Association Between Forced Expiratory Volume in one Second and Glycated Hemoglobin Values in Patients With Chronic Obstructive Pulmonary Disease

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Received: 04 Mar. 2019; Accepted: 12 Sep. 2019

Abstract- Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of mortality worldwide. Evidence shows that COPD increases the risk of type 2 diabetes possibly due to insulin resistance induced by inflammatory cytokines. The aim of the current study was to evaluate the association between forced expiratory volume in one second (FEV1) and plasma glycated hemoglobin (HbA1c) level in patients with COPD. In this study, 50 non-hospitalized patients with COPD were studied. For all patients, a spirometry test was performed and FEV1 was determined. The quality of spirometry was assessed based on Guidelines from the American Thoracic Society/European Respiratory Society Task Force and the severity of COPD was determined based on GOLD criteria. HbA1c was measured by commercial kits. Anthropometric indices were measured and a questionnaire was applied to collect general characteristics of patients. The mean age of patients was 60.18±7.63 years. Seventy-eight percent and 22% of patients were male and female, respectively. Twenty-seven subjects were current smokers and 23 subjects were non-smokers. A significant inverses association was found between HbA1c level and FEV1% in (r= -0.722, P<0.001). There was a statistically significant correlation between weight and HbA1c level (r=0.349, P<0.05), and BMI and HbA1c (r=0.242, P<0.05). We could not find any significant correlation between age and smoking and the level of HbA1c and FEV1 (P>0.05). Our study showed there is a negative correlation between the level of HgA1c and respiratory function in COPD patients.

Acta Med Iran 2019;57(9):554-559.

Keywords: Chronic obstructive pulmonary disease (COPD); Respiratory function; Forced expiratory volume in one second (FEV1); Glycated hemoglobin (HbA1c); Diabetes

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent respiratory disease worldwide and is considered one of the major causes of death globally (1). The primary risk factor for COPD is tobacco smoking. Other risk factors are air pollution, exposures to dust at the workplace, chemical substances, fumes, genetic factors, aging, female sex, poor lung growth and development, severe infection during childhood, and asthma (2).

Assessment of COPD is recommended in any patient with a history of dyspnea, prolonged cough and sputum, and exposure to known risk factors of this respiratory disease, mainly cigarette smoking. Clinically, COPD is diagnosed based on persistent airflow obstruction, confirmed by post-bronchodilator spirometry (3). A post-bronchodilator ratio of Forced expiratory volume in one second to forced vital capacity (FEV1/FVC) of <0.7 is considered as the traditional definition of chronic airflow limitation. Further, the value of FEV1 as a percent of the predicted value is applied to categorize the severity of airflow limitation (4).

COPD, as a systemic inflammatory disease, is related to several comorbidities, including diabetes (5). Research has shown a higher occurrence of diabetes among patients with COPD compared to the general population (6). It has been suggested that insulin resistance induced by some cytokines such as interleukin-6 and tumor necrosis factor-alpha soluble receptor, support the connection between COPD and increased risk of diabetes (5). In addition, pulmonary function declines in diabetic patients and prediabetic subjects compared to people with a normal level of fasting blood glucose (7,8). The biochemical changes in the structures of the lung resulted from inflammation,

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oxidative stress, hypoxemia, and chronic hyperglycemia are possible underlying mechanisms (6).

According to current data, there is an association between glycemic status and lower adjusted mean residual FEV1 (6). Plasma glycated hemoglobin (HbA1c) concentrate, as a minor component of hemoglobin, indicates the mean level of blood glucose during a period of 2 to 3 months. Its normal value varies between 5 and 7, while the level of this component increases in uncontrolled glycemia (9,10).

Based on our knowledge, there is limited data on the association between HgA1c concentrations and FEV1 in non-diabetic patients. Therefore, the aim of our study was to evaluate the association between HbA1c level and FEV1 in non-hospitalized patients who suffered from COPD without a history of overt diabetes.

Materials and Methods

Study design

In this cross-sectional study, patients were selected from those who referred to the Hormoz Clinic of Shahid Mohammadi Hospital, Bandar Abbas, Iran. At the time of our study, there was no study reporting correlation between HbA1c and EFV1 in non-diabetic patients with COPD. So, to calculate the correlation coefficient between HbA1c and EFV1, we conduct a pilot study on 15 patients. Then, using the suggested formula for sample size calculating for correlation studies and considering the correlation coefficient between HbA1c and EFV1 equal to 0.6 (based on our pilot study), 36 patients were calculated. We selected 50 patients according to inclusion and exclusion criteria, and we did not include the patients attended the pilot study. Inclusion criteria were as follows: non-hospitalized male and female patients with COPD, over the age of 18, whose diseases had been diagnosed by a pulmonologist, according to clinical findings, chest radiography, arterial blood gases analysis, and spirometry, as well as their tendency to attend the study. Whereas the exclusion criteria were: those with oral corticosteroid therapy, history of overt diabetes, treated with insulin and oral antihyperglycemic agents, Cushing's syndrome, pheochromocytoma, acromegaly, glucagonoma, chronic kidney disease, heart failure, splenectomy, and anemia. Data on the medical condition of participants were collected by patients self-reporting. Among 173 patients, 50 patients met the research criteria and were recruited into the study. At the first step, goals, methods, and procedures of the research were explained and all participants signed an informed consent form. The study protocol was approved by the medical ethics committee of Hormozgan University of Medical Sciences, Bandar Abbas, Iran with certificate No: HUMS.REC.1396.95.

Data collection

For all participants, the spirometry test was performed by a trained and experienced operator using MIR Spirolab III diagnostic spirometer, and FEV1 was determined. At the beginning of each session, the equipment was calibrated and the instruction was explained to each participant. Subjects were instructed to sit upright, put their feet flat on the floor with legs uncrossed and lose tight-fitting clothing. They were then asked took a deep full inspiration, followed by a full expiration as hard, as fast and as long as possible. Three consecutive maneuvers were done and the best effort of each patient was selected. Quality of spirometry was assessed based on Guidelines from the American Thoracic Society (ATS)/ European Respiratory Society (ERS) Task Force (11). The peripheral blood sample was collected and HbA1c value was measured using the Pishtazteb kit. A general information questionnaire was used to collect data on demographic features, smoking habits, and medical conditions. Anthropometric indices including height (without shoes with the precision of 0.5 cm), weight (with light clothes and with the precision of 100 g using Seca scale), BMI (by dividing the weight (kg) by the height squared (m^2) were measured.

Statistical analysis

SPSS software (IBM SPSS Statistics 25) was used to perform statistical analysis. The normality of data distribution was assessed using the Shapiro-Wilks test. Descriptive statistics were used to describe the mean, standard deviation, frequency, and percentage of variables. Independent T-test (for data with normal distribution) and Manne-Whitney test (for non-Normally distributed data) were used to compare the mean of HbA1c and FEV1 between two genders and between Smokers (ex- and current smokers) and non-smokers. In order to assay the correlation between variables, Spearman's correlation coefficient was conducted. $P<0.05$ considered statistically significant.

Results

Amongst the total number of participants, 78% (n=39) were men, and 22% (n=11) were women. Twnety-seven subjects were a current smoker and 23 subjects were a non-smoker. The mean age of attendees

was 60.18±7.63 years. Data on anthropometric measurements, smoking, HbA1c value, and pulmonary function are shown in table 1.

Table 1. Characteristics of participants

Variables	Mean±SD	Range
Age (y)	60.18±7.63	46-79
Weight (kg)	83.97± 15.20	56.22-124.96
Height (cm)	170.26±8.98	154-188
BMI	22.5±4.44	22.5-40
Smoking Duration (year)	14.4±14.03	0-40
HbA1c (%)	6.06±1.01	5-7.2
FEV1 (%)	64.98±14.28	30-88
FEV1/FVC	59.74±6.52	44-69

BMI: Body mass index

We use GOLD classification (FEV1/FVC<70%, and post-bronchodilator FEV1 predicted) to classify the severity of COPD (12). Based on the spirometric assessment of FEV1, mild, moderate, and severe COPD were detected in 18%, 62% and 20% of patients, respectively. Although at the study baseline subjects with overt diabetes were excluded, type 2 diabetes was diagnosed in 24% (n=12) of subjects based on the HbA1c concentration. 30% and 46% of attendees had normal and pre-diabetic values of HbA1c respectively (Table 2). Data on the distribution of COPD severity grade in each category of BMI has been shown in table 3. Thirty-six patients with moderate and severe COPD were in pre-obesity and obesity categories.

Table 2. Frequency of HbA1c and FEV1 by category

Variables		Frequency (n=50)	Percentage (100)
HbA1c values (%)	4-5.6	15	30
	5.7-6.4	23	46
	≥6.5	12	24
FEV1 predicted values (%)	81-100	9	18
	50-80	31	62
	30-49	10	20

Table 3. Distribution of COPD severity grade in BMI categories

Variable		COPD severity grade*		
		mild	**moderate**	**severe**
Categories of BMI	**Normal weight (n=10) 18.5≤BMI<25**	4	5	1
	Overweight (n=21) 25≤ BMI<30	3	13	5
	Obesity (n=19) BMI≥30	1	13	5

*Based on GOLD classification (FEV1/FVC<70%, and post-bronchodilator FEV1 predicted)

We found a significant inverse correlation between HbA1c level and FEV1% in current study (r= -0.722, *P*<0.001), and in both genders (r= -0.689, *P*<0.001 for men, and r= -0.943, *P*<0.001 for women). We also assessed the correlation between age, sex, anthropometric measurements, and smoking with HbA1c level and FEV1 (Table 4, 5).

Table 4. The correlation between relevant variable, and FEV1 and HbA1c

Variables	FEV1		HbA1c	
	r*	***P***	**r***	***P***
Age (y)	-0.112	0.479	0.102	0.439
Height (cm)	-0.165	0.253	0.270	0.058
Weight (kg)	-0.206	0.15	0.349	0.013
BMI	-0.144	0.32	0.242	0.019
Smoking duration (year)	-0.231	0.107	0.145	0.316

* Spearman's Correlation Coefficient
** $P < 0.05$ is statistically significant
BMI: Body mass index

Table 5. The association between sex and cigarette smoking, and FEV1 and HbA1c*

Variables		HbA1c		FEV1	
		Mean±SD	**P	Mean±SD	**P
Sex	Male (n=39)	6.15±1.06	0.342	64.13±14.57	0.433
	Female (n=11)	5.76±0.85		68±13.42	
Cigarette smoking	Yes (n=27)	6.14±0.97	0.166	63±15.48	0.293
	No (n=23)	5.98±1.09		67.3±12.68	

* Analyzed by Mann-Whitney Test
** $P < 0.05$ is statistically significant

There was a statistically significant correlation between weight and HbA1c level (r=0.349, $P<0.05$), and BMI, and HbA1c (r=0.242, $P<0.05$). We could not find any significant correlation between other variables and the level of HbA1c and FEV1.

Discussion

The aim of our study was to assess the connection between HbA1c and FEV1 in non-hospitalized patients with COPD. Our findings showed a significant correlation between HbA1c and FEV1 in patients in both sexes so that the lower level of FEV1 was correlated with a higher level of HbA1c. Many studies have confirmed the connection between COPD and diabetes (6). In the present study, the HbA1c values of 54% of patients were in pre-diabetic and diabetic ranges, and the mean of FEV1 was lower in patients with HbA1c values in pre-diabetic and diabetic ranges compared to normal range, which demonstrate in patients with COPD rise in HbA1c might increase the risk of type 2 diabetes. Our finding was similar to the finding of Davis *et al*., which indicated a 1% increase in the mean of HbA1c was associated with a 4% decrease in FEV1 (13). Abd El-Azeem *et al.,* also found that pulmonary function tests were impaired in patients with diabetes in a restrictive pattern (14).

In addition, we saw a significant direct correlation between weight, BMI, and HbA1c, which shows the association between obesity and increased level of HbA1c. According to the study of Verberne *et al*., (15), obesity is one of the main reasons for the high prevalence of type 2 diabetes in patients affected by COPD. Some researchers have reported that the prevalence of overweight and obesity among the COPD population is more than 60% (15). Obesity is related to a decrease in FEV1, FVC, and total lung capacity, functional residual capacity and expiratory reserve volume. It has been suggested that the mechanical pressure of fat on the diaphragm and the chest wall is one of the main causes of impaired respiratory function in obese people (16). In our study, although the frequency of overweight and obesity was higher among patients with moderate and severe COPD (Table 5), we could not find any association between weight, BMI and COPD. Our results were similar to the findings of Benslimane *et al.,* (17) who did not observe an association between BMI and COPD. In another study by Eriksson *et al*., (18) also overweight and obesity were not related to COPD and the COPD severity grades. We did not measure waist circumference in the current study. Central obesity might be a better marker of obesity (17). Helala *et al*., (19) found a highly significant negative association between central obesity and COPD, in which every 1-cm rise in waist circumference was related to a 20 ml decrease in forced vital capacity amongst patients with waist circumference higher than 102 cm.

Smoking is known as the main causative factor for COPD, and smoking cessation is considered as the best approach for its treatment (20). Research also confirmed the correlation between smoking and raised levels of HgA1c. Surprisingly, we could not find an association between smoking and duration of smoking, with FEV1 and HgA1c concentration. Liu *et al*., (21) assessed 4,135 adults aged 45 or more with a history of smoking, and they reported that respiratory symptoms and prevalence of COPD increased with prolonged smoking duration in males and females. Furthermore, in another study by Løkke *et al.,* (22) development of COPD was assessed over a period of 25 years among 8045 subjects of the general population. They found out that the absolute risk of developing COPD among continuous smokers is larger than the estimated risk in previous studies. With regard to the relationship between smoking habits and HgA1c level, the study of Hong JW and *et al.,* (23) on 10, 241 Korean non-diabetic adults indicated a significant correlation between current smoking and higher HbA1c values in a cigarette exposure-dependent pattern. However, similar to our result, a study on 102 types 2 diabetic patients revealed that smoking did not exert a significant direct effect on HbA1c level (24). An

overview of research shows that most studies which found a positive correlation between smoking, and COPD and HgA1c level are population-based studies conducted on a large number of people. Therefore, the small sample size is possibly the main reason for finding no relationship between smoking and FEV1 and HgA1c in our study.

Besides the small sample size, patients self-reporting about their medical condition is another limitation of current research, which can reduce the accuracy of collected data. Furthermore, this type of study cannot provide a cause-effect association.

In conclusion, we revealed a direct connection between levels of FEV1 and HgA1c. Maintaining the HgA1c level at the normal ranges might be effective development of pulmonary dysfunction in COPD patients, although more studies with larger sample sizes are necessary to reach strong evidence.

Acknowledgments

We would like to thank the staff of Hormoz Clinic, Shahid Mohammadi Hospital, Bandar Abbas, Iran. This study was financially supported by Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

References

1. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health 2015;5:020415.
2. Disease GIfCOL. Pocket Guide to COPD Diagnosis Management and Prevention, 2016.
3. Lange P, Halpin DM, O'Donnell DE, MacNee W. Diagnosis, assessment, and phenotyping of COPD: beyond FEV1. Int J Chron Obstruct Pulmon Dis 2016;11:3-12.
4. Burkhardt R, Pankow W. The diagnosis of chronic obstructive pulmonary disease. Dtsch Arztebl Int 2014;111:834-46 .
5. Baba S, Takashima T, Hirota M, Kawashima M, Horikawa E. Relationship between pulmonary function and elevated glycated hemoglobin levels in health checkups: A cross-sectional observational study in Japanese participants. J Epidemiol 27:511-5 .
6. Rogliani P, Lucà G, Lauro D. Chronic obstructive pulmonary disease and diabetes. COPD Res Clin Pract 2015;1:3 .
7. Van den Borst B, Gosker HR, Zeegers MP, Schols AMWJ. Pulmonary Function in Diabetes: A Metaanalysis. Chest 2010;138:393-406.
8. Yamane T, Yokoyama A, Kitahara Y, Miyamoto S, Haruta Y, Hattori N, et al. Cross-sectional and prospective study of the association between lung function and prediabetes. BMJ Open. 2013;3. e002179.
9. Akram F, Asharaf E, Masood H, Ali M. Association of Pulmonary Functions and HbA1c in Diabetics. P J M H S. 2013;7-307-9.
10. Li C-I, Li T-C, Liu C-S, Lin W-Y, Chen C-C, Yang S-Y, et al. Extreme values of hemoglobin a1c are associated with increased risks of chronic obstructive pulmonary disease in patients with type 2 diabetes: a competing risk analysis in national cohort of Taiwan diabetes study. Medicine 2015;94:e367 .
11. Pellegrino R, Viegi G, Brusasco V, Crapo R, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.
12. Rennard SI. Treatment for Stable COPD. In: Barnes PJ, Drazen JM, Rennard SI, Thomson NC, eds. Asthma and COPD. Second Ed. Oxford: Academic Press; 2009:823-36.
13. Davis WA, Knuiman M, Kendall P, Grange V, Davis TME. Glycemic Exposure Is Associated With Reduced Pulmonary Function in Type 2 Diabetes. Diabetes Care 2004;27:752-7.
14. I AAE-A, Hamdy G, Amin M, Rashad A. Pulmonary function changes in diabetic lung. Egypt J Chest Dis Tuberc 2013;62:513-7 .
15. Verberne LDM, Leemrijse CJ, Swinkels ICS, van Dijk CE, de Bakker DH, Nielen MMJ. Overweight in patients with chronic obstructive pulmonary disease needs more attention: a cross-sectional study in general practice. NPJ Prim Care Respir Med 2017;27:63 .
16. Poulain M, Doucet M, Major GC, Drapeau V, Sériès F, Boulet L-P, et al. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. CMAJ 2006;174:1293-9 .
17. Benslimane A, Najdi A, El Biaze M, Nejjari C, Garcia Larsen V, El Rhazi K. Association between COPD and obesity among adults in Morocco. Eur Respir J 2016;48.
18. Eriksson B, Backman H, Bossios A, Bjerg A, Hedman L, Lindberg A, et al. Only severe COPD is associated with being underweight: results from a population survey ERJ Open Res 2016;2:00051-2015
19. Helala L, Wagih K, Abl El Monem M. Study the relation between body mass index, waist circumference and spirometry in COPD patients. Egypt J Chest Dis Tuberc 2014;63:321-7.
20. Laniado-Laborín R. Smoking and Chronic Obstructive Pulmonary Disease (COPD). Parallel Epidemics of the 21(st) Century Int J Environ Res Public Health

2009;6:209-24 .

21. Liu Y, Pleasants RA, Croft JB, Wheaton AG, Heidari K, Malarcher AM, et al. Smoking duration, respiratory symptoms, and COPD in adults aged ≥45 years with a smoking history. Int J Chron Obstruct Pulmon Dis 2015;10:1409-16.
22. Løkke A, Lange P, Scharling H, Fabricius P, Vestbo J. Developing COPD: a 25 year follow up study of the general population. Thorax 2006;61:935-9.
23. Hong JW, Ku CR, Noh JH, Ko KS, Rhee BD, Kim D-J. Association between Self-Reported Smoking and Hemoglobin A1c in a Korean Population without Diabetes: The 2011–2012 Korean National Health and Nutrition Examination Survey. PLoS ONE 2015;10:e0126746.
24. McCulloch P, Lee S, Higgins R, McCall K, Schade DS. Effect of smoking on hemoglobin A1c and body mass index in patients with type 2 diabetes mellitus. J Investig Med 2002;50:284-7.