Original Article

ISSN: 1735-0344 *Tanaffos 2020; 19(3):208-215*

TANAFFOS

Comparison of Serum Heart-Type Fatty Acid Binding Protein Levels in Stable Chronic Obstructive Pulmonary Disease and Healthy Subjects

Mohammad Reza Aslani [1], Hassan Ghobadi [2], Khadijeh Sarikhani [3], Saeid Hosseininia [2], Saeid Sadeghieh-Ahari [4]

[1] Lung Inflammatory Diseases Research Center, Department of Physiology, Ardabil University of Medical Sciences, Ardabil, Iran, [2] Department of Internal Medicine (Pulmonary Division), School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran, [3] Department of Internal Medicine, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran, [4] Department of Community Medicine, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.

Received: 16 June 2019
Accepted: 16 January 2020

Correspondence to: Ghobadi H
Address: Department of Internal Medicine (Pulmonary Division), School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran
Email address: h.ghobadi@arums.ac.ir

Background: The present study was done to compare serum heart type-fatty acid-binding protein (H-FABP) levels in patients with stable chronic obstructive pulmonary disease (COPD) and healthy subjects and address the correlation of this marker with airflow limitation and health-related quality of life using the COPD assessment test (CAT).

Materials and Methods: In this cross-sectional study, we measured serum H-FABP levels in 50 patients with stable COPD and 34 healthy controls and compared them in terms of smoking history, airflow limitation according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and CAT score. We also tested the association between serum H-FABP level and the COPD patients' clinical parameters. For statistical analysis, we used the Student's t-test, ANOVA, and Pearson's (or Spearman's rank -order) correlation test.

Results: Serum H-FABP level increased in the COPD patients compared with the control group (P<0.01). Although there was no association between serum H-FABP levels and disease severity based on the GOLD criteria, FABP levels increased in the subjects with a history of smoking in compared with the non-smoker control subjects (P< 0.01). In addition, there was a significant positive correlation between serum H-FABP level and smoking history (r = 0.367, P = 0.001).

Conclusion: The serum H-FABP level increased in both the stable COPD patients and healthy subjects with smoking history. However, no correlation was found between serum H-FABP and the severity of airflow limitation based on the GOLD criteria. Based on the results, it is unclear whether the H-FABP level is a causative factor in COPD patients or healthy smokers.

Key words: Chronic Obstructive Pulmonary Disease; Serum H-FABP; Cigarette Smoking

INTRODUCTION

The main characteristic of chronic obstructive pulmonary disease (COPD) is airflow limitation. The airflow limitation is irreversible and usually associated with progressive inflammatory responses in the lung induced by noxious particles and gases (1). In over 90% of COPD patients, cigarette smoking is a causative factor, indicating the impact of environmental factors in developing the disease (2). In COPD patients,

inflammatory responses to noxious stimuli are important pathogenesis of the disease, which makes it possible to apply a variety of immune cells and inflammatory factors (3). Chronic inflammation and airflow obstruction lead to decreased physical activity and poor health-related quality of life (HRQL) (4). Moreover, many COPD patients are affected by co-morbidities, such as cardiovascular disease, which has been shown to affect the quality of life and prognosis of the disease (5). In addition to COPD, smoking history is the most common risk factor for systemic inflammation and cardiovascular disease (6). Reportedly, smoking and cardiovascular disease are associated with systemic inflammatory disease, such as COPD.(5).

Various factors, including adipocytes, are involved in the development of systemic inflammation in COPD (7). In pulmonary inflammatory diseases, it has been reported that adipocytokines have a key role in airway inflammation (8, 9). Some studies have shown that various adipocytokines, such as leptin, adiponectin, and visfatin are candidate biomarkers for lung inflammatory diseases (7, 10, 11). Heart type-fatty acid-binding protein (H-FABP), as one of the adipocytokines, is a member of the FABP family (12). Fatty-acid binding proteins are relatively low molecular weight cytosolic proteins (12-15ka) that are found in tissues with a high metabolism of fatty acids, such as the heart (13). H-FABP is involved in the intracellular transport of insoluble fatty acids, as well as in providing energy for the heart for myocardial lipid homeostasis (14). In myocardial cell damage, it has been demonstrated that H-FABP rapidly appears in the circulation due to its small molecular size (14). Accordingly, it has been identified that H-FABP is a sensitive marker in myocardial damage, and in chronic heart failure, it is a very sensitive marker compared with troponin (15). More recently, an increased serum level of H-FABP has been reported in patients with COPD exacerbations (16). Accordingly, the aim of the current study was to investigate the serum H-FABP levels in stable COPD patients and healthy subjects, and also to evaluate the relationship between circulating H-FABP levels and smoking history, and airflow limitation according to the Global Initiative for chronic obstructive pulmonary disease (GOLD) criteria and health status using the COPD assessment test (CAT).

MATERIALS AND METHODS

Study Participants

In this cross-sectional study, 50 patients with stable COPD and 34 controls (17 individuals with a history of smoking and 17 individuals without a smoking history) were recruited from November 2016 to November 2017. The controls and patients with stable COPD were male subjects matched for age. COPD was diagnosed according to the American Thoracic Society (ATS) guidelines (5). Inclusion criteria for COPD patients were a ratio of the forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) of <70%. Controls and COPD patients with a history of hospitalization ≤1 month before the study, cardiac ischemia, heart failure, pulmonary disorders other than COPD, diabetes, surgery, chronic renal failure, infectious disease, an autoimmune disorder, and cancer were excluded from the study.

The patients with stable COPD were sequentially enrolled in a respiratory clinic. The control groups were volunteers recruited at the same hospital who visited other outpatient clinics and had normal spirometry without respiratory symptoms. A designed questionnaire was used for data collection, including demographic data, height, weight, and smoking habits. Pulmonary function testing was performed using a spirometer (Chest Inc., 801, Tokyo, Japan) according to the ATS guidelines under standard conditions. Three acceptable tests were performed for each patient and the highest obtained score was used for data analysis. Pulmonary function and biochemical tests were conducted on the same day.

The GOLD guidelines were used to categorize the severity of COPD as stage I (mild ; FEV1 ≥80% predicted);

stage II (moderate; 50% ≤ FEV1 < 80% predicted; stage III (severe ; 30% ≤ FEV1 < 50% predicted); and stage IV (very severe; FEV1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure) (5).

All patients were examined by a cardiologist for the exclusion of concurrent cardiac comorbidity. Then, all the patients completed the CAT questionnaire that is scored from 0–40 (17, 18). The total CAT score was calculated for each individual by summing the points for each CAT variable. The CAT scores were classified into four groups based on the level of COPD impact on health status, with low scores defined as <10, medium as 10–20, high as 21–30, and very high as 31–40.

The study was approved by the Ardabil University of Medical Sciences Ethics Committee, and all the study participants signed written consent forms (IR.ARUMS.REC.1395.125).

Biochemical Measurements

Peripheral blood samples (3-5 mL) were collected for measuring serum H-FABP in tubes containing EDTA. Serum H-FABP concentrations were measured using a commercial kit (EastBioPharm CO., LTD, CK-E11179, China), and an electrochemiluminescent method with an Elecsys 2010 automated analyzer (Roche Diagnostics) was used. The results are presented as ng/mL.

Statistical Analysis

The Kolmogorov Smirnov test to determine the normality of data was performed. The results are given as mean ± standard deviation (SD), or median and the 25th and 75th percentiles. Continuous variables were compared using the student's t-test. Comparison between the groups was made by the Kruskal-Wallis test, and if significant, it was followed by the Mann-Whitney U test for ***post hoc*** analysis, or analysis of variance (ANOVA) with Tukey–Kramer post hoc test. Correlation coefficients were assessed using the Pearson's (or Spearman rank order) correlation test. A P-value of < 0.05 was considered significant. All statistical analyses were performed using SPSS 16.

RESULTS

Baseline Characteristics of Study Population

The study population consisted of 84 men, including 34 control subjects (40.48%) and 50 patients with stable COPD (59.52%). Seventeen cases of the control subjects and all the patients in the COPD group had a history of smoking. The mean age of the participants in the study was 53.24± 5.69 years for the non-smoker control group, 55.53 ± 10.29 years for the smokers in the control group, and 57.30 ± 8.86 years for the COPD group, which showed no statistically significant difference among the group (p=0.241) (Table 1).

The serum H-FABP levels were significantly higher in the stable COPD group [3.58 (3.16-7.24) ng/mL] than in the non-smokers of the control group [3.12 (2.42-3.69) ng/mL, p<0.01] (Figure 1). In addition, the serum level of H-FABP was higher in the smoker of the control group [3.89 (3.21-6.41) ng/mL] in comparison with the non-smokers of the control group (p<0.01) (Figure 1). On the other hand, we found no statistically significant differences in serum levels of H-FABP between the smokers of the control group and the COPD group (p = 0.977) (Table 1).

The COPD severity based on the GOLD criteria is summarized in Table 2. There were statistically significant differences in the SpO_2 and CAT score (p< 0.001 for both) between the COPD and control groups based on the GOLD criteria. Also, there were no significant differences in age (p = 0.252), smoking history (P= 0.136), body mass index (p= 0.961), and H-FABP (p= 0.668) according to the stages of COPD.

The CAT score of the COPD patients based on the GOLD criteria was higher in cases with the stages III-IV (24.64±5.61) than in cases with the stages I-II (13.84±6.43, *P*< 0.001; Figure 2). On the other hand, there was no significant difference in serum H-FABP levels between the COPD and control (smoker and non-smoker) groups (P=0.681).

There was a positive correlation between H-FABP and the history of smoking (r=0.367 and p<0.01, Figure 3).

Table 1. Characteristics of the patients with stable COPD and control subjects

Parameters	COPD group (n=50)	Control group	
		Smoker (n=17)	Non-smoker (n=17)
Mean age (year)	57.30±8.86	55.53±10.29	53.24±5.69
Body mass index (kg/m²)	24.75±4.88	26.25±5.11	27.47±2.72
Pulmonary function test:			
FEV1 (% of predicted)	52.40±21.95***+++	90.05±9.88	90.64±9.25
FVC (% of predicted)	69.54±23.98**+	84.41±9.05	86.23±8.84
FEV1/FVC	58.86±9.35***+++	86.52±4.04	86.23±4.49
Serum H-FABP	3.58 (3.16-7.24)**	3.89 (3.21-6.41)**	3.12 (2.42-3.69)

Data are presented as mean±SD or median (25th–75th percentiles). FEV1: forced expiratory volume in 1 second, FVC: forced volume capacity, H-FABP: heart-type fatty acid binding protein; for statistical differences between the non-smoker healthy subjects with other groups: ** *P*< 0.01, *** *P*< 0.001. For statistical differences between the healthy smoker subjects with COPD group: + P<0.05, +++ P<0.001.

Table 2. COPD stage and baseline characteristics of the study population

Variables	Stage I	Stage II	Stage III	Stage IV	P value
Number	8	17	16	9	
Age	56.62±10.28	54.59±7.35	57.94±5.92	61.89±13.21	P= 0.252
Smoking (pack per year)	25.87±9.80	30.05±11.33	31.62±12.07	38.77±11.87	P= 0.136
FEV1 (% predicted)	85.37±5.92	62.47±12.36	42.06±5.79	22.44±5.29	P< 0.001
FVC (% predicted)	98.87±11.61	81.05±17.25	61.75±11.71	37.33±9.32	P< 0.001
FEV1/FVC (%)	66.75±3.05	62.35±7.64	56.81±9.73	48.88±5.03	P< 0.001
Spo_2 (%)	96(96-97)	96 (94-96)	94 (93-95)	85 (82-89)	P< 0.001
BMI	25.34±2.74	24.51±5.23	24.17±4.91	24.70±6.19	P= 0.961
H-FABP(ng/ml)	4.15 (3.24-7.83)	4.04 (3.19-8.85)	3.33 (3.10-5.05)	3.75 (3.35-3.79)	P= 0.668
CAT score	7.75±1.83	16.70±5.77	22±4.71	29.33±3.74	P< 0.001

Data are depicted as mean±SD or median (25th to 75th percentiles). FEV1: forced expiratory volume in 1 sec, FVC: forced volume capacity, Spo_2: O_2saturation, BMI: body mass index, H-FABP: heart-type fatty acid binding protein, CAT: COPD assessment test

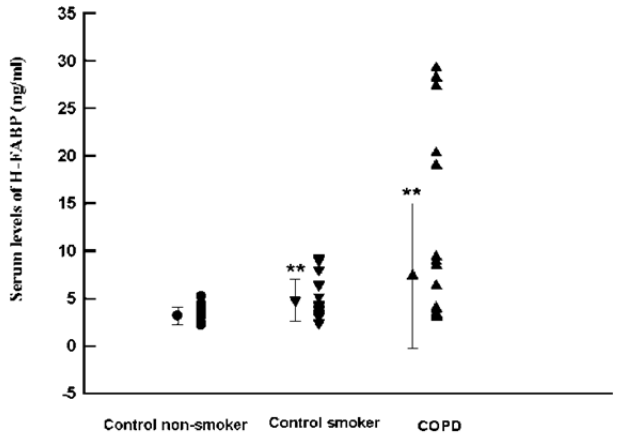

Figure 1. Individual values and mean±SD of serum H-FABP levels in the case and control groups. For statistical differences between the control non-smoker and other stages**: p<0.01; H-FABP, heart-type fatty acid binding protein.

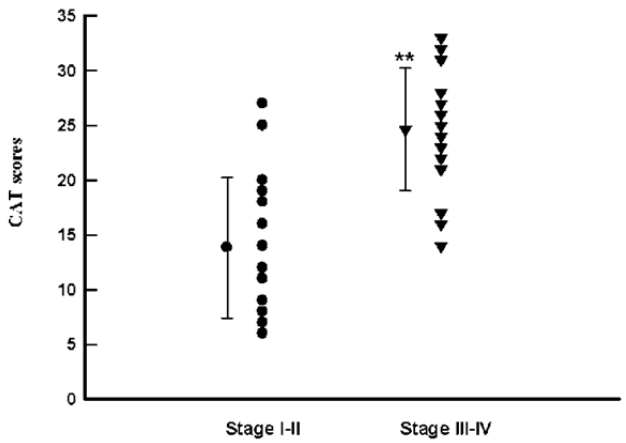

Figure 2. Individual values and mean±SD of the CAT score in the stage I-II and stage III-IV of COPD based on the GOLD criteria. Statistical differences **: p<0.01; CAT: COPD assessment test

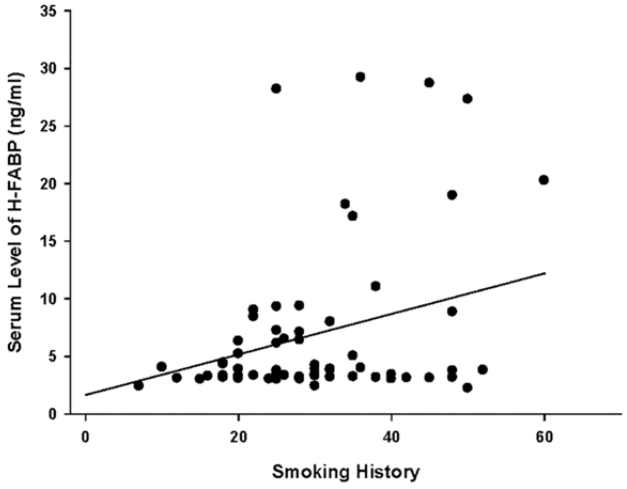

Figure 3. Spearman rank order correlation analysis of smoking history and H-FABP serum levels; Significant positive correlation between smoking history and H-FABP (correlation coefficient = 0.367, P=0.001); H-FABP=heart-type fatty acid binding protein.

DISCUSSION

In the present study, serum H-FABP levels were significantly higher in both the patients with stable COPD and control subjects with smoking history compared with the non-smoker controls. There was a positive correlation between serum H-FABP levels and history of smoking. However, the results showed that there was no correlation between the H-FABP and severity of airflow limitation based on GOLD criteria. The main finding of this study was that cigarette smoking was an important determinant factor in increasing H-FABP levels.

The use of cardiovascular biomarkers as prognostic factors in patients with COPD has been suggested, which can be pointed to pro-B-type natriuretic peptide (19) and cardiac-specific troponins (20). On the other hand, some studies have shown that some cardiovascular biomarkers, such as the cardiac troponin I and T, myoglobin (21), and pro-B-type natriuretic peptide have high sensitivity in detecting the right ventricular myocardial dysfunction (12). Reportedly, H-FABP is a very sensitive marker of minor myocardial damage compared with myoglobin or troponin T (21). H-FABP due to some features, such as small molecular size and tissue specificity (myocardial), is an excellent candidate for the marker of heart injury (22). Therefore, the increased H-FABP level represents myocardial injury. It can also be conceivable that in patients with COPD, an increase in H-FABP level is can reflect heart damage; however, its mechanism is not known. In the present study, in stable COPD, the serum levels of H-FABP were higher than in the controls without a smoking history. A study conducted by Sato et al. showed that the serum level of H-FABP was higher in cases with COPD exacerbation (16). The important point of our study results was that serum levels of H-FABP were not significant in patients with different stages of stable COPD based on the GOLD criteria. We assume that a limited number of participants in each GOLD group may have an effected our results.

Our results showed that serum H-FABP levels in those with a smoking history were significantly higher than in those without a smoking history. On the other hand, the patients with COPD in our study all had a history of smoking and an elevated serum level of H-FABP compared with the control subjects without a history of smoking. We also found a positive correlation between cigarette smoking and elevated serum H-FABP levels; however, a causal relationship between the two was not clear, and the complex contents of cigarette tobacco and its combustion products may play a role in this correlation.

Cigarette smoking can cause vascular lesions and endothelial dysfunction in COPD, which can cause vascular smooth muscle malfunction (23, 24). It is worth noting that in the current study, we excluded patients with a history of heart failure or ischemia; however, it seems that vascular remodeling slowly appears in patients with COPD, and cigarette smoking impacts vascular alternations. Tobacco products cause endothelial dysfunction, resulting in increased inflammatory cells or increased growth factors, such as VEGF (25). The lack of correlation between H-FABP and variables other than cigarette smoking, at least in part, can suggest that cigarette smoking in the COPD patients or healthy subjects had a key role in the occurrence of vascular remodeling in the early phase of the disease.

However, the role of other possible factors in increasing H-FABP, such as the role of systemic inflammation and minor thromboembolisms in small coronary vessels cannot be ruled out. It has been shown that there is an association between high serum levels of H-FABP and D-Dimer (a marker of fibrinolysis) in patients with severe COPD exacerbation (16). Therefore, arterial thrombosis in small coronary vessels may be involved in right ventricle dysfunction in COPD patients, which needs more studies. On the other hand, it is reported that elevated H-FABP may occur in inflammatory conditions, such as sepsis, coronary heart disease, heart failure, and non-alcoholic fatty liver disease (26). Since COPD and cigarette smoking are associated with chronic airway and systemic inflammation, an increase in H-FABP may be due to its inflammatory conditions.

In this study, we also examined the relationship between H-FABP levels and the quality of life in patients with COPD using the CAT score. The St. George's respiratory questionnaire (SGRQ) and CAT were validated respiratory questionnaires for the assessment of the quality of life in COPD patients and some studies showed a linear positive correlation between the two tests. However, the CAT is simple and easy to use in clinical practice (27). The CAT score is a reliable indicator of both exacerbation and recovery in COPD (28). We found that patients with severe and very severe COPD had high CAT scores, which is consistent with the findings of a previous study (4). Nevertheless, we did not find any association between serum levels of H-FABP and high CAT score. Perhaps the reason is that the level of H-FABP in the end stage of COPD and COPD exacerbations significantly increased, as previously illustrated (16).

The present study had some limitations. First, in studies on FABP, there is a sex difference, which its levels are higher in females with COPD than in their male counterparts (7). Our study was conducted only on male patients and the effect of sex differences in serum H-FABP level was not clear. The variation of biological markers in males and females may be due to age, circadian rhythm, and muscle mass (29). Second, we found that smoking can be a factor in increasing H-FABP levels in patients with COPD and healthy smokers; however, we did not include non-smokers in the COPD group. Finally, we assume that a limited number of participants in the COPD group can affect the results. Thus, conducting a study using a larger sample size including both genders is recommended.

CONCLUSION

In conclusion, we found that serum levels of H-FABP were higher in subjects with stable COPD and healthy subjects with a smoking history. Based on our results, it is unclear whether H-FABP is a causative factor in COPD patients or healthy subjects with a smoking history.

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