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"MEASUREMENT OF ECO AS A BIOMARKER OF OXIDATIVE STRESS IN OBSTRUCTIVE PULMONARY DISEASE"

Medicine

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ABSTRACT

COPD is a disease of increasing public health importance around the world. COPD has become a major but neglected public health problem and is leading cause of death and disability worldwide with a growing population prevalence of 4-10% based on spirometry test. The aim of our study to measure the level of exhaled CO as a non-invasive biomarker in COPD.

The present study was conducted at department of TB & Respiratory Diseases, JN Medical College, AMU, Aligarh. The clinical severity of asthma and COPD was determined using the criteria defined in the GINA and GOLD guidelines. Spirometry was used to confirm the presence of airway obstruction.

In this study we found that on applying One Way ANNOVA difference in the mean eCO level was found to be significant ($p<0.05$).

It has been shown that exhaled CO levels increases during an asthma and COPD exacerbation. Therefore, measurement of exhaled CO may be a simple method of detecting and assessing airway inflammation in asthma and COPD.

KEYWORDS

COPD, Asthma, eCO, spirometry, Non-invasive biomarkers

Introduction:- Chronic Obstructive Pulmonary Diseases (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious gases.

COPD is a disease of increasing public health importance around the world. COPD has become a major but neglected public health problem and is leading cause of death and disability worldwide with a growing population prevalence of 4-10% based on spirometry test [1].

The World Bank estimates that COPD is responsible for >29 million disability adjusted life years and 1 million years of life lost per annum. In 2005 COPD was the 4th leading cause of death in the world, suppressing HIV. The World Bank and the WHO ranked COPD as the 12th leading cause of disease burden in the world as it is expected to rank 5th in 2020 [2].

Cigarette smoking is the notorious cause of COPD. It is associated with an abnormal inflammatory response of the lungs to noxious stimuli predominantly smoking. Hereditary deficiency of alpha-1-trypsin is one of the best documented generic risk factor [3]. Besides all these many inhalation exposure other than cigarette smoke including occupational dusts and exposure to biomass fuel in confined spaces are known to cause COPD in their own [4,5].

The forced expiratory spirogram is the most useful test of airflow dynamics. Yearly measurement for atleast 3 years is required to assess the rate of decline FEV1 (Forced expiratory volume in 1 second) and rates >50 ml/year suggest accelerate decline. Post-bronchodilator FEV1 is the mainstay of classification of severity of COPD and it is strongly predictive of subsequent mortality from COPD [6,7,8].

Oxidative stress is a major pathogenic component of COPD [9]. It increases in chronic healthy smokers. The measurement of exhaled CO may represent a new method for non-invasive monitoring of airway inflammation and oxidative stress in COPD patients. CO is produced in the body by heme oxygenase as a breakdown product of heme [9,10,11].

eCO has been proposed as a practical, non-invasive diagnostic tool for health professional to assess and monitor smoking status. eCO values increased in smokers with normal lung function relative to non-smokers.

The aim of our study to measure the utility of exhaled CO level in monitoring and treatment of COPD.

Material and Methods: - The present study was conducted at department of TB & Respiratory Diseases, JN Medical College, AMU, Aligarh.

This study was comprised of two phase. For first phase, 45 asthmatic and 45 COPD patients were enrolled respectively. All the patients who had a progressive symptom like cough, productive sputum, breathlessness and chest tighten. Only non-smoking individuals were recruited for first phase of this study. 80 healthy controls were selected without respiratory abnormalities and normal lung function. Control and asthmatic patients were non-smokers and they had no previous smoking history whereas COPD patients who had previous smoking history should have stopped smoking before 6 month.

For the second phase of this study 30 COPD patient, 30 asthmatic patient and 45 healthy controls were enrolled. They all having smoking habit. The clinical severity of asthma and COPD was determined using the criteria (appropriate clinical and respiratory function tests) defined in the GINA and GOLD guidelines. The diagnosis of asthma and COPD were established on the basis of reversibility of airways obstruction with greater than 12% and less than 12% improvement in FEV1 after inhalation of 200 µg of salbutamol from a nebulizer.

Spirometry was used to confirm the presence of airway obstruction. None of the patients were taking any antioxidant supplements and did not show any symptoms of upper and lower respiratory tract infection. Patients with systemic, vascular, renal and hepatic diseases were in exclusion criterion. None of the drug will be allowed on the day of testing.

Main items of observation to be recorded and arrangement for analysing dates. All the patients were subjected to record their demographic profile, clinical, radiological findings, pulmonary function measurement and smoking history. The informed consent were obtained in written form from all the recruited subjects

- Pulmonary function test will be performed by Easy on PC spirometer (ndd Medizintechnik AG, Zurich, Switzerland).
- Anthropometric measurement
- All anthropometric measurements will be taken according to

method described

- Exhaled CO and %COHb measurement

Exhaled CO and %COHb were measured on a portable piCO+ smokerlyzer (Breath CO monitor, Bedfont Scientific Ltd., Kent, England). In this procedure, participants are said to inhale deeply and hold their breath fully for 15 sec before exhaling into a disposable mouthpiece. The subjects exhaled slowly from total lung capacity with a constant flow. This procedure was repeated three times with 1 min of normal breathing between each repetition and the mean value was used for analysis. Exhaled CO level was measured by the analyzer and reported to correlate closely with blood COHb concentration.

Statistical analysis:- All statistical analyses were performed using SPSS Statistics (version-20). The study parameters will be compared among patients with different groups by using one-way ANOVA. The relationship between different study parameters and the degree of airways obstruction will be evaluated. $p<0.05$ will be considered statistically significant.

Results: - The present study was conducted at department of TB & Respiratory Diseases, JN Medical College, AMU, Aligarh. COPD patients were divided in to three groups: smokers, Ex-smokers and Non-smokers, while healthy subjects were divided in to smokers and non-smokers. The prevalence of COPD is more among males than females [table 1 & 2].

In this study we have studied level of CO in exhaled air of COPD patients. We have found a >3 fold increase in the level of exhaled CO in ex-smokers with COPD compared to healthy non-smokers. A similar relative increase in CO was observed in current smokers with COPD compared to healthy smokers matched for age and smoking habits.

In this study we found that on applying One Way ANNOVA difference in the mean eCO level was found to be significant ($p<0.05$). The mean exhaled CO level were decreased with improvement in disease after treatment ($p<0.05$) (table 3, 4 & 5). Most of COPD patients in our study were treated with steroids, our result shown that CO is sensitive to inhaled steroid treatment.

Discussion:- COPD is a preventable and treatable disease characterized by chronic airflow limitation that is not fully reversible. It is associated with an abnormal inflammatory response of the lungs to noxious stimuli, predominantly smoking (GOLD).

Exacerbation also occurs, where there is a rapid and sustained worsening of symptoms beyond normal day to day variations [12]. COPD is overwhelmingly dominated by smoking. Globally, the most important risk factor for COPD is thought to be smoking of tobacco [13 NHLBI/WHO 2001].

Environmental pollution, chemical exposure, inhaled smoke, passive smoking, exposure to biomass smoke, alpha-1-antitrypsin deficiency and other associated illness are consider as important risk factor for the development of COPD [14,15].

An inflammatory response in the airways and lung parenchyma are established feature of COPD and previous studies shown that all airways of COPD patients are persistently inflamed [16]. Once COPD is established, airway inflammation persists even after many years of smoking cessation [17].

Previous study shown that macrophages play a pivotal role in COPD as they are activated by cigarette smoke extract and secret many inflammatory proteins that may orchestrate the inflammatory process in COPD [18].

COPD is a disease of major importance in public health is diagnosed only after spirometric evaluation according to GOLD guidelines. The use of exhaled biomarker as a diagnostic tool for COPD was overviewed by van Beurden and his collaborators in 2002, and he suggested that there was a need for standardization of the measurement for comparison of COPD patient with healthy persons matched for age and smoking status for data on reproducibility and variability for correlation of exhaled markers with other parameters and for invention studies.

Biomarkers of airway inflammation in exhaled breathe might aid in the early diagnosis of COPD. Biomarkers could help identify different phenotypes of COPD patients who might respond differently to therapeutic interventions such as inhaled corticosteroids and long term oxygen therapy [19].

CO level in air has also been associated with emergency visits in people with COPD. Our findings suggest that increased arterial Hb-CO may relate to severity in patients with COPD because of lung and systemic inflammation and production of reactive oxygen species.

In non-smoking COPD patients there is elevation of exhaled CO level and also during exacerbation but decrease during recovery [20, 21].

With respect to exhaled breathe analysis, COPD patients had higher measured eCO value than non-smokers without COPD.

The need to monitor inflammation in the lungs has led to the exploration of exhaled gases and condensates. Non-invasive monitoring may assist in differential diagnosis of pulmonary diseases, assessment of disease severity and response to treatment, because these treatments are completely non-invasive. Breathe analysis is currently a research procedure but there is increasing evidence that it may have an important place in the diagnosis and management of lung disease in the future [22].

Conclusions:- In our study we found that quantification of eCO along with spirometry could be a better choice than spirometry alone in the diagnosing and management of COPD cases.

eCO level may be a reliable test of smoking status or pulmonary inflammation independently of each other, the predictive value of this test may be compromised in situations involving combinations of smoking, pulmonary disease or high environmental background.

Further clinical studies may refine clinical applications for eCO as a biomarker of disease severity in COPD.

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TABLE-1 DEMOGRAPHIC CHARACTERISTIC OF COPD GROUP

VARIABLES		SMOKER 33 (22%)	NON-SMOKER 35 (23.3%)	EX-SMOKER 82 (54.7%)
AGE	MALE	48.81 8.03	48.39.65	58.1910.07
	FEMALE	50.00	52.838.77	53.2510.91
	TOTAL	**48.857.91**	**51.469.14**	**57.9510.09**
SEX	MALE 122 (81.3%)	32 (26.2%)	12 (9.8%)	78 (63.93%)
	FEMALE 28 (18.7%)	1 (3.6%)	23 (82.14%)	4 (14.28%)
LOCALITY	RURAL 84	17 (16 male, 1 female)	20 (7 male, 13 female)	47 (44 male, 3 female)
	URBAN 66	16 (male)	15 (5 male, 10 female)	35 (34 male, 1 female)
SOCIOECONOMIC CONDITION	POOR 89 (59.3%)	20	18	51
	FAIR 36 (24.0%)	8	13	15
	GOOD 25 (16.7%)	5	4	16
PACK YEAR	RURAL	24.0612.00	-	22.0610.74
	URBAN	30.008.14	-	28.9713.02
TOTAL		**26.9410.30**	**-**	**25.0112.19**

TABLE-2 DEMOGRAPHIC CHARACTERISTIC OF CONTROL GROUP

VARIABLES		SMOKER	NON-SMOKER
AGE	MALE	49.758.86	54.71
	FEMALE	56.008.73	48.896.98
TOTAL		**50.648.73**	**52.829.39**

SEX	MALE 92 (73.6%)	36 (39.1%)	56 (60.9%)
	FEMALE 33 (26.4%)	6 (18.2%)	27 (81.8%)
LOCALITY	RURAL 73 (58.4%)	22 (16 male, 6 female)	51 (37 male, 14 female)
	URBAN 52 (41.6%)	20 (male)	32 (19male, 13 female)
SOCIOECONOMIC CONDITION	POOR 75 (60%)	26	49
	FAIR 29 (23.2%)	9	20
	GOOD 21 (16.8%)	7	14
PACK YEAR	RURAL	20.6411.65	-
	URBAN	1910.38	-
TOTAL		**20.1710.94**	**-**

TABLE-3 COMPARISON OF eCO AND FEV1 IN DIFFERENT GROUPS OF COPD

GROUPS	Eco	FEV1
NON-SMOKER COPD	2.940.87	43.9112.66
SMOKER COPD	12.554.51	35.0914.19
EX-SMOKER COPD	5.211.55	38.0114.48

TABLE-4 (a) COMPARISON OF eCO AND FEV_1 IN DIFFERENT GROUPS OF COPD

eCO	TEST GROUP	N	MEAN	STD. DEVIATION	STD. ERROR MEAN
	NON-SMOKER COPD	35	2.94	.873	.147
	HEALTHY NON-SMOKER	83	1.52	.571	.063

TABLE-4 (b) COMPARISON OF eCO AND FEV_1 IN DIFFERENT GROUPS OF COPD

eCO	TEST GROUP	N	MEAN	STD. DEVIATION	STD. ERROR MEAN
	EX-SMOKER COPD	82	5.21	1.546	.171
	HEALTHY NON-SMOKER	83	1.52	.571	.063

TABLE-4 (c) COMPARISON OF eCO AND FEV_1 IN DIFFERENT GROUPS OF COPD

eCO	TEST GROUP	N	MEAN	STD. DEVIATION	STD. ERROR MEAN
	SMOKER COPD	33	12.55	4.514	.786
	HEALTHY SMOKER	42	9.71	5.649	.872

TABLE-4 (d) COMPARISON OF eCO AND FEV_1 IN DIFFERENT GROUPS OF COPD

eCO	TEST GROUP	N	MEAN	STD. DEVIATION	STD. ERROR MEAN
	SMOKER COPD	33	12.55	4.514	.786
	EX- SMOKER COPD	82	5.21	1.546	.171

TABLE-5 COMPARISON OF eCO LEVEL IN DIFFERENT GROUPS OF COPD WITH CONTROL

eCO	TEST GROUP	N	MEAN	STD. DEVIATION	STD. ERROR MEAN
	COPD	150	6.29	4.218	.344
	CONTROL	125	4.27	5.087	.455

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