumonitis

RESULTS: In this study 154 patients from the outpatient department of psoriasis clinic of dermatology department of government general hospital, Chennai who were receiving methotrexate for psoriasis were screened. Out of which 30 patients who were eligible as per inclusion criteria were included in the study. Out Of these patients 7 were smokers, 2 were diabetic, 2 were hypertensive out of which 1 was known patient of rheumatic heart disease on treatment and 4 were known bronchial asthma patients. None of these patients with co-morbidity had methotrexate induced fibrosis but had diffusion and spirometric defects of lung functions which will be detailed later.

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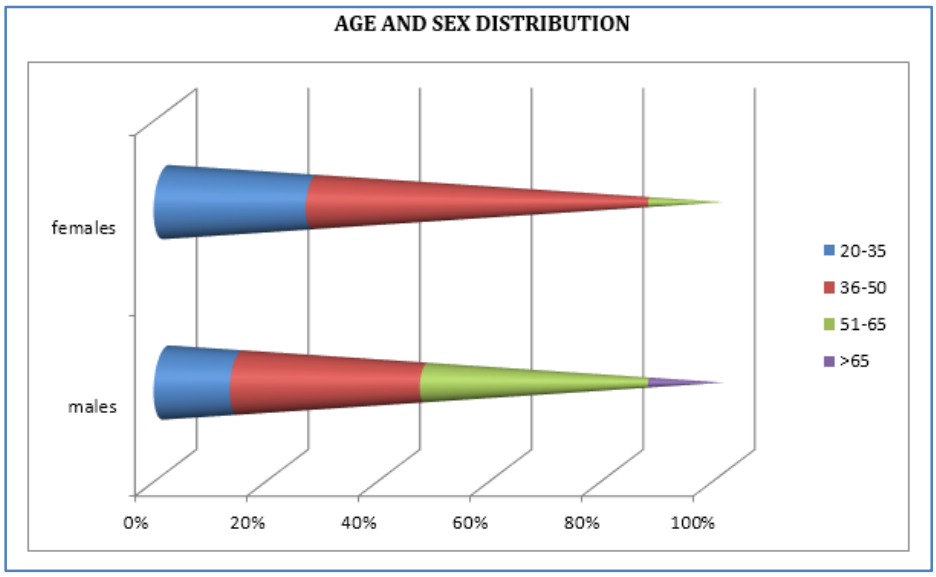
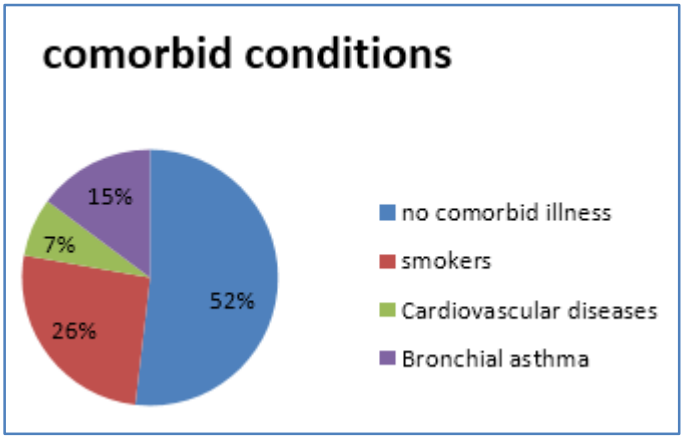


In this study, there were 15 males and 15 females. Their age distribution was:

	20-35 years	35-50 years	51 to 65 years	>65 years
Males	2	5	6	2
Females	4	9	2	0



RADIOLOGICAL LESION VS PFT:

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	Restriction	Obstruction	Early obstruction	normal	Total
With radiological lesion	3	0	0	0	3
Without radiological lesion	10	3	5	9	27
Total	**13**	**3**	**5**	**9**	**30**

RADIOLOGICAL LESION VS SPIROMETRY

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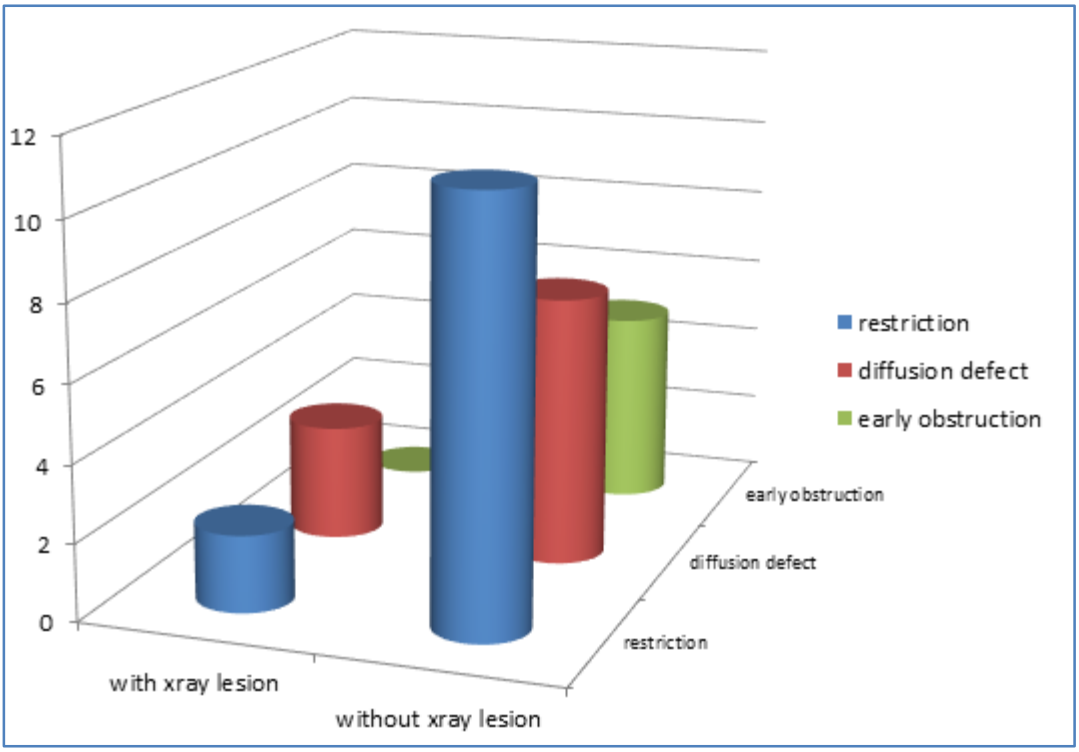
There were 21 patients with spirometric abnormalities. 3 patients with radiological lesions had restrictive pulmonary function defect. 10 patients without radiological lesions had restrictive pulmonary function defect. 3 patients had obstruction.5 patients had early obstruction as suggested by decrease in mid mean expiratory flow, normal fev_1 and normal chest x-ray.



There were 11(36.6%) patients with restrictive ventilatory defect without radiological abnormalities, 7(23.3%) patients with diffusion defects without radiological abnormalities. There were 5 (16.6%) of patients with small airway disease as evidenced by decrease in mean mid expiratory flow without other ventilatory defects and normal x-ray chest.

There were 3 patients with restrictive ventilatory defect and no diffusion defect and 2 patients with diffusion defect and no restrictive ventilatory defect. 2 patients had diffusion defect, small airway disease (decreased mmef) radiological lesions but no restrictive ventilatory defect.

CUMULATIVE DOSE VS PFT: Diffusion defect and restrictive ventilatory defect occurred with least cumulative dose of 150mgs. Small airway disease occurred with a least cumulative dose of 860mgs. Least cumulative dose at which methotrexate induced pulmonary toxicity (10%) occurred was 2250mgs. 3 (10%) patients had received above this cut off cumulative dose without developing radiological lesions or pulmonary function defects. Hence in this study pulmonary toxicity seems to be independent of cumulative dose and is not dose dependant

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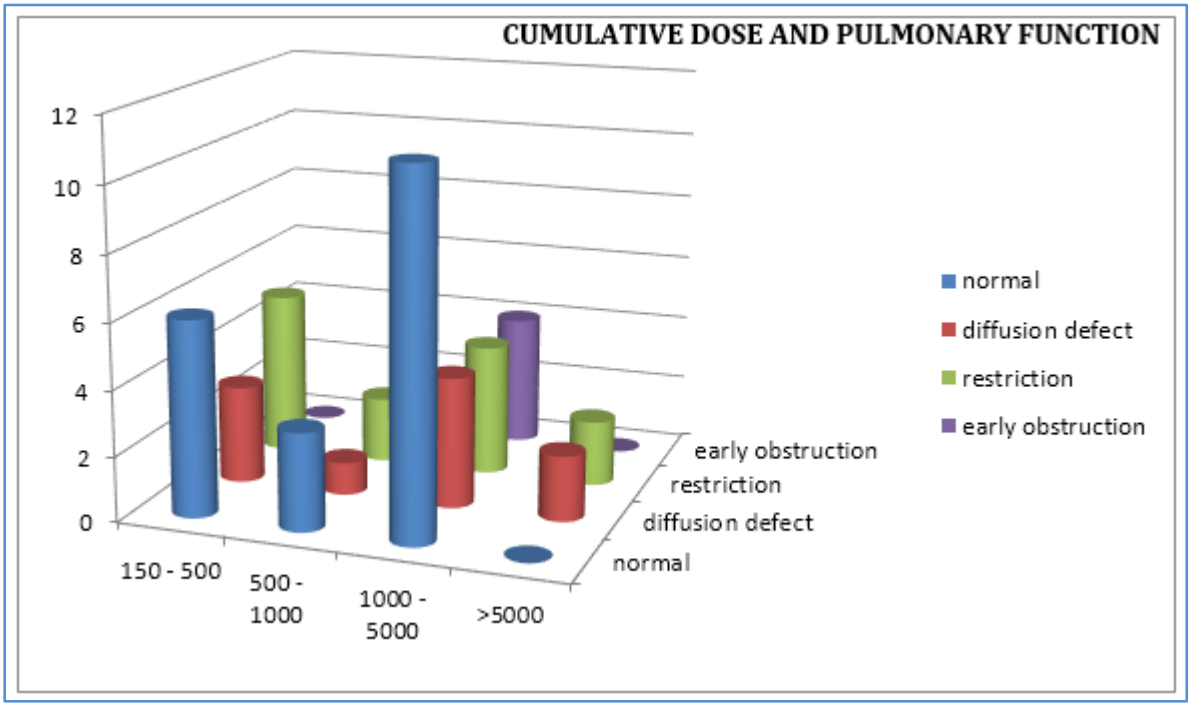

Ventilatory Defects Eosinophils %	Restriction	Diffusion defect	Early Obstruction	Normal
< 7%	9	8	2	8
>7%	4	2	3	3
Total	**13**	**10**	**5**	**11**

Eosinophils Vs Pft

There was no relevance between pulmonary function defects and eosinophil count.

SYMPTOMS VS PFT:

	Restriction	Obstruction	Early Obstruction	Total (no:21)
Symptoms >1 month	4	2	2	8
Total	**13**	**3**	**5**	**21**

Symptoms Vs Spirometry

All 3 patients with pulmonary fibrosis presented with respiratory symptoms more than 1 month. There were 5 patients with symptoms, no pulmonary fibrosis and diffusion defect. There were 2 patients without symptoms, no pulmonary fibrosis and diffusion defect. There were 2 patients with symptoms, restrictive pattern and no pulmonary fibrosis. There were 8 patients without symptoms, restrictive pattern and no pulmonary fibrosis. There were 2 patients with symptoms, early obstruction and no pulmonary fibrosis. There were 3 patients without symptoms, early obstruction and no pulmonary fibrosis.

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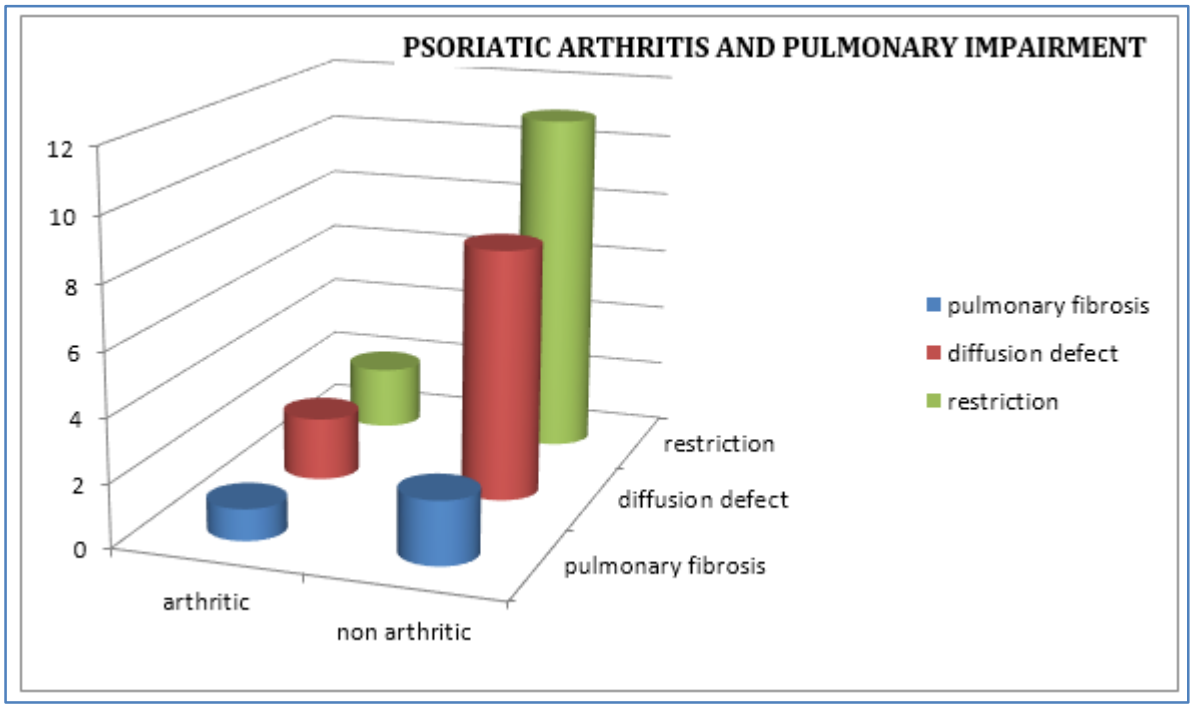
	Diffusion defect	Normal diffusion	Total
Symptoms > 1 month	5	3	8
Symptoms < 1month	5	17	22
Total	10	20	30

Symptoms Vs Diffusion Defect



There were 5 patients with psoriatic arthritis in this study.1 patient had pulmonary fibrosis.2 patients had diffusion defect and 2 patients had restrictive pattern in spirometry.

METHOTREXATE INDUCED PULMONARY FIBROSIS: There were 3(10%) cases of methotrexate induced pulmonary toxicity according to modified searles and mckendry criteria. All of them (100%) had pulmonary diffusion defects. 2(66%) had restrictive ventilatory defects only. There were 2 males and 1 female patient. 2 males were above 50 years with psoriasis vulgaris and female was 20 years with pustular psoriasis. All 3 patients had dry cough and dyspnoea for more than 1 month. 2 patients (66%) had bilateral diffuse interstitial fibrosis. 1(33%) patient had bilateral lower lobe traction bronchiectasis.

Cumulative dose	9360	8340	2250
Dose/ week	30mg	15mg	7.5mg

DISCUSSION: In this study 9 patients showed normal radiology and pulmonary function test.21 patients had pulmonary function abnormalities.

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	Patient 1	Patient 2	Patient3
Age	60	20	56
Sex	male	Female	Male
Psoriasis type	Psoriasis vulgaris	Pustular psoriasis	Psoriasis vulgaris
Fever	no	no	No
cough	yes	yes	No
Expectoration	No	no	No
Dyspnoea	yes	yes	Yes
Duration of symptoms	4 months	4 months	4 months
Total count	8000/cmm	14600/cmm	7600/cmm
Eosinophils	2%	4%	2%
X-ray chest	B/L Interstitial pattern	B/L lower zone reticular shadows	B/L Interstitial pattern
HRCT Chest	B/L Interstitial fibrosis	B/L Lower lobe traction bronchiectasis	B/L Interstitial fibrosis
PFT	Severe restriction	Moderate restriction	Normal
Diffusion capacity	Severe	Mild	Mild
Arthritis	No	No	Yes

In this study there were 13 (43%) patients with restrictive pulmonary function defect. Belzenegui.[14] et al reported 2 cases with mild restriction among 27 patients in a similar study,

There were 10 (33%) patients with diffusion defect in this study. Belzenegui et al reported 2 cases among 27 patients in a similar study.

There were 5(16%) patients with small airway disease as suggested by decrease in mean mid expiratory flow. Belzenegui et al reported 5 cases among 27 patients in a similar study.

There were 3 (3%) patients with radiological lesions, 1 had bronchiectasis and 2 had interstitial fibrosis.

Patients with Co-morbidities like bronchial asthma (n=3), rheumatic heart diseases (n=1), hypertension (n=1), diabetes mellitus (n=1) and habits like smoking (n=7) did not have radiological features of methotrexate induced pulmonary fibrosis.

There was no case of acute pneumonitis during the study period.

Average duration of respiratory symptoms in suspected patients was more than 1 month.

The study is comparable with the previous studies with prevalence rate for methotrexate induced pulmonary fibrosis nearing 2% of 154 patients receiving methotrexate from dermatology outpatient department.

Diffusion capacity was an useful aid in all 3 patients with methotrexate induced pulmonary toxicity.

CONCLUSIONS: There were 3(10%) patients with radiological evidence of methotrexate induced pulmonary fibrosis.

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There were 10(33%) patients with restrictive pulmonary function defect without radiological evidence of methotrexate induced pulmonary fibrosis.

There were 7(23%) patients with diffusion defect in this study without radiological evidence of methotrexate induced pulmonary fibrosis. Of these 7 patients, 5 patients had spirometric defect in the form of restriction.

There were 14(47%) patients with symptoms, no radiological abnormality and no spirometric abnormalities. Of the above 14 patients, 2 patients (6.6%) had diffusion defect.

Prevalence of pulmonary function abnormalities in this study matches similar studies elsewhere.

DLco could be an early predictor of pulmonary function impairment in psoriasis. Patients on long term methotrexate.

Regular follow up of patients who are taking methotrexate on a long term basis with spirometry and dlco may be an effective tool in early identification and treatment of pulmonary complications in these patients.

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