METABOLIC SYNDROME AND CHRONIC DISEASES IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

KRONİK OBSTRÜKTİF AKCİĞER HASTALIĞINDA METABOLİK SENDROM VE KRONİK HASTALIKLAR

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ÖZET

Amaç: *Kronik obstrüktif akciğer hastalığı (KOAH), metabolik sendrom (MS) ve komorbidite arasındaki ilişki üzerine yapılan önceki çalışmalarda bulunan sonuçlar tartışmalıdır. Bu nedenle biz bu çalışmada, KOAH'lı hastalarda eşlik eden metabolik sendrom ve komorbiditeleri ayrı ayrı olacak şekilde inceledik.*

Yöntem: *Bu çalışma periyodu sırasında, 66 KOAH ve kontrol grubu olarak da 40 kişi dahil edildi. Solunum fonksiyon testleri (SFT) flow sensitif spirometri ile ATS kriterlerine göre yapıldı. BODE indeksleri hesaplandı. Kronik hastalıklar şiddet indeksi Modifiye kümülatif hastalıklar değerlendirme ölçeği (MKHDÖ) kullanılarak değerlendirildi. MS, National Cholesterol Education Program (NCEP)'a göre tanımlandı. Total metabolik bozukluk skoru da ayrıca hesaplandı.*

Bulgular: *MKHDÖ skoru KOAH'lı hastalarda kontrol grubundan anlamlı olarak yüksekti fakat total metabolik skor KOAH ve kontrol grubu arasında farklı değildi. MS KOAH'lı hastalarda 18 kişide (%27.3), kontrol grubunda 8 kişide (%20) görüldü. MS görülme oranı evre II KOAH'lı hastalarda evre IV KOAH'lı hastalardan daha yüksekti (p:0.04). Lineer regresyon analizinde, MKHDÖ skoru BODE indeksi ile pozitif ilişki gösterirken, FEV1%, FVC%, FEV1/FVC% ile anlamlı negatif ilişki gösterdi. Ancak, MKHDÖ PO2 ile anlamlı ilişki göstermedi.*

Sonuç: *Komorbiditeler ve MS KOAH'ın farklı evrelerinde görülür. Bu nedenle eşlik eden bu hastalıklar birbirinden ayrı ayrı olarak incelenmelidir.*

SUMMARY

Aim: *Results of the previous studies on the relationship amongst the comorbidity, metabolic syndrome (MS) and Chronic Obstructive Pulmonary Disease (COPD) are controversial. Therefore, these accompanying comorbidities and MS were assessed on an individual basis in patients with COPD in the present study.*

Method: *During the study period, 66 consecutive patients with COPD and 40 subjects as a control group were enrolled. Pulmonary Function Tests (PFT) were performed with flow sensitive spirometer according to ATS guidelines. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) index was calculated. The index severity of chronic diseases was evaluated using the Modified Cumulative Illness Rating Scale (MCIRS). MS was defined according to National Cholesterol Education Program. Total score of metabolic disorders was also calculated.*

Results: *MCIRS score was significantly greater in patients with COPD than in control group but the total score of metabolic disorders was the same for the patients with COPD and the control group. MS was detected in 18 subjects (27.3%) in patients with COPD as compared to 8 of subjects in control group (20%). The rate of MS in patients with stage II COPD was higher than the patients with stage IV COPD (p: 0.04). In linear regression model, the MCIRS score exhibited significant inverse associations with FEV1%, FVC% and FEV1/FVC% while exhibiting significant positive association with BODE index. However, the MCIRS did not exhibit significant association with PO2.*

Conclusion: *Comorbidities and MS were seen in different stages of COPD. Thus these accompanying diseases should be assessed on an individual basis.*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is primarily characterized by the presence of airflow limitation resulting from airways inflammation and remodeling often associated with the parenchymal destruction and the development of emphysema (1). Extrapulmonary comorbidities are common and important in COPD, often with a significant impact on morbidity and mortality (2). The most common comorbidities of COPD that are possibly related to the systemic effects of smoking are chronic heart failure, arhythmias, hypertension, peripheral and coronary artery diseases, metabolic syndrome, diabetes and osteoporosis, skeletal muscle abnormalities, cancer (especially lung cancer), pulmonary vascular abnormalities, cachexia, psychiatric disorders and infections (3, 4).

Both smoking and obesity are well known major risk factors for chronic disease (5). Obesity is a component of Metabolic Syndrome (MS). The relationship between the obesity and COPD has been poorly investigated. In addition, this relationship is still unclear and obesity may affect respiratory function in different ways (6). Although obesity itself may affect lung function, it was determined that obese and overweight subjects had better lung function than normal weight subjects in patients with COPD (7, 8). In addition, it is clear that being underweight is a poor prognostic factor in COPD. MS represents a cluster of risk factors (abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, and elevated fasting glucose) that predispose affected patients to systemic inflammation (9). Systemic inflammation may be related to the pathogenesis of both COPD and MS (10).

Results of the previous studies on the relationship amongst the comorbidity, MS and COPD are controversial. The components of this systemic inflammation may account for the systemic manifestations of COPD and may worsen comorbid diseases. Systemic inflammation appears related to an accelerated decline in lung function (11). COPD is associated with many comorbidities, but the relationship between these comorbidities and severity of COPD was not studied sufficiently. Although the relationship between MS and COPD has been recognized, it was showed that the patients with mild COPD had the highest prevalence of obesity being major component of MS and obese patients with COPD had the lowest level of airflow obstruction (12). It is also clear that undernutrition is at least in part associated with the severity of airflow obstruction (13).

Thus in this study, we examined accompanying comorbidities by using the Modified Cumulative Illness Rating Scale (MCIRS) and MS in patients with COPD on individual basis In addition, the relationship amongst these comorbidities, MS with C-reactive protein (CRP), severity of COPD determined with BODE index, parameters of pulmonary function tests and arterial blood gas were determined.

MATERIAL AND METHODS

Subjects

Consecutive subjects presented with diagnosed COPD to the policlinic at the Faculty of Medicine, Department of Pulmonary Medicine were enrolled in this study. The diagnosis of COPD was confirmed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (14). Eligible patients

received optimal therapy according to guidelines had a stable condition and with no physical findings or symptoms suggestive of acute exacerbation or therapy modifications in the 6 weeks before enrollment. Forty healthy volunteers without COPD and smoking history more than 20 packet-years were selected. The age range of patients with COPD and smoking history was from 25 to 70 years. Exclusion criteria were as follows: severe congestive heart failure, other respiratory diseases such as asthma, interstitial lung disease, obstructive sleep apnea, acute infections, and uncontrolled comorbidities such as malignancy, severe hepatic failure. A questionnaire on demographics, smoking history, medical history, and medications was completed. All patients gave written informed consent. The study was approved by the local ethics committee.

Clinic Measurements

Body mass index (BMI) (kg/m^2) was calculated by measuring weight and height. Arterial blood gas was measured by arterial puncture in the morning, sitting at rest (15 min) and breathing room air at least for 45 minutes. Pulmonary Function Tests (PFT) were performed with flow sensitive spirometer according to American Thoracic Society (ATS) guidelines (15). Systemic blood pressure measurements were determined with three or more readings of systolic and diastolic blood pressure obtained at 5-min intervals using conventional mercury sphygmomanometer after subjects sitting at rest for at least 15 min. Patients who had hypertension diagnosed previously and their medications were recorded. In addition, hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (16).

BODE index calculation: Exercise capacity was measured using the 6 minute walk distance (6MWD) test according to the ATS guidelines (17). Dyspnea was assessed using the Medical Research Council (MRC) dyspnea scale (18). The multidimensional BODE index was calculated according to BMI, FEV1%, MRC dyspnea scale, 6MWD (19).

Laboratory Measurements

Fasting venous blood samples were taken from subjects. Serum levels of CRP, glucose, triglycerides, cholesterol, LDL and HDL were analyzed.

The Modified Cumulative Illness Rating Scale (MCIRS): MCIRS is a comprehensive recording of all comorbid diseases of a patient. It classifies comorbidities by 14 organ systems affected and rates them according to their severity from 0 to 4. Within each category, when two diseases are present, the disease with the higher score is counted. We generated four ratings for each patient according to the instructions of the MCIRS: total score, number of categories endorsed, severity index (total score/ number of categories endorsed) and number of categories at level 3 (20).

Definition of MS: National Cholesterol Education Program (NCEP)-MS was defined according to the guidelines as having at least 3 of the following NCEP metabolic abnormalities: fasting glucose ≥110 mg/dL or taking medication for diabetes, abdominal obesity (waist circumference >102 cm in men or >88 cm in women), triglycerides ≥150 mg/dL, low HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women), or high blood pressure (HBP ≥130/≥85 mm Hg) (21).

Statistical Analysis

All clinical parameters were summarized by descriptive statistics and expressed as mean ± SD. Patients with COPD and control group were compared using an unpaired t-test and chi-square test for continuous parameters. Analysis of variance was used to compare the rate of MS according to severity of COPD. Correlation amongst MCIRS and BODE index, CRP, PO2, FEV1%, FVC% and FEV1/FVC% were examined using Pearson Correlation in all subjects. The determining of MCIRS and the

total score of MS were investigated using multivariable linear regression analysis.

RESULTS

During the study period, 66 consecutive patients with COPD and 40 subjects as a control group were enrolled. The characteristics of these 106 subjects were summarized in Table 1. No difference observed in the mean age, sex distribution and smoking history between patients with COPD and control group. BMI was significantly lower in patients with COPD than in control group (26.3 ± 4.8 and 28.1 ± 3.7 respectively; p = 0.02). The values of FEV1% (52.9 ± 18.0 and 97.9 ± 13.5 respectively; p = 0.0001), FVC% (60.6 ± 20.0 and 90.5 ± 15.8, respectively; p = 0.0001), FEV1/FVC% (67.5 ± 13.8 and 86.2 ± 8.2, respectively; p = 0.0001), PEF% (54.8 ± 17.5 and 97.6 ± 21.4, respectively; p = 0.0001) and MEF% (34.5 ± 14.5 and 99.7 ± 31.5, respectively; p = 0.0001) were significantly lower in patients with COPD than in control group. In addition, the values of PaO2 (68.9 ± 12.1 and 77.4 ± 8.4, respectively; p = 0.0001) was significantly lower in patients with COPD than in control group while the values of PaCO2 (37.3 ± 4.8 and 34.9 ± 3.0, respectively; p = 0.01) was significantly higher in patients with COPD than in control group. The BODE index (3.2 ± 2.2 and 0.2 ± 0.4, respectively; p = 0.0001) and MCIRS (20.9 ± 3.4 and 17.9 ± 3.1, respectively; p = 0.0001) values were significantly greater in patients with COPD than in control group. However, no difference observed in CRP score of metabolic disorders between groups (Table 1).

MS was detected in 18 of patients with COPD (27.3%) as compared to 8 of subjects in control group (20%) but no difference observed in the rate of MS between patients with COPD and control group (Table 2). MS was not detected in stage I patients with COPD. However, it was detected in 13 of stage II patients with COPD (37.1%), in 4 of stage III patients with COPD (23.5%), in only 1 of stage IV patients with COPD (10%). The rate of MS was significantly higher in stage II patients with COPD than in stage IV patients with COPD (p = 0.04) (Table 3).

Table 1. The Comparison of Patients with COPD and Control Group

	Patients with COPD mean ± SD	Control Group mean ± SD	p value
Age	63.10 ± 9.6	60.9 ± 10.6	0.2
Sex male/female	57/9	31/9	0.8
BMI	26.3 ± 4.8	28.1 ± 3.7	0.02
Smoking packet/year	33.6 ± 13.8	25.7 ± 26.0	0.08
FEV1%	52.9 ± 18.0	97.9 ± 13.5	0.0001
FVC%	60.6 ± 20.0	90.5 ± 15.8	0.0001
FEV1/FVC%	67.5 ± 13.8	86.2 ± 8.2	0.0001
PEF%	54.8 ± 17.5	97.6 ± 21.4	0.0001
MEF%	34.5 ± 14.5	99.7 ± 31.5	0.0001
PO2	68.9 ± 12.1	77.4 ± 8.4	0.0001
PCO2	37.3 ± 4.8	34.9 ± 3.0	0.01
Score of Metabolic Disorders	1.5 ± 1.2	1.7 ± 1.2	0.5
MCIRS	20.9 ± 3.4	17.9 ± 3.1	0.0001
BODE index	3.2 ± 2.2	0.2 ± 0.4	0.0001
CRP	6.7 ± 11.7	5.7 ± 8.5	0.6

Statistical significance p<0.05
SD: Standard deviation
BMI: Body mass index
CRP: C reactive protein
MCIRS: The modified cumulative illness rating scale

Table 2. The Comparison of the Rate of Metabolic Syndrome in Patients with COPD and Control Group

	Patients with COPD	Control group	p values
The Rate of Metabolic Syndrome	18/66 27.3%	8/40 20%	0.3

Statistical significance p<0.05
COPD: Chronic Obstructive Pulmonary Disease

Table 3. The Comparison of the Rate Disorders of Metabolic Syndrome according to Stage of COPD

	Stage I COPD	Stage II COPD	Stage III COPD	Stage IV COPD
The rate of Metabolic Syndrome	0/4 0 %	13/35* 37.1 %	4/17 23.5 %	1/10 10 %

Statistical significance p<0.05
** The presence of statistical significance difference according to the stage IV COPD*

Pearson Correlation analysis showed that there was significant positive relation of MCIRS with age (r: 0.45, p: 0.0001), BODE index (r: 0.48, p: 0.0001) and CRP (r: 0.38, p: 0.0001) while there was significant inverse relation of MCIRS with PO2 (r:-0.29, p: 0.005), FEV1 % (r:-0.41, p: 0.0001), FVC % (r:-0.43, p: 0.0001) and FEV1/FVC % (r:-0.23, p: 0.02) (Table 4, Figure 1, 2, 3).

In a linear regression model, the MCIRS showed significant inverse association with FEV1% (B: -0.30, p: 0.001), FVC% (B: -0.25, p: 0.005) and FEV1/FVC% (B: -0.23, p: 0.01) while it was associated significant positive with BODE index (B: 0.32, p: 0.0001). However, MCIRS did not show significant association with PaO2 and BMI (Table 5). According to linear regression analyses, the total score of MS exhibit significant positive association with BMI (B: 0.44, p: 0.0001) while exhibiting no association with age, sex, smoking packet/year and CRP values (Table 6).

Table 4. Correlation between MCIRS and Age, PaO2, FEV1%, FVC%, FEV1/FVC%, BODE index, CRP

	Age	PaO2	FEV1 %	FVC %	FEV1/FVC %	BODE index	CRP
	r value p value	r value p value	r value p value	r value p value	r value p value	r value p value	r value p value
MCIRS	0.45 0.0001	-0.29 0.005	-0.41 0.0001	-0.43 0.0001	-0.23 0.02	0.48 0.0001	0.38 0.0001

p < 0.05
Statistical significance p<0.05
CRP: C reactive protein
MCIRS: The Modified Cumulative Illness Rating Scale

Table 5. The predictors of MCIRS in all Subjects

MCIRS			MCIRS			MCIRS			MCIRS			MCIRS		
	B	p		B	p		B	p		B	p		B	p
Age	0.32	0.007	Age	0.29	0.002	Age	0.37	0.0001	Age	0.34	0.0001	Age	0.41	0.0001
Sex	-0.20	0.04	Sex	-0.20	0.02	Sex	-0.21	0.02	Sex	-0.21	0.02	Sex	-0.25	0.01
BMI	-0.11	0.2	BMI	- 0.06	0.5	BMI	-0.09	0.2	BMI	-0.12	0.1	BMI	-0.06	0.5
PO2	-0.14	0.1	BODE index	0.32	0.0001	FEV1%	-0.30	0.001	FVC%	-0.25	0.005	FEV1/FVC%	-0.23	0.01

Statistical significance p<0.05
BMI: Body mass index
MCIRS: The modified cumulative illness rating scale

Table 6. The predictors of Total Score of Metabolic Syndrome in all Subjects

	Total Score of MS	
	B	p
Age	0.12	0.2
Sex	-0.10	0.3
BMI	0.44	0.0001
CRP	0.09	0.3
Smoking packet/year	0.04	0.6

Statistical significance p<0.05
BMI: Body mass index
MS: Metabolic syndrome

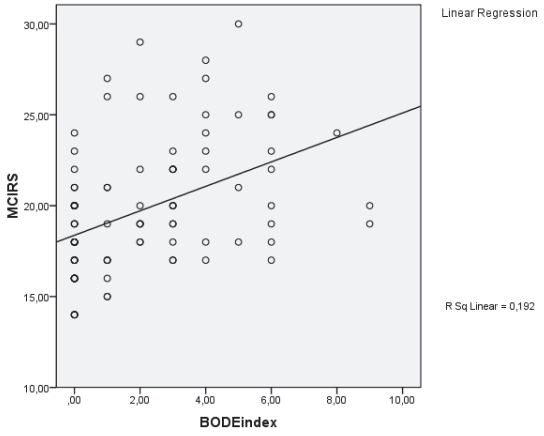

Figure 1. The relation between MCIRS and BODE index

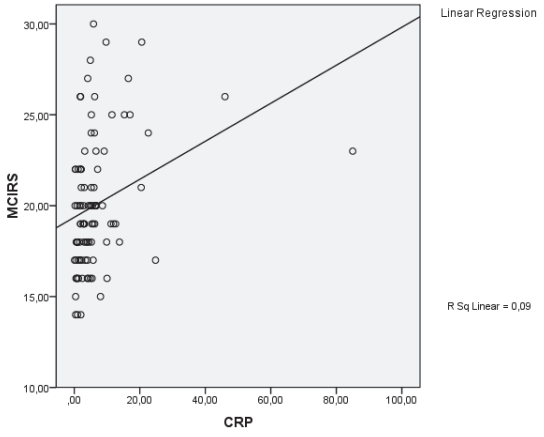

Figure 2. The relation between MCIRS and CRP

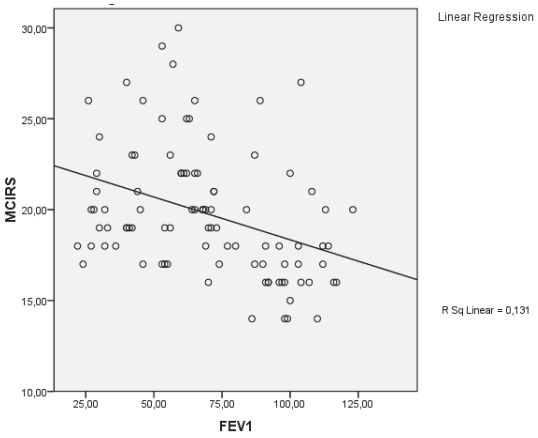

Figure 3. The relation between MCIRS and FEV1%

DISCUSSION

This study showed that comorbidity index calculated using MCIRS was significantly higher in patients with COPD than in control group. In Pearson analysis, MCIRS was positively associated with CRP and BODE index. In addition MCIRS was inversely associated with PaO2, FEV1%, FVC%, and FEV1/FVC% according to this analysis. Moreover, the MCIRS was inversely associated with FEV1%, FVC% and FEV1/FVC% while it was positively associated with BODE index according to linear regression model. On the other hand no difference observed in the rate of MS between patients with COPD and smokers without COPD. However, the rate of MS was decreasing as the disease progressing from state II to state III, IV. The findings of this study suggest that accompanying comorbidities without MS in patients with COPD may be associated with inflammation and severity of COPD. On the other hand MS is more common in only patients with early COPD. In addition the rate of MS was lower in severe COPD. The most interesting finding of this study is that the comorbidities without MS were increased but MS was decreased in COPD patients as the severity of disease increased.

The present study showed that the severity of comorbidity index was associated with CRP values according to Pearson Correlation analysis. Serum CRP concentration is biomarker important for of systemic inflammation and was showed to be increased in almost all chronic diseases (22). Patients with COPD, particularly in the setting of severe disease and exacerbations, have evidence of systemic inflammation related to increase circulating cytokines (23). Systemic inflammation may also initiate or worsen comorbid diseases such as ischemic heart disease, heart failure, osteoporosis, anemia, lung cancer, depression and diabetes (24). Furthermore, airflow obstruction has important effects on cardiac function and gas exchange with its systemic consequences. Decreased functional capacity of patients with COPD was associated with affected cardiac function secondary to hyperinflation and increased cardiac load resulting from large swings in intrathoracic pressures (25). In our study, comorbidity index was determined using MCIRS associated with both BODE index and obstructive parameters of PFT such as FEV% and MEF%. As the severity of COPD increased, the frequency of comorbidities increased. Celli et al. developed the BODE multidimensional index (BMI, airflow obstruction, dyspnea, and exercise capacity in COPD) based on four relevant variables related to COPD mortality (19). They showed that this index is a better predictor of mortality for COPD patients than the classical variable FEV1 alone. It is showed that BODE index values increased in patients with more severe disease. Thus, increase in the BODE index may explain more hypoxemia in these patients. In addition, comorbidity index was not associated with hypoxemia according to linear regression but it was associated with PO2 in Pearson Correlation analysis. There was no study in literature examining comorbidities using MCIRS and the relation between comorbidity and BODE index in COPD patients.

The present study showed that the total score of MS was associated with BMI according to linear regression analysis. Arterial hypertension, triglycerides, and fasting plasma glucose significantly increase together with increasing BMI (26). Thus, obesity is a major component of MS. The obesity increases mortality of cardiovascular diseases (27). Obesity has emerged as an important risk factor for respiratory disorders, and a link between obesity and/or MS and COPD is increasingly recognized (28, 29). It was determined that MS, obesity and atherosclerosis have an inflammatory etiology (30). Enlarged adipose tissue mass causes overproduction of proinflammatory cytokines such as IL-6, TNF-alpha and CRP (31).

No difference observed in the rate of MS between patients with COPD and control group in our study. However, the rate of MS in state II of COPD was higher than in patients with severe COPD. MS was not detected among patients with stage I COPD because stage I COPD group has only four cases. There were different results between MS and severity of COPD in literature. Funakoshi et al. showed that MS was higher in patients with airflow obstruction of GOLD stage II-IV compared to those with normal lung function. MS components such as waist circumference and blood pressure were associated with airflow obstruction parameters in patients with stage II-IV. On the other hand, the other study showed that the frequencies of the MS in patients with chronic bronchitis who had GOLD stages I, II, III, and IV were 53%, 50%, 53%, 37%, and 44% respectively (average, 47.5%) and it is observed a lower frequency of central obesity and lipid abnormalities among patients with severe and very severe COPD compared to those with chronic bronchitis and mild-to-moderate COPD (32). Kern et al. found the overall prevalence of MS was 21%, being more prevalent in earlier stages of COPD. Similarly to our study, their study showed that patients with COPD and MS were younger and had higher BMI, better pulmonary function, less static hyperinflation and air-trapping,

better diffusing capacity for carbon monoxide and BODE index (33). Again, similarly our study, Alpaydin et al found that FEV_1% and FEV_1/FVC were higher in COPD patients with MS compared to those without MS. Prevalence of MS was significantly different among the COPD patients with different stages with the highest value in stage 2 (34). Akpinar et al showed that prevalence of MS was found higher in stable COPD patients, especially in patients with GOLD stage II (35). MS is commonly diagnosed in obese patients, whereas cachexia is common in patients with severe COPD, and this may be the reason why MS was found more frequently in the early stages of the disease (34). On the other hand, comorbidities is more frequent in advanced stage of COPD. The severity of inflammation is important factor determining comorbidity in patients with COPD. However, obesity is significant factor for development of the MS but the most severe patients with COPD is widely weak. Therefore, in patients with severe COPD, comorbidity may be frequent but MS may be rare.

In conclusion comorbidities were common in patients with COPD. As the severity of COPD increased, the frequency these accompanying chronic diseases increased in patients with COPD. However MS was not common in patients with COPD compared to those without COPD. In addition, the patients with COPD and MS had lower severity of disease. Moreover, comorbidities and MS were common diseases which were seen in different forms of COPD. Thus these accompanying diseases should be assessed on an individual basis.

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