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Evaluating the Serum Homocysteine Level in the Patients with Chronic Obstructive Pulmonary Disease and its Correlation with Severity of the Disease

Alireza Moayyedkazemi[1*], Mohammad Hossein Rahimirad[2]

[1]Department of Internal Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran
[2]Department of Internal Medicine, Urmia University of Medical Sciences, Urmia, Iran

ABSTRACT

Background: The patients with chronic obstructive pulmonary disease (COPD) are exposed to increased atherothrombotic events. The recent studies have shown that serum homocysteine (tHcy) and COPD are both risk factors for heart disease, and few studies have been conducted on serum tHcy level in COPD patients. This study aims to measure the serum tHcy level in the COPD patients and compare them with control group.
Method: A case control study has been performed on 40 COPD patients and 51 controls. The tHcy, blood gases, and spirometry were evaluated in COPD patients, and tHcy were investigated in the healthy adults (control group).
Results: The COPD patients had a higher serum tHcy level than the control group (19.51 mmol/L compared to 18.21 mmol/L), but the difference is not significant (p=0.5).
Conclusion: Although there was no significant correlation between tHcy and COPD; however further and larger studies are required for evaluating hyperhomocysteinemia in COPD patients.

Key words: Pulmonary disease, Homocysteine, Iran.

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Corresponding author: Alireza Moayyedkazemi
e-mail✉: amr.kazemi@gmail.com
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a disease caused by air flow restriction that is not completely reversible, and there will be a COPD only when chronic airway obstruction occurs. The sustainable reduction in the expiratory pressure flow is the most prominent feature in COPD. The inflammation plays a major role in the pathogenesis of COPD. It is strange that, in the final stages of the disease, long after the cessation of smoking, the inflammation induced by cigarette smoke in early stages of disease will persist [1]. A dose-response relationship between reduced pulmonary function and intensity of smoking explains an increase in COPD as the age increases, and the causal relationship between smoking and COPD is completely approved [2]. It is known that the indoor exposure to biomass smoke such as wood, fertilizer, remaining product, and charcoal, causes acute respiratory infections in children and COPD and lung cancer in women, and is responsible for 2.7% of the disability-adjusted life years (DALYS) worldwide [3]. Above half of the world's population uses the biomass for cooking, heating, or baking bread, and the epidemiological studies have proven the relationship between biomass smoke, chronic bronchitis, and COPD [3]. According to the World Health Organization (WHO), COPD is a common disease that will be known as the fifth common disease and the third leading cause of death worldwide by 2020. This is due to the decreased mortality caused by cardiovascular diseases in developed countries and reduced infectious causes in developing countries, and also a clear increase in smoking and environmental pollution in developing countries [1].

Homocysteine (Hcy) is produced in the liver as a metabolic intermediate during methionine-to-cysteine metabolism. The increase in tHcy through auto-oxidation generates reactive oxygen species (Ros). Folate and Vit B12 are effective in reducing the [2,3]. Ros is a risk factor for ischemic heart diseases [4,5], and increase in plasma they leads to an increased mortality rate of cardiovascular diseases [6]. Plasma tHcy concentration is affected by age, sex, diabetes and renal failure [7-9], and smoking is also a major factor for increase in plasma tHcy [10]. Hyperhomocysteinemia is a known risk factor for atherothrombosis and thromboembolic events, and could be a risk factor for diseases such as congestive heart failure, dementia, and osteoporosis [11-15].

Most studies on the risk factors and causes of COPD such as Hcy were conducted in developed countries, and no study has been performed in Iran with different lifestyle and dietary habits such as the use of vitamins and antioxidants. It is assumed that tHcy is increased in patients with COPD, and there is a relationship between plasma they level with severity of COPD and quality of life in these patients. Perhaps, with the treatment of Hyperhomocysteine, the severity of the disease can be reduced and it can be controlled.

MATERIALS AND METHODS

Patients

In this study, the target population was considered as all patients with COPD who are diagnosed by diagnostic tests (Spirometry). The prospective data were collected from 40 COPD patients who were admitted to Pulmonary Ward, Imam Khomeini Hospital, Urmia, in 2013, and 51 asymptomatic individuals were selected as control group. COPD patients underwent spirometry tests, and the severity of disease was determined by the global initiative for chronic obstructive lung disease (GOLD).

Study design

The inclusion criteria for COPD patients were having symptoms or history of COPD with forced expiratory volume (FEV1)/forced vital capacity (FVC) below 70% after using bronchodilator. The diseases such as hemoptysis, pneumothorax, acute coronary disease, recent myocardial infarction (MI), pulmonary embolism, vascular aneurysm, recent surgery, acute infection, history of malignancy, or any inflammatory process other than COPD were the exclusion criteria for COPD patients. The inclusion criteria for the control group were being over 55 years old, not having the exclusion criteria of the COPD group and no history of COPD, shortness of breath, or coughing.

PROCEDURE

In this study, all individuals in the control and COPD groups were visited, all individuals were examined, history was taken, and the information was entered in a special form. In all the subjects, information such as age, sex, history of smoking, baking, medical history of the patient, as well as the vital signs were recorded. In the COPD group, the patient's tests, including complete blood count (CBC) and biochemistry, were examined, and in case of exclusion criteria, the patients were excluded. In the control group, patients were selected based on examination and history, and in case of a history of earlier diseases, they were excluded based on exclusion criteria. In both groups, the individuals underwent blood sampling, and the serum sample of the patients was centrifuged. For each individual, three samples were separated to measure homocysteine, and one sample was separated as a backup. The samples were stored at temperature of -20°C. Homocysteine was measured in 40 COPD patients and 51 control patients.

RESULTS

In this study, 91 subjects were investigated (40 COPD patients and 51 in control group). The COPD group consisted of 22 men (55%) and 18 women (45%). The healthy adults (control group) consisted of 29 men (56%) and 22 women (43%). Thus, COPD and control groups were matched in terms of sex, and there was no significant difference between them (Table 1). The mean age was 66.98 ± 10.3 years in the COPD group and 66.02 ± 8.7 years in the control group. Thus, the COPD and control groups were matched in terms of age.

Table 1: Demographic characteristics and studied variables among COPD patients' asymptomatic individuals (control group)

Variables	Control	COPD	P value
Age	66.02 ± 8.7	66.98 ± 3.1	0.63
Gender			
Male	29 (56.9%)	22 (55%)	
Female	22 (43.1%)	18 (45%)	
Smoking			
Now smoking	8 (15.7%)	23 (57.5%)	
Past smoking	4 (7.8%)	7 (17.5%)	
Baking	5 (9.8%)	14 (35%)	
Lung Function			
FEV1/L	-	1.15	
FVC/L	-	2.026	
FEV1/FVC	-	57.30%	
tHcy (mmol/L)	18.224	19.514	0.5

In the COPD group, 23 subjects (57.5%) noted cigarette smoking during the study, 7 subjects (17.5%) noted cigarette smoking in the past, and 14 subjects (35%) reported a history of baking. In the control group, 8 subjects (15.7%) noted cigarette smoking during the study, four subjects (7.8%) noted cigarette smoking in the past, and five subjects (9.8%) reported the history of baking. In the healthy adults, 34 patients (66.6%) had no history of smoking or baking.

In the COPD group, the average plasma serum tHcy level was 19.51 ± 9.5 mmol/L, and in the control group, the average serum tHcy level was 18.22 ± 9.5 mmol/L, there was no significant difference in the comparison of tHcy between groups using *t*-test (p=0.5).

The COPD group underwent spirometry and blood gas measurements, and the FEV1, FEV1%, FVC, and FEV1 / FVC parameters were measured. The severity of the disease was determined by the GOLD, where 12 subjects (30%) were GOLD II, 19 subjects (47.5%) were GOLD III, and 9 subjects (22.5%) were GOLD IV. There was no GOLD I among the subjects because patients were

hospitalized. The mean FEV1 was 1.5 L/s, and the mean FVC was 2.026 L, and the mean FEV1/FVC was 57.3%.

In order to investigate the effect of smoking and baking on serum tHcy, the control group was divided into two groups of never smoker control group (NSCG) with no history of smoking or baking in the past and present, and smoker control group (SCG) with a history of smoking or baking in the present or past. These two groups were compared with COPD GOLD IV patients. The mean serum tHcy was 17.34 µmol/L in the NSCG group, 9.95 mmol/l in the SCG group, and 22.21 mmol/l in the GOLD IV group and in the pair comparison of these groups using t-test, no significant relationship was obtained.

The correlation between age, FEV1 partial pressure of oxygen (PaO_2), and FEV1/FVC with serum tHcy was studied in patients with COPD, where the Pearson correlation coefficient between tHCy and the above variables was -0.052, -0.074, -0.253, and –0.136, respectively (P>0.4).

In this study, regarding smoking and its relationship with severity of COPD, 23 patients reported now smoking, where 9 subjects had moderate COPD, 12 subjects had severe COPD, and 2 subjects had very severe COPD (Table 2). In this category of individuals, there was a significant relationship between the severity of COPD and now smoking (P=0.042). Seven subjects reported past smoking. In this group, there is a significant relationship between severity of COPD and history of smoking (P<0.001). In COPD patients, 14 patients noted a history of baking. In this group, there was no significant relationship between the severity of COPD and history of baking (P=0.243). The correlation between tHcy in patients with COPD is r=0.035 and P=0.8, and the correlation between tHcy in the healthy adults is r=0.001 and P=0.8. The correlation between severity of COPD and tHcy is r=0.26 and P=0.1. Therefore, there is no correlation between the severity of COPD and tHcy.

Table 2: Smoking and its relationship with severity of COPD

Smoking status	COPD severity			Total	P value
	Moderate No. (%)	Severe No. (%)	Very severe No. (%)		
Now smoking	9 (39.1)	12 (52.2)	2 (8.7)	23	0.042
Past smoking	-	1(14.3)	6 (85.7)	7	<0.001
Baking	5 (35.7)	8 (57.2)	1 (7.1)	14	0.243

DISCUSSION

This study is one of the few studies that evaluate the serum tHcy level in patients with COPD. In this study, the serum tHey level was measured in patients with COPD and control group, and the correlation between PaO_2 and FEV1 and age is examined with the two above-mentioned blood factors. Since hyperhomocysteinemia (HHcy) is a risk factor for cardiovascular and thromboembolic diseases, evaluating Hcy level in COPD patients would determine the risk of cardiovascular diseases and help plan preventive measures. Recently, a meta-analysis showed that administration of folic acid effectively reduces the risk of the first stroke, and this effect is more significant when plasma tHcy is reduced by more than 20% [16-20]. In this study, the mean plasma tHcy in the control group, GOLD II, III COPD group, and patients with COPD GOLD IV, is 18.22, 18.78, 21.22 mmol/L respectively. Although, there is a difference between the three groups, the difference is not significant. However, in the study by Seemungal in India, 2007, the plasma tHcy level showed a significant difference between control and COPD groups [14]. It is important to note that the difference belonged to COPD GOLD IV and III patients, and plasma tHcy was lower in GOLD I,II patients compared to the control population.

According to the study by Kai et al. in Japan, the plasma tHcy level showed a significant difference between the control and COPD groups [15], but it is interesting to note that in this study, the plasma tHcy level is significantly increased in patients with mild COPD (near-normal-pulmonary function) compared to the control group, while in patients with GOLD IV, plasma tHcy is not increased compared to the control group, which is due to lower PaO_2 and higher hypoxemia in patients with GOLD IV, because the hypoxia leads to dysfunction of methionine adenosyl transferase enzyme (effective in tHcy).

The difference between this study and the studies of Seemungal et al. and Kai et al. [14,15] is probably because of: 1) the difference between folic acid and vitamin B12 levels in the studied populations, 2) above 70% of the plasma tHcy is albumin-bound, and the Alb level could be affected by different nutritional statuses [16,21] difference in constitutional predisposition of various populations [22].

In this study, there was a correlation coefficient of r=0.253 and P=0.1 between plasma FEV1 and tHcy in the COPD group. This finding was consistent with Fimognari et al. study [20] (P<0.1), but in contrast, in the studies by Seemungal et al. and Kai et al. [14,15], there was a negative correlation between FEV 1% and plasma tHcy in patients with COPD (P>0.05).

In this study, there is no correlation between age and plasma tHcy in patients with COPD (r=-0.52 and P=0.7), and this finding is consistent with the study of Seemungal et al. [14] (r=0.022 and P=0.105), but in the study by Fimognari et al. [20], in Italy there is a correlation between age and plasma tHcy in patients with COPD (r=0.3 and P=0.04). In this study, there is no correlation between plasma tHcy and PaO_2 (partial pressure of oxygen) in the patients with COPD (r=0.074 and P=0.069), which is consistent with the study by Saetta et al. [23] (P<0.01).

CONCLUSION

Although there was no significant correlation between tHcy and COPD; however further and larger studies are required for evaluating hyperhomocysteinemia in COPD patients. Moreover, evaluating the correlation between cigarettes smoking, and serum Hcy levels are required in patients with COPD.

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