

Assessment of Pulmonary Function of Psoriatic Patients Receiving Methotrexate

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Abstract:

Background: Psoriasis is associated with altered pulmonary function. Methotrexate affects the lung function status in psoriatic patients: effect of other antipsoriatic medication on lung function was not evaluated.

Objectives: To assess the Pulmonary Function Test among the Psoriatic Patients Receiving methotrexate with the Duration of Treatment.

Methods: This cross sectional study was carried out in the Department of Physiology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, from July 2012 to June 2013. A total number of 120 subjects were selected, among which 30 were apparently healthy subjects (control group-A) for comparison and 90 were diagnosed male Psoriatic patients (study group-B). Controls were selected from the community and the patients from the Indoor and Out Patient Department (OPD) of Dermatology and Venereology, BSMMU, Dhaka. Based on treatment, these study subjects were further divided into three groups consists of 30 male subjects in each group.

Results: The mean±SE age were 33.5±1.424, 34.5±1.401, and 35.27±1.44 and 34.8±1.212 years in group A, B₁, B₂ and B₃ respectively and ranging from 25 to 45 years. All the values were almost similar and the differences among the groups were statistically non-significant. Therefore, all the groups were matched for age. The mean±SE BMI were 23.557±0.584, 23.089±0.721, 23.986±0.579 and 23.155±0.595 years in group A, B₁, B₂ and B₃ respectively. In this study, all the groups (healthy and diseased) were matched for BMI, as the values were almost similar and the difference among the groups were statistically non-significant. In this study, all the control subjects (A) were with normal lung function tests (LFT). On the contrary, 19 (63.33%), 20 (66.67%) and 29(96.67%) Psoriatic patients were with abnormal lung function tests in the experimental groups B₁, B₂ and B₃ respectively. In group B₁, restrictive disorder was found in 9(30%) patients, small airway obstruction was in 0(0%) patients and large airway obstruction in 20(0%) patients. In group B₂, restrictive disorder was found in 10 (33.33%) patients, small airway obstruction was in 0 (0%) patients and large airway obstruction in 0 (0%) patients. In group B₃, restrictive disorder was found in 23(76.67%) patients, small airway obstruction was in 0(0%) patients and large airway obstruction in 0 (0%) patients. In this study, among those 90 Psoriatic patients 42(46.67%) were diagnosed as restrictive disorder; where 12 Psoriatic patients were presented with different type of pulmonary symptoms and rest 30 were without any pulmonary complain. On the contrary, in the group B₂ FVC and FEV₁ were negatively correlated but FEV₁/FVC%, PEFR, FEF_{25-75%}, FEF_{25%}, FEF_{50%} and FEF_{75%} were positively correlated with the duration of therapy. Moreover, in group B₃, FVC, FEV₁, FEF_{50%} were negatively and FEV₁/FVC, PEFR, FEF_{25-75%}, FEF_{25%} and FEF_{75%} were positively correlated with the duration of therapy. However, most of these relationships (e.g. FEV₁/FVC, PEFR, FEF_{25-75%}, FEF_{25%} and FEF_{75%}) were not statistically significant, but FVC, FEV₁ were statistically significant in group B₁ and B₃.

Conclusion: From this cross sectional study it may be concluded that, the pulmonary Function Test among the Psoriatic Patients were with abnormal lung function tests in the experimental groups B₁, B₂ and B₃ respectively. However, most of these relationships (e.g. FEV₁/FVC, PEFR, FEF_{25-75%}, FEF_{25%} and FEF_{75%}) were not statistically significant, but FVC, FEV₁ were statistically significant in group B₁ and B₃.

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Introduction:

Psoriasis is a common chronic recurrent non-contagious inflammatory skin disease with a complex pathophysiology and a strong genetic background.^{1,2,3,4} Plaque psoriasis is the most common type, account for 80-90% of all cases of Psoriasis usually manifested as raised, well-demarcated erythematous, oval plaques with adherent silvery scale.^{5,6,7} In about 5 to 40% To cases of Psoriasis develops Psoriatic arthritis.⁸ Etiology of Psoriasis remains unknown; however, it has been linked to complex interactions between predisposing genes and the environment.⁹ The pathophysiology of Psoriasis is characterized by epidermal hyperproliferation, enhanced antigen presentation Th-1 cytokine production, T cell expansion and angiogenesis. These condition usually occurred by genetic pathways, common immune mechanisms and treatment related toxicities.⁹ Smoking and obesity were also found to be independent risk factors for the development of Psoriasis.¹⁰ In the recent years, Psoriasis has been recognized as a systemic disease associated with numerous multiorgan abnormalities and complication. In Psoriatic patients an increased risk of cardiovascular abnormalities, hypertension, dyslipidemia, atherosclerosis, type-2 diabetes mellitus, obesity, chronic obstructive pulmonary disease, cerebral stroke, osteoporosis, cancer and depression was noticed.^{11,12,13} Several studies showed Methotrexate induced pulmonary toxicity and this condition commonly presents within 24-32 weeks of taking the drug.^{14,15,16,17,18} McKenna and Burrows¹⁹ reported that pulmonary function tests deteriorated further despite stopping methotrexate for the few months though remains in asymptomatic condition. Pulmonary function tests are the most sensitive means of detecting any pulmonary involvement in any disease. Spirometry is probably the most important tool for screening of pulmonary disease and most frequently perform pulmonary function test.²⁰ Various ventilatory variables like FVC, FEV1, FEV1/FVC ratio, PEF, FEF 25-75% can be measured by Spirometry.^{21,22,23,24} Along with other organ involvement lungs were also affected in patients with Psoriasis. A multivariate logistic regression model demonstrated that Psoriasis was significantly associated with COPD, after controlling for confounders, including age, sex, socioeconomic status, smoking and obesity.²⁵

It has been suggested that COPD is an autoimmune disease with a chronic inflammatory state, similar to Rheumatoid arthritis or Psoriasis.^{26,27} Several investigator of different countries have suggested that systemic inflammation plays an important role in both Psoriasis and COPD.^{28,29} Inflammation Psoriasis results in a Th1 lymphocyte cytokine milieu, such as interleukin (IL)-1, IL-6, IL-8, and TNF- α , and signs of systemic inflammation, including increased C-reactive protein (CRP) levels and platelet activation.⁷ The elevation of interleukins and CRP was also noted in COPD and linked to the severity of the clinical presentation of both Psoriasis and COPD.^{29,30,31} There is increasing evidence that COPD is a complex systemic disease than just an airway and lung disease. Cachexia, skeletal muscle abnormalities, Hypertension, Diabetes, Coronary heart disease, pulmonary infection, cancer and pulmonary disease are the most common comorbidities that are associated with COPD.³² Inflammatory cytokines such as CRP, TNF- α , IL-6, IL-8 have been found to be aetiologically involved in both Psoriasis and COPD.^{26,27,32}

Materials and Methods:

Type of Study: Cross-sectional study

Place of Study: Department of Physiology, BSMMU, Dhaka, Bangladesh. Study Period: 1st July 2012 to 30st June 2013.

Ethical Issue: Protocol was approved by Institutional Review Board, BSMMU, Shahbag, Dhaka. Sample Size: A total number of one hundred and twenty (120) male subjects with age range from 25 to 45 years.

Grouping of the subjects:

Group A (Control Group): 30 apparently healthy male subjects.

Group B (Study Group): 90 diagnosed male patients with Psoriasis. On the basis of different types of treatment the study group was subdivided into-

- B₁** 30 diagnosed psoriatic patients receiving only topical therapy (e.g. Corticosteroid, Coal tar, Dithranol, Salicylic acid, etc.).
- B₂** 30 Psoriatic patients treated with PUVA therapy.
- B₃** 30 Psoriatic patients treated with Methotrexate therapy.

Inclusion criteria:

For both groups:

- Age: 25-45years
- Sex: Male

For study groups:

- Psoriatic patients diagnosed by the physicians of Dermatology and Venereology.
- Psoriatic patients under treatment with Topical (e.g. Corticosteroid cream/ointment, Coal Tar, Dithranol, Tazarotene, Vitamin D, etc.) therapy, PUVA therapy and Methotrexate medication.

For control group:

Age, sex, socioeconomic structure matched apparently healthy male subjects.

Exclusion Criteria:

For both groups

- Other type of dermatological disorders.
- History of any type of smoking (Cigarettes, Hookah, Biri, Tobacco etc).
- Patients with acute or chronic lung & chest wall disease e.g. Pneumonia, Tuberculosis, Asthma, COPD, Malignancy etc.
- History
 - Any heart disease
 - Chronic liver diseases
 - Chronic renal failure (0.68-1.36mg/dl)[33]
 - Diabetes mellitus:
Fasting- 65-104mg/dl or 3.6-5.8mmol/L[33] 2 hrs. after breakfast-<140mg/dl or <7.8mmol/L (WHO1999).
 - Other autoimmune diseases

All the diseases mentioned above were excluded by taking history except diabetes mellitus, chronic renal failure, which were diagnosed biochemically.

Site of sample collection: Controls were collected from the community and the Psoriatic patients from the indoor and Out Patient Department (OPD) of Dermatology and Venereology, BSMMU, Dhaka.

Study outline

On the first day of enrollment, the objectives, nature, purpose and potential risk of all the procedures used for the study were explained in detail to each subject, with a cordial attitude giving emphasis on the benefits he might obtain from this study. He was encouraged for voluntary participation & was allowed to withdraw himself from the study even after participation, whenever he felt uneasy. If he agreed to enroll in the study, an informed written consent was taken in a prescribed form. Detailed family

history, medical history and thorough physical examination of each patient were done and all the information was recorded in a standard questionnaire. Then all the patients were requested to attend the Department of Physiology of BSMMU, in fasting state at 8 am on the day of biochemical and Spirometric examination. On the day of examination, 5 ml of venous blood was collected for estimation of fasting serum glucose and serum creatinine. The blood sample was taken to the hematology laboratory as soon as possible and the subject was examined for the

- Height (in meter) and weight (in kg).
- Lung function variables by using a RMS computer based Spirometer, described by Clement Clark International.

Collection of blood sample

With all aseptic precaution, 5 ml of venous blood was drawn from the antecubital vein by a disposable plastic syringe and was transferred immediately into a dry, clean test tube with a gentle push after removing needle, to avoid hemolysis. The test tube was kept in slanting position till formation of clot. After centrifuging the clotted blood (at 3000 rpm for 10 minutes) the serum was separated and taken from the test tube into an eppendr of tube and was preserved in the refrigerator at -4°C in the laboratory. The serum level of glucose and creatinine was done by an autoanalyzer in the hematology laboratory of the Department of Physiology.

Laboratory investigations

- **Serum glucose:** Glucose Oxidase Phenol Amino Phenazone (GOD- PAP) method using reagents of Randox Laboratories Ltd. UK.
- **Serum Creatinine:** Picric acid method using reagents of Randox Laboratories Ltd. UK.

Test procedure for Spirometry

- Subject was asked to take rest sitting on a chair and remain calm and quiet for 5 minutes.
- The detailed procedure was explained to the subject to ensure his maximum cooperation.
- Mouthpiece of the Spirometer was cleaned with alcohol and cotton and then the mouthpiece was placed in between the lips.

- The subject was asked to hold the mouthpiece in his hand horizontally.
- To make good seal, the subject was asked to put the lips tightly around the outside of the mouthpiece.
- The switch of Spirometer was on and window (dialog box) was opened.
- Patient information form was filled up and saved.
- Subject was asked to inhale as deeply and rapidly as possible.
- Then he was asked to exhale as force fully as possible for possible longest period into the mouthpiece.
- The readings of measured, predicted, and percentage of predicted values of FVC, FEV₁, FEV₁/FVC%, PEFR, FEF₂₅₋₇₅%, FEF₂₅%, FEF₅₀% and FEF₇₅% was recorded from the Spirometer monitor.
- Three consecutive readings for each parameter were taken and the best value was noted.

Statistical Analysis

The results were expressed as mean of measured, predicted and percentage of predicted values with $\pm$ SE (Standard Error). The data were statistically analyzed by a computer with SPSS for windows version 16. Independent samples 't' test, ANOVA, Chi-square test and Pearson's correlation coefficient test were used as the tests of significance as applicable. In the interpretation of results, P value <0.05 was accepted as significant.

Results:

The mean $\pm$ SE age were 33.5 $\pm$ 1.424, 34.5 $\pm$ 1.401, and 35.27 $\pm$ 1.44 and 34.8 $\pm$ 1.212 years in group A, B₁, B₂ and B₃ respectively and ranging from 25 to 45 years. All the values were almost similar and the differences among the groups were statistically non-significant. Therefore, all the groups were matched for age. The mean $\pm$ SE BMI were 23.557 $\pm$ 0.584, 23.089 $\pm$ 0.721, 23.986 $\pm$ 0.579 and 23.155 $\pm$ 0.595 years in group A, B₁, B₂ and B₃ respectively. In this study, all the groups (healthy and diseased) were matched for BMI, as the values were almost similar and the differences among the groups were statistically non-significant.

Table I : Age and BMI in different groups (n=120)

Groups	n	Age (Year)	BMI(Kg/m ²)
A	30	33.5 $\pm$ 1.424 (25-45)	23.557 $\pm$ 0.584 (18.256-28.515)
B ₁	30	34.5 $\pm$ 1.401 (25-45)	23.089 $\pm$ 0.721 (17.527-31.53)
B ₂	30	35.27 $\pm$ 1.44 (25-45)	23.986 $\pm$ 0.579 (17.578-29.615)
B ₃	30	34.8 $\pm$ 1.212 (25-45)	23.155 $\pm$ 0.595 (17.968-31.163)

Data expressed as mean $\pm$ SE. Figures in parentheses indicate ranges. ߝOne Way ANOVA, o - Independent sample 't' test, Group A : Apparently healthy subjects (control group), Group B : Diagnosed Psoriatic patients (experimental group), B : Medication with only Topical therapy, B₁ : After medication with PUVA therapy, B₃:After medication with Methotrexate (MTX)therapy, ***: Significant (p $\leq$ 0.001), **: Significant (p $\leq$ 0.01), ns: Non significant, n: Number.

Table II: Frequency distribution of subjects by lung function tests (normal/abnormal LFT) in different groups

Groups	n	With normal LFT no. (%)	With abnormal LFT no. (%)
A	30	30 (100%)	0 (0%)
B ₁	30	11 (36.67%)	19 (63.33%)
B ₂	30	10 (33.33%)	20 (66.67%)
B ₃	30	1(3.33%)	29 (96.67%)

Cut point for abnormal lung function tests: FEV₁/FVC%: <70% of predicted, FEV : <80% of predicted, FVC: <80% of predicted, FEF₂₅₋₇₅%: <50% of predicted, PEFR: <70% of predicted, American Thoracic Society (ATS) 1991.

Frequency distribution of subjects by lung function tests (normal/abnormal LFT) in different groups: The results are shown inTable-2. In this study, all the control subjects (A) were with normal lung function tests (LFT). On the contrary, 19 (63.33%), 20 (66.67%) and 29(96.67%) Psoriatic patients were with abnormal lung function tests in the experimental groups B₁, B₂ and B₃ respectively.

Table III: Distribution of subjects by abnormal pulmonary function variables in different study groups (n=90)

Lung functionparameter	Group B (n=30)	Group B ₁ (n=30)	Group B ₃ (n=30)	Total B +B ₁ +B ₃ (n=90)
FVC	10(33.33%)	13(43.33%)	25(83.33%)	48(53.33%)
FEV ₁	9(30%)	10(33.33%)	24(80%)	43(47.78%)
FEV ₁ /FVC	0(0%)	0(0%)	0(0%)	0(0%)
PEFR	4(46.67%)	12(40%)	14(46.67%)	40(44.44%)
FEF ₂₅₋₇₅	0(0%)	0(0%)	0(0%)	0(0%)

Table-IV : Frequency distribution of Psoriatic patients by the type of pulmonary disorders in different study groups (n=90)

Groups	Large airway obstruction(LAO)	Small airway obstruction(LAO)	Restrictive disorder(RD)
B ₁ (n=30)	0 (0%)	0 (0%)	9 (30%)
B ₁ (n=30)	0 (0%)	0 (0%)	10 (33.33%)
B ₃ (n=30)	0 (0%)	0 (0%)	23 (76.67%)
Total=90(B ₁ +B ₁ +B ₃)	0 (0%)	0 (0%)	42(46.67%)

Relationships of different lung function variables with duration of therapy in different study groups:

The results are shown in Table-5. In this study, all the lung function variables were negatively correlated with the duration of therapy, in group B₁. On the contrary, in the group B₂ FVC and FEV₁ were negatively correlated but FEV₁/FVC%, PEFR, FEF₂₅₋₇₅%, FEF₂₅%, FEF₅₀% and FEF₇₅% were positively

correlated with the duration of therapy. Moreover, in group B₃, FVC, FEV₁, FEF₅₀% were negatively and FEV₁/FVC, PEFR, FEF₂₅₋₇₅%, FEF₂₅% and FEF₇₅% were positively correlated with the duration of therapy. However, most of these relationships (eg. FEV₁/FVC, PEFR, FEF₂₅₋₇₅%, FEF₂₅% and FEF₇₅%) were not statistically significant, but FVC, FEV₁, were statistically significant in group B₁ and B₃.

Table-V: Relationships of different lung function variables with the duration of therapy in different study groups (n=90)

Variables	Groups					
	B ₁		B ₂		B ₃	
	r value	p value	r value	p value	r value	p value
FVC	-0.541	0.002"	-0.320	0.085	-0.475	0.008"
FEV ₁	-0.517	0.003"	-0.261	0.164	-0.461	0.010"
FEV ₁ /FVC(%)	-0.161	0.395	0.113	0.554	0.023	0.905
PEFR	-0.247	0.189	0.001	0.997	0.069	0.716
FEF ₂₅₋₇₅ %	-0.158	0.405	0.045	0.812	0.218	0.247
FEF ₂₅ %	-0.377	0.040	0.001	0.998	0.027	0.887
FEF ₅₀ %	-0.218	0.248	0.250	0.183	-0.095	0.616
FEF ₇₅ %	-0.047	0.805	0.225	0.231	0.168	0.374

Discussion:

The present study has been undertaken to observe some aspects of Spirometric pulmonary function in diagnosed male psoriatic patients after Topical, PUVA, and Methotrexate therapy in order to evaluate their pulmonary function status. Therefore, pulmonary function were assessed by measuring FVC, FEV, FEV/FVC (%), PEFR, FEF_{25-75%}, FEF_{25%}, FEF_{50%} and FEF_{75%} with a spirometer. All these variables were also studied in apparently healthy age, BMI, socioeconomic status and occupation matched male subjects for comparison. In this study, values of lung function variables of healthy subjects were within normal limit and were almost similar to those reported by different investigators abroad. Again, both the groups (control and study) were comparable, as there was no significant difference in the confounding variables such as age, BMI, socioeconomic status and occupation, between two groups. In this study, 19(63.33%), 20(66.67%) and 29(96.67%) diagnosed Psoriatic patients after medication with only topical therapy, PUVA therapy and Methotrexate therapy respectively were with abnormal lung function test. On the other hand, none of the control subjects were with abnormal lung function tests. No similar observation was available for comparison. In this study, among the 90 Psoriatic patients after antipsoriatic only 42 (46.67%) were diagnosed with restrictive type of pulmonary disorder. However, among them 9(30%), 10(33.33%) and 23(76.67%) patients were treated by Topical therapy, PUVA therapy and Methotrexate therapy respectively. However, none of the patients of different study groups were diagnosed with any type of obstructive disorder, either small airway obstructive disorder or large airway obstructive disorder. In the present study, Pearson's correlation coefficient (r) test was performed to observe the relationships of all the lung function variables with duration of different drug therapy in patients with Psoriasis. In this study, all the lung function variables were negatively correlated with the duration of Topical therapy in Psoriatic patients. On the other hand, FVC and FEV₁ were negatively correlated but FEV₁/FVC %, PEFR, FEF_{25-75%}, FEF_{25%}, FEF_{50%}, and FEF_{75%} were positively correlated with the duration of PUVA therapy in Psoriatic patients and these relationship were not statistically significant (p>0.05). Moreover, FVC, FEV₁, FEF_{50%} were negatively but FEV₁/FVC %, PEFR, FEF_{25-75%}, FEF_{25%}, and FEF_{75%} were positively correlated with the

duration of Methotrexate therapy in Psoriatic patients and these relationship were not statistically significant. However, most of these relationships were not statistically significant (p>0.05) in the different study group. Only FVC and FEV₁, were statistically significant (p<0.01) in those Psoriatic patients taking Topical and

Methotrexate therapy. No research data was found to compare these relationships. The correlations of different lung function parameters with ESR level were analyzed by Pearson's correlation coefficient (r) tests in normal subjects (control) and also in rheumatoid arthritis female patients. In this study, in the patients of Rheumatoid Arthritis, all spirometric lung parameters like FVC, FEV₁, FEV₁/FVC, PEFR, FEF_{25-75%}, FEF_{25%}, FEF_{50%} and FEF_{75%} were negatively correlated with ESR level. These relationships were statistically significant but not in control group. These observations are in partially agree to those of Vergnenegre et al³⁴ Al-Assadi et al³⁵. They found significant negative correlation of FVC, FEV₁, FEV₁/FVC%, FEF_{25-75%} with ESR. However, in our country no published data are available to compare these findings. Patients with methotrexate induced lung toxicity usually demonstrate a restrictive pattern on pulmonary function tests with decreased carbon monoxide diffusing capacity and increased alveolar-arterial gradient with hypoxemia^{22,37,38}. Pulmonary fibrosis is characterized by fibroblast proliferation with minor signs of inflammation and extracellular matrix remodeling³⁹. Neutrophils are involved in pulmonary fibrosis and the increase in cytokines such as hepatocyte growth factor for type 2 alveolar cells by neutrophils can progress to the development of pulmonary fibrosis^{40,41}. The release of collagenase-2 and gelatinase B in neutrophils plays a key role in pulmonary fibrosis.

Conclusion:

From this cross sectional study it may be concluded that, the pulmonary Function Test among the Psoriatic Patients were with abnormal lung function tests in the experimental groups B₁, B₂ and B₃ respectively. However, most of these relationships (e.g. FEV₁/FVC, PEFR, FEF_{25-75%}, FEF_{25%} and FEF_{75%}) were not statistically significant, but FVC, FEV, were statistically significant in group B₁ and B₃.

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