

Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome

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ABSTRACT

Objective: We tried to understand presence of any effect of excess weight on respiratory system by means of excessive adipose tissue functioning as an endocrine organ and causing a pulmonary inflammation.

Methodology: Mild (stage 1), moderate (stage 2), and severe (stage 3 and 4) chronic obstructive pulmonary disease (COPD) patients were detected, and compared according to the metabolic parameters in between.

Results: There were 145, 56, and 34 patients in the mild, moderate, and severe COPD groups, respectively. The mean age increased gradually (52.4, 56.4, and 60.0 years) from the mild towards the severe COPD groups, respectively ($p < 0.05$ nearly in all steps). Similarly, the mean pack-years increased gradually and significantly (26.7, 34.8, and 36.8 pack-years) in the same direction ($p < 0.05$ nearly in all steps). Parallel to them, the mean body mass index increased up to the moderate COPD cases (28.2 versus 29.6 kg/m², $p = 0.039$), and then decreased significantly (29.6 versus 26.8 kg/m², $p = 0.006$).

Conclusion: The metabolic syndrome includes some reversible indicators such as overweight, hyperbetaipoproteinemia, hypertriglyceridemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, and white coat hypertension for the development of terminal diseases including obesity, hypertension, diabetes mellitus, peripheral artery disease, coronary heart disease, and stroke. In our opinion, COPD may be one of the terminal end points of the syndrome.

KEY WORDS: Chronic obstructive pulmonary disease, Metabolic syndrome, Smoking, Aging.

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INTRODUCTION

A significant relationship between some metabolic parameters and obesity, hypertension (HT), type 2 diabetes mellitus (DM), peripheral artery disease (PAD), coronary heart disease (CHD), stroke, and eventually an increased all-cause mortality is known for many years, and defined as the metabolic syndrome.^{1,2} The syndrome is characterized by a group of metabolic risk factors including overweight, dyslipidemia, elevated blood pressure (BP), insulin resistance, and a prothrombotic and proinflammatory state instead of being a final disease, since it can be reversed completely with appropriate nonpharmaceutical approaches including lifestyle changes, diet, and

exercise.³⁻⁸ So it actually contains the reversible risk factors for development of irreversible diseases which decrease quality and duration of life, such as obesity, HT, DM, CHD, PAD, and stroke.

On the other hand, chronic obstructive pulmonary disease (COPD) is also frequent, and a continuously increasing cause of morbidity and mortality in the world.⁹ It is expected that COPD will be the third common cause of mortality and 5th common cause of morbidity all over the world by the year of 2020.¹⁰ COPD is a disease characterized by chronic bronchitis and/or emphysema and airflow obstruction that is generally progressive. It may also be accompanied by airway hyperreactivity, and may be partially reversible. It is generally accepted that COPD is not solely a pulmonary disease but also causes systemic consequences.¹¹ Its prevalence and mortality rates increase with age.⁹

Additionally, tobacco smoke and coal and/or biomass smoke are some other risk factors of COPD.¹² We tried to understand presence of any effect of excess weight on the respiratory system by means of the excessive adipose tissue functioning as an endocrine organ and causing a pulmonary inflammatory process in the present study.

METHODOLOGY

The study was performed in the Internal Medicine Service of the Mustafa Kemal University between March 2007 and December 2011. All patients with COPD were detected via spirometric pulmonary function tests. The criterion for diagnosis is post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) of less than 70%. Then the patients were subdivided into the three groups according to the severity of COPD. Stage 1 COPD patients are those with a FEV1 \geq 80%, stage 2 patients are those with a FEV1 $<$ 80%, and stage 3 and 4 are those with a FEV1 $<$ 50% of predicted according to the Global initiative for Obstructive Lung Disease guideline definition.¹⁰

The stage 3 and 4 cases were put into the same group, since the advanced stages of COPD are thought to affect nutritional status of the patients, and will put them into an increased basal metabolic rate that terminates with cachexia.

Their medical history including smoking habit and already used medications was noted and a routine check up procedure including low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) was performed. Current daily smokers at least for one pack-year and cases with a history of at least five pack-years were accepted as smokers. Cigar or pipe smokers were excluded. Body mass index (BMI) of each case was calculated by the measurements of the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared.¹³ Eventually, mild (stage 1), moderate (stage 2), and severe COPD patients (stage 3 and 4) were compared according to the mean age, sex, BMI, weight, height, LDL-C, TG, mean pack-years, and prevalence of smoking in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

RESULTS

There were 145, 56, and 34 patients in the mild, moderate, and severe COPD groups, respectively (Table-I). The mean ages of groups increased gradually (52.4, 56.4, and 60.0 years) from the mild towards the severe COPD groups, respectively ($p < 0.05$ nearly in all steps). Although the female ratios were 24.1% and 23.2% in the mild and moderate groups, it was relatively and significantly higher in the severe COPD group (41.1%, $p < 0.05$ for both). Prevalence of smoking was similar in all groups ($p > 0.05$ between all groups), whereas the mean pack-years increased gradually (26.7, 34.8, and 36.8 pack-years, respectively) from the mild towards the severe COPD groups, significantly ($p < 0.05$ nearly in all steps).

Table-I: Characteristic features of the study cases.

Variables	Mild COPD* cases	p-value	Moderate COPD cases	p-value	Severe COPD cases	p-value†
Number	145		56		34	
Mean age (year)	52.4 \pm 11.0 (25-76)	0.026	56.4 \pm 12.0 (36-85)	ns	60.0 \pm 12.1 (31-81)	0.001
Female ratio	24.1% (35)	ns‡	23.2% (13)	<0.05	41.1% (14)	<0.05
Prevalence of smoking	79.3% (115)	ns	73.2% (41)	ns	58.8% (20)	ns
Mean pack-years	26.7 \pm 16.9 (5-150)	0.005	34.8 \pm 16.7 (5-80)	ns	36.8 \pm 18.6 (15-100)	0.017
Mean BMI§ (kg/m ²)	28.2 \pm 4.4 (17.7-41.2)	0.039	29.6 \pm 4.3 (20.1-37.8)	0.006	26.8 \pm 5.0 (14.8-36.7)	ns
Mean weight (kg)	79.6 \pm 12.9 (50-108)	ns	81.2 \pm 13.0 (54-111)	0.002	72.4 \pm 14.2 (42-116)	0.005
Mean height (cm)	167.7 \pm 9.4 (140-187)	ns	165.2 \pm 8.6 (147-184)	ns	163.7 \pm 7.6 (149-180)	0.006
Mean LDL-C (mg/dL)	131.1 \pm 32.4 (50-282)	ns	134.1 \pm 42.7 (71-265)	ns	122.3 \pm 30.1 (66-179)	ns
Mean TG¶ (mg/dL)	198.6 \pm 162.0 (47-1380)	ns	186.8 \pm 126.0 (62-562)	ns	162.0 \pm 99.5 (58-418)	ns

*Chronic obstructive pulmonary disease †Comparison value between mild and severe cases

‡Nonsignificant ($p > 0.05$) §Body mass index §Fasting plasma glucose ||Low density lipoprotein cholesterol ¶Triglyceride

As one of the most significant results, the mean BMI increased up to the moderate COPD cases (28.2 versus 29.6 kg/m², $p=0.039$), and then decreased significantly (29.6 versus 26.8 kg/m², $p=0.006$). Similarly, the mean body weight increased up to the moderate COPD group, then decreased significantly ($p<0.05$ nearly in all steps). Probably due to aging, the mean body height decreased from the mild towards the severe COPD groups, gradually ($p<0.05$ nearly in all steps). On the other hand, there were nonsignificant differences between the mild, moderate, and severe COPD cases ($p>0.05$ between all) according to the mean LDL-C and TG values probably due to the small sample sizes of the groups.

DISCUSSION

Nowadays, the metabolic syndrome is becoming one of the most significant public health problem both for developing and already developed countries, affecting nearly all age groups even the children of the society. For example, it is estimated that 50 millions of Americans have it.¹⁴ Metabolic syndrome is a collection of reversible metabolic risk factors for many terminal diseases. Although there is no universally accepted definition for the syndrome, it basically includes obesity (increased body weight, BMI, or waist circumference), increased plasma glucose and insulin levels, low HDL-C, high TG, and high BP values.¹⁵ But the already used definitions as a BP of 135/85 or 140/90 mmHg or above and a FPG of 100 or 110 mg/dL or above also include patients with DM and HT. But actually the syndrome is a collection of risk factors instead of the final diseases, and it is a reversible condition with appropriate nonpharmaceutical approaches.

The diseases including HT, DM, and symptomatic atherosclerosis are irreversible and final states almost always require drug therapy to delay complications. For example in a previous study¹⁶, prevalences of hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and WCH showed a parallel fashion to excess weight by increasing until the seventh decade of life and decreasing afterwards ($p<0.05$ nearly in all steps). On the other hand, prevalences of HT, DM, and CHD always continued to increase by aging without any decrease ($p<0.05$ nearly in all steps), indicating their irreversible properties.¹⁶

So metabolic syndrome alone is a disadvantageous but reversible status but not a final disease,

and after the development of one of the terminal diseases, the term of metabolic syndrome probably loses most of its significance. From now on the nonpharmaceutical approaches will provide little benefit to prevent development of the others, probably due to cumulative effects of the risk factors on systems for a long period of time. So the definition of metabolic syndrome should include reversible metabolic risk factors such as overweight, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IFG, IGT, and WCH but not obesity, HT, DM, CHD, PAD, and stroke like terminal diseases. We feel that COPD may be one of the irreversible end points of the syndrome, too.

COPD is an inflammatory disease, mainly affecting the pulmonary vasculature. The origin of this inflammation is unclear, but excess weight, smoking, and aging may be three of the several possible causes of the inflammation. Any type of irritation causes an innate inflammatory response. The inflammatory process is enhanced by the release of various chemical factors by the lymphocytes to repair the damaged pulmonary tissues, especially endothelial cells of the pulmonary arteriols. However, due to the continuous irritation process of the endothelial cells in case of excess weight, smoking or aging, prominent changes develop in the architecture of the airways and alveolar spaces, since the chronic inflammatory process of the endothelial cells terminates with fibrosis and atherosclerosis in the lungs. Probably the accelerated atherosclerotic process is the main structural background of the functional changes characteristic of the disease.

Although COPD is mainly an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about existence of an associated systemic endothelial inflammation in the literature.¹⁷⁻¹⁹ For example, there may be a close relationship between COPD and cardiovascular diseases probably due to the accelerated atherosclerotic process.²⁰ In a multicenter study performed on 5,887 smokers aged between 35 and 60 years, two-third of mortality cases were caused by cardiovascular diseases and lung cancer, and coronary heart disease was the most common cardiovascular complication among them.²¹ When the hospitalizations were searched, the most common causes were the cardiovascular diseases again.²¹ In another study, 27% of all mortality cases were due to the cardiovascular causes in the moderate and severe COPD cases.²²

Probably excess weight, smoking, and aging are the most significant causes of the systemic

atherosclerosis. Excessive adipose tissue may function as an endocrine organ, and may cause a systemic inflammatory process. The systemic inflammatory effect of smoking on endothelial cells is already known with Buerger's disease in the literature. Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic inflammation on endothelial system in smokers. The inflammation particularly affects the pulmonary endothelial cells due to the higher concentrations of irritant substances in lungs. Similarly, aging may be the other significant cause of systemic atherosclerotic process that prevents adequate tissue repair. On the other hand, frequency of COPD is increasing in society. For example, although age-matched mortality for all other diseases decreased with a 32% ratio in the last 30 years, the COPD related mortality increased with a 102% ratio in the same period of time.²³ This increase can be explained by the increasing frequency of excess weight in societies, and aging of the population.

According to the most optimistic estimates, the COPD mortality rates will increase by 50% over the next 15 years.²⁴ Although the achieved development in the health services and decreased smoking prevalence worldwide, the increased COPD mortality and morbidity may only be explained by the increasing frequencies of excess weight and aging in the world. Similarly, the mean age, mean pack-years, and mean BMI increased progressively from the mild towards the severe COPD cases in the present study ($p < 0.05$ nearly in all steps). The only exception was the decreased mean BMI after the moderate COPD cases, probably due to the severe COPD induced cachexia in the body. The overall male predominance of the COPD cases in the present study may also indicate the effects of smoking in COPD, since the smoking is significantly higher in males all over the world. There were nonsignificant differences between the mild, moderate, and severe COPD cases according to the mean LDL-C and TG values probably due to the small sample sizes of the groups in the present study.

As a conclusion, the metabolic syndrome includes some reversible indicators such as overweight, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IFG, IGT, and WCH for the development of terminal diseases including obesity, HT, DM, PAD, CHD, and stroke. In our opinion, COPD may be one of the terminal end points of the syndrome.

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