The value of coronary artery calcium score in the early diagnosis of coronary artery disease in patients with stable chronic obstructive pulmonary disease

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Abstract

Objective: Our aim was to assess the value of coronary artery calcium score (CACS) in the early diagnosis of coronary artery disease in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II chronic obstructive pulmonary disease (COPD) patients and to identify high-risk patients.

Methods: Forty-two patients with GOLD stage II COPD and 31 healthy control subjects were enrolled in the study. This study was designed as a prospective observational cross-sectional study. Pearson's correlation coefficient was used for comparisons between groups. Criteria for stage II COPD diagnosis were forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) of <70% and 50%≤FEV_1<80%. Excluded from the study were individuals who had a previous diagnosis of coronary artery disease, GOLD stage I-III-IV COPD, or left ventricular systolic dysfunction.

Results: As compared with the control group, CACS values were significantly higher in the patient group (p=0.030 and 0.001, respectively). CACS was significantly higher in male patients with a positive family history, physical inactivity, long duration of disease, and low FEV_1 (0.027, 0.008; 0.001 and 0.001; 0.001, respectively). Logistical regression analysis of sex, age, diabetes mellitus, hypertension, cigarette smoking, family history, physical inactivity, and FEV_1 values showed that physical inactivity was independently correlated with high CACS [odds ratio (OR): 7; confidence interval (CI): 3–20; p=0.001].

Conclusion: The value of CACS is high in stage II COPD patients. Male stage II COPD patients with a disease duration of 10 years, physical inactivity, and/or a positive family history should be monitored for early stage coronary artery disease and coronary events, regardless of risk factors such as diabetes, hypertension, and hyperlipidemia. *(Anatol J Cardiol 2016; 16: 283-9)*

Keywords: chronic obstructive pulmonary disease, coronary artery calcium score, coronary artery disease

Introduction

Recent research has shown that inflammation in chronic obstructive pulmonary disease (COPD) is not limited to the lungs and respiratory passageways but also affects other organ systems (1, 2). Systemic effects mainly include impaired functional capacity, shortness of breath, lower quality of life, and higher mortality (3). Coronary artery calcification is pathognomonic for coronary artery disease and is part of the development of atherosclerosis (4-8). Several studies have reported a correlation between the coronary artery calcium score (CACS) and the degree of vascular stenosis. A strong correlation has also been found between segmental CACS analysis and conventional coronary angiography in terms of stenosis detection (9, 10).

Electrocardiogram (ECG)-gated computed tomography (CT) can conclusively detect coronary atherosclerosis based on coronary artery calcification. A CACS of >0 indicates atheromatous plaques with approximately 100% specificity, but it is not specific for obstructive coronary artery disease as the plaques can be localized in the intima. Patients with a CACS of >100 (or above the 75th percentile) are accepted as high-risk patients, whereas a CACS of >400 is considered to be equivalent to obstructive coronary artery disease (11-13).

According to the Multi-Ethnic Study of Atherosclerosis, the risk of cardiovascular disease increases by 26% when CACS doubles (14). In this meta-analysis of 6722 cases that included asymptomatic individuals and disregarded cardiovascular risk factors, the relative risk was found to be 10 in the group with a

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CACS of >400 and 2.1 in those with a CACS between 1 and 100 (15).

In our study, we aimed to determine whether CACS had predictive value in the early diagnosis of coronary artery disease in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II COPD patients and to identify those with higher risk based on risk factors.

Methods

Study population

In this prospective observational cross-sectional study. Thirty-one healthy individuals and 42 GOLD stage II COPD patients with no previous history of coronary artery disease who presented to the Uludağ University Medical Faculty and the outpatient clinic of the Cardiology and Chest Diseases Department of the İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center and Research Hospital between June 2011 and June 2013 were enrolled in this study. Criteria for stage II COPD diagnosis were included as forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) of <70% and between 50≤FEV_1<80% (of the expected value).

The subjects in the study and the control group complained of dyspnea on exertion and atypic chest pain. This may be related to COPD or coronary artery disease because both of two groups had strong comorbid conditions such as a family history of premature coronary artery disease, smoking history, hypertension, hyperlipidemia, and diabetes mellitus as well as physical inactivity and advanced age. Coronary calcium score adds modest prognostic information to the extent of coronary artery disease (16); therefore, we used this imaging method.

Individuals who had a previous diagnosis of coronary artery disease, GOLD stage I-III-IV COPD, or left ventricular systolic dysfunction (ejection fraction of <55%) were excluded from the study. The project of the study was approved by the Uludağ University Medical Faculty Ethical Committee. All patients signed the informed consent form. This study was designed as a prospective observational cross-sectional study.

Detailed history including both the patient and the control group included age, sex, history of diabetes mellitus, hypertension, smoking status, and a family history of coronary artery disease. Based on disease duration, patients were divided into three groups: ≤5 years, 6–9 years, and ≥10 years. To evaluate study subjects for obesity, both height and weight were measured and body mass index (BMI) was calculated.

Based on FEV_1 test results, patients were divided into the following three groups: 50%–59%, 60%–69%, and 70%–79%. Hemoglobin, urea, creatinine, serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels were tested upon admission.

Physical activity levels

Patients' physical activity levels were assessed with the help of the International Physical Activity Questionnaire (17). We obtained permission for using data collection forms from the relevant authority and the Ethical Committee. This survey contained seven questions regarding the amount of time respondents daily spend sitting, walking, and doing other moderate and vigorous activities. The total score comprises time spent walking, doing moderate and vigorous activities (minutes a day), and frequency (number of days a week). The sitting score (sedentary behavior level) is calculated separately. The measure for each activity is obtained by performing it for at least 10 minutes at a time. Minutes, days, and the metabolic equivalent of task (MET) are multiplied and the score is calculated as MET-minute/week. The walking score was calculated by multiplying the time spent walking (minutes) by 3.3 MET; a MET value of 4 was assigned to moderate activity and a MET value of 8 to vigorous activity. Physical inactivity was defined as <600 MET-minutes/week.

International physical activity questionnaire

1. In the past 7 days, how many days did you perform vigorous physical activities, for example, heavy lifting, digging, aerobics, or fast bicycle riding?

2. While performing vigorous physical activities in the past 7 days, how much time did you usually spend?

3. Did you perform moderate physical activities such as riding, light lifting, cycling at normal speed, dancing, bowling, or playing tennis in the last 7 days?

4. While performing moderate physical activities, how much time did you usually spend in one of those days?

5. In the past 7 days, how many days did you walk for at least 10 minutes?

6. How much time did you spend while you were walking in the last 7 days?

7. How much time did you spend while you were sitting in the last 7 days?

Multi-slice computed tomography

All patients underwent multi-slice CT with ECG monitoring using a 128-slice CT device (Aquilion 16; Toshiba Medical Systems Corporation, Japan). Patients with a heart rate over 75 bpm and no contraindications received 2-mg intravenous metoprolol succinate before the procedure. All patients were administered with sublingual nitroglycerin for coronary dilatation. From the carina to the cardiac apex, axial single breath-hold 128-slice CT images were acquired with 0.6-mm collimation and retrospective ECG gating.

Coronary artery calcium score

The calcium score of calcified plaques appearing on tomographic slices of the four main coronary arteries (left main coronary, left anterior descending, circumflex, and right coronary arteries) was calculated by multiplying the area of the calcification by its density. The total artery calcium score was calculated by summing up all of the individual calcium scores. Based on the total score, patients were divided into four groups (0; 1–100; 101–400; >400) and further into two groups (0, >0) (18).

Table 1. Demographic and basic clinical characteristics of patient and control groups

	Patient group (n=42)	Control group (n=31)	*P*
Age (years, mean±SD)	49.7±7.6	48.1±6.0	0.573
Woman (n, %)	22 (52)	17 (54)	1.000
Diabetes mellitus (n, %)	9 (21)	5 (16)	0.765
Hypertension (n, %)	26 (62)	18 (58)	0.811
BMI (kg/m^2, mean±SD)	27.02±7.0	28.01±4.1	0.055
Cigarette (n, %)	36 (85)	9 (29)	0.001
Family history (n, %)	10 (23)	7 (22)	1.000
Physical inactivity (n, %)	19 (45)	2 (6)	0.001

BMI-body mass index; SD-standard deviation
Student's t-test (age and BMI) and chi-square test (others)

Table 2. Serum cholesterol levels of patient and control groups

	Patient group	Control group	*P*
Total cholesterol (mg/dL, mean±SD)	203.7±32.6	203.4±34.8	0.182
LDL cholesterol (mg/dL, mean±SD)	131±27.4	130.5±34.0	0.361
HDL cholesterol (mg/dL, mean±SD)	46.0±11.3	43.9±9.9	0.884
Triglyceride (mg/dL, mean±SD)	144.3±68.9	145.6±66.4	0.253

HDL-high-density lipoprotein; LDL-low-density lipoprotein; SD-standard deviation
Student's t-test

Table 3. Coronary artery calcium score values of patient and control groups

Coronary artery calcium score	Patient group	Control group	*P*
0 (n, %)	25 (59.5)	28 (90)	0.030
0–99 (n, %)	13 (31)	3 (10)	
100–399 (n, %)	3 (7)	0	
>400 (n, %)	1 (2.5)	0	
Coronary artery calcium score			
0 (n, %)	25 (60)	29 (93)	0.001
>0 (n, %)	17 (40)	2 (6)	
Total (n)	42	31	

chi-square test

Statistical analysis

Statistical analysis was performed using the SPSS v11.5 software (SPSS Inc., Chicago, IL, USA). The normally distributed continuous variables were assessed using the Kolmogrov–Smirnov test. Student's t-test was used to compare the mean values between groups, while chi-square and Fisher's exact tests were used to compare ratios. Pearson's correlation coefficient was used for correlation comparisons between groups.

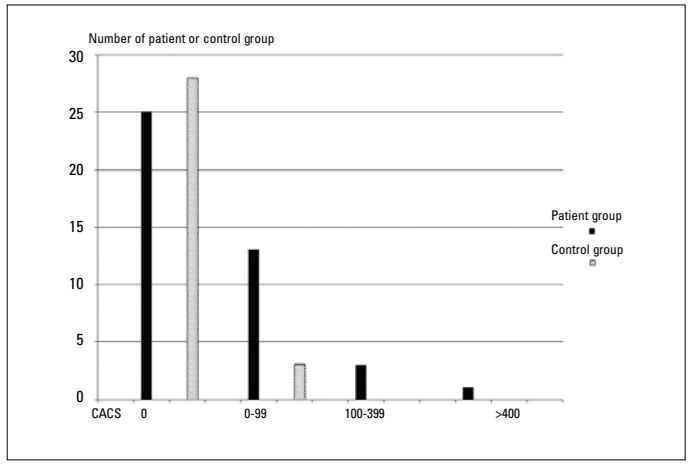

Figure 1. Image showing the number of patient and control groups according to coronary artery calcium score
CACS: Coronary artery calcium score

In addition, logistic regression analysis was performed to demonstrate the effectiveness of variable. A p value of <0.05 was considered statistically significant.

Results

The demographic and clinical features of patient and control groups are presented in Table 1. The number of patients who smoked was 36 (85%) and smoking control subjects was 19 (45%) as well as the number of physically inactive patients was 9 (29%) and physically inactive controls was 2 (6%) (p=0.001 vs. 0.001). The serum cholesterol levels of both groups are listed in Table 2, demonstrating no statistically significant differences (p=0.182, 0.361, 0.884, and 0.253, respectively). CACS was significantly higher in the patient group as compared control group (Table 3 and Fig. 1).

There was no difference in CACS between patients with body mass index, diabetes mellitus, hypertension, and smokers (p=0.233, 1.000, 0.757, and 1.000, respectively). In the patient group, CACS was correlated with the male sex, positive family history, physical inactivity, long duration of disease, and low FEV_1 value (p values 0.027, 0.008, 0.001 and 0.001, and 0.001, respectively) (Table 4).

A comparison of those with a CACS of 0 and CACS of >0 showed no significant difference in mean hemoglobin, urea, creatinine, total cholesterol, LDL, HDL, and triglyceride levels (Table 5). In the group with a CACS of 0, CACS had a positive correlation with age (p=0.02).

Logistical regression analysis of sex, age, diabetes mellitus, hypertension, cigarette smoking, family history, physical inactivity, and FEV_1 value showed that physical activity was independently correlated with high CACS (odds ratio (OR): 7; confidence interval (CI): 3–20; p=0.001) (Table 6).

Discussion

The main result of our research was identifying the factors correlated with the following: high CACS independent of diabetes, hypertension, and hyperlipidemia as well as low FEV_1; dis-

Table 4. Comparison of coronary calcium scores and risk factors in patients group.

		Coronary artery calcium score		
		0	>0	*P*
Sex (n)	Woman	8	12	0.027
	Man	17	5	
Body mass index (kg/m^2, n)	<25	7	4	0.233
	25–29	7	9	
	>30	11	4	
Diabetes mellitus (n)	Yes	5	4	1.000
	No	20	13	
Hypertension (n)	Yes	16	10	0.757
	No	9	7	
Cigarette (n)	Yes	21	15	1.000
	No	4	2	
Family history (n)	Yes	2	8	0.008
	No	23	9	
Physical inactivity (n)	Yes	4	15	0.001
	No	21	2	
Duration of disease (years, n)	<3	14	1	0.001
	3–9	11	11	
	>10	0	5	
FEV_1 (n %)	50–59	1	9	0.001
	60–69	1	1	
	70–79	23	7	

FEV_1-forced expiratory volume in 1 second. Chi-square test

Table 5. Comparison between coronary artery calcium score and cholesterol levels and biochemistry values

	Coronary artery calcium score		
	0 (n=25)	>0 (n=17)	*P*
Total cholesterol, mg/dL, mean±SD	198.1±29.42	211.9±36.26	0.182
LDL cholesterol, mg/dL, mean±SD	127.7±24.7	135.7±31.2	0.202
HDL cholesterol, mg/dL, mean±SD	46.2±10.1	45.7±13.3	0.884
Triglyceride, mg/dL, mean±SD	134.2±64.1	159.2±74.7	0.253
Hemoglobin, gr/dL, mean±SD	12.8±1.3	14.2±1.1	0.060
Urea, mg/dL, mean±SD	23.1±9.7	22.8±11.1	0.928
Creatinine, mg/dL, mean±SD	0.73±0.14	0.79±0.11	0.138

HDL - high-density lipoprotein; LDL - low-density lipoprotein. Student's t-test

ease duration of ≥10 years, physical inactivity, positive family history, and male sex. CACS appears to have an important predictive and diagnostic value. To the best of our knowledge, this is the first study to assess the value of CACS in stage II COPD patients.

Table 6. Logistic regression analysis of the risk factors affecting the CACS in patients with stage II COPD

Variable	*P*	OR (95% Confidence interval)
Gender	0.227	4.6 (0.4–57)
Age	0.455	1.0(0.9–1.2)
Diabetes mellitus	0.364	0.3 (0.1–4)
Hypertension	0.727	0.68 (0.1–9)
Cigarette smoking	0.159	0.4 (0.1–3.6)
Family history	0.080	12 (7–108)
Physical inactivity	0.001	7 (3–20)
FEV_1	0.180	2.8 (0.2–4)

FEV_1-forced expiratory volume in 1 second; OR - odds ratio. Logistic regression analysis

Physically inactive individuals are at a higher risk of coronary artery disease (upto 2–3 times) than physically active individuals and are strongly advised to undergo a change in lifestyle. Physical inactivity is common in COPD patients because of shortness of breath, aggravates systemic inflammation, and plays a role in peripheral insulin resistance in addition to causing endothelial dysfunction. As a result, COPD progresses rapidly, increasing the incidence of coronary artery disease. Troosters et al. (19) found that physical activity stopped the progression of COPD in stage II patients. In our study, the rate of physical inactivity in the patient group was 45% and was significantly higher in those with a CACS of >0. This suggests that physically inactive COPD patients would benefit from monitoring for coronary artery disease.

Longer duration of disease was found to be correlated with CACS, and all patients with a disease duration of >10 years had a CACS of >0. The longer the duration of COPD, the long-term effects of systemic inflammation begin to manifest more. These include impaired functional capacity and the related increased risk of obesity and diabetes, all of which accelerate the development of atherosclerosis leading to high CACS. In a study with 874 patients monitored over a 24-year follow-up period, cardiovascular mortality was higher in the group with the lowest FEV_1 values (20). On the other hand, several studies found low FEV_1 to be an important risk factor for cardiovascular mortality independent of factors such as age, sex, smoking status, hypertension, and total cholesterol. Similarly, those of our patients with the lowest FEV_1 values were found to have significantly higher CACS (20-23).

High cholesterol levels and low HDL are known to be independent risk factors for coronary artery disease (24, 25). We found no correlation between CACS and total cholesterol/LDL/triglyceride levels/low HDL. While most studies in the literature indicate a link between high CACS and LDL/high triglycerides/low HDL, a study by Orakzai et al. (26) reports none. The correlation between coronary calcification and family history as a risk factor for coronary artery disease has not been well researched. However, those with a positive family history are known to have upto 1.3–1.6 times as

high a risk of atherosclerosis (27). We also found a correlation between family history and CACS in the patient group.

Coronary artery disease is chronic; onset generally precedes cardiovascular events by several years. COPD and coronary artery disease are both associated with age and have smoking as a risk factor. Atherosclerosis-related coronary calcification and cytokine changes in COPD lead to an inflammatory process (28). Systemic inflammation is thought to accelerate the development and progress of coronary artery disease independent of risk factors. On the other hand, COPD patients have more cardiovascular risk factors as compared with other same-age groups (29). Those diagnosed and treated for COPD have a higher risk of hospitalization and death because of cardiovascular disease (30, 31). Calcium deposits in coronary arteries play a role in the development of atherosclerosis, and as such are absent in normal vessels (4-8).

Testing for CACS can be performed quickly and does not require a contrast agent. A CACS of >0 is 100% specific for atheromatous coronary plaques (11-13), while it is not specific for obstructive coronary disease. CACS also has a high predictive strength for cardiovascular death and myocardial infarction in asymptomatic patients. In a 2001 study, electron beam tomography showed coronary artery disease in 50% of the screened COPD patients (32). Similarly, 40% of our COPD patients had a CACS of >0, with CACS being significantly higher in the patient group than in the control group. According to a multi-center study, CACS testing is cost-effective in male patients even if they are asymptomatic (32). Age is a major risk factor for coronary artery disease and high CACS (33). Guidelines list the age of >45 years in men and >55 years in women as an important risk factor for atherosclerosis. We also found a positive correlation between age and CACS. COPD and coronary artery disease are more prevalent in the male population. Similar to our findings, all studies published by the PREDICT research network found a correlation between the male sex and CACS (34, 35). However, one study found no evidence of a link between sex and CACS (36). Although most studies demonstrate a link between obesity and CACS, we found no statistically significant correlation. In a study by Greenland et al. (36), there was no correlation between obesity and CACS in asymptomatic patients. By causing endothelial dysfunction, diabetes prepares the base for coronary artery disease. In fact, diabetes is now considered to be equivalent to coronary disease (37). COPD patients with systemic inflammation develop insulin resistance that increases the risk of diabetes mellitus by 1.5 even in the early stages of the disease. A study of 10,711 COPD patients from Spain reported a prevalence of diabetes at 16.9% (38). In our patient group, the rate of diabetes was 21%. The rate of hypertension in COPD patients was 40% in the Atherosclerosis Risk in Communities Study (2) and 62% in our study. A study by Lange et al. (39) reported a strong positive correlation between CACS and hypertension. We did not find CACS to be significantly correlated with diabetes mellitus or hypertension, possibly because of the short duration of hypertension.

Study limitations

The main limitations of this study are its cross-sectional nature, short follow-up period, small patient sample, and connection to two different departments of Cardiology and Chest Diseases. Other limitations include the lack of control indicators such as severity of diabetes, presence of chronic complications, HbA1C, severity of hypertension, and end-organ damage. Another limitation of this study is the exclusion of significant coronary artery disease via coronary angiography or stress tests. Also, frequency of smoking is significantly higher in the patient group that is a major risk factor for CAD and, therefore, there is high CACS in patients with COPD.

Conclusion

According to our findings, patients with stable stage II COPD have higher CACS than healthy control subjects. Particularly, male patients with a COPD duration of over 10 years, low FEV_1, physical inactivity, and/or positive family history (independent of hypertension and hyperlipidemia) may benefit from early screening for coronary artery disease as well as from prevention and treatment of possible coronary events.

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