Journal of
Cardio - Thoracic Medicine

http://jctm.mums.ac.ir

Metabolic Syndrome in Chemical Warfare Patients with Chronic Obstructive Pulmonary Disease

Shahrzad M. Lari[1], Davood Attaran[2]*, Haleh Rokni Yazdi[3], Mohammad Towhidi[2], Omid Shadkam[4], Abbas Asadi[4], Mohammad Khajehdaluee[5], Hossein Ayatollahi[6], Majid Ghayour-Mobarhan[7]

[1] *Pulmonologist, Cardio-Thoracic Surgery & Transplant Research Center, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2] *Pulmonologist, COPD Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3] *Endocrinologist, Endocrinology Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[4] *Internist, COPD Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[5] *Specialist in Community Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[6] *Pathologist, Cancer Molecular Pathology Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[7] *Clinical Nutrician, Cardiovascular Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLEINFO

Article type:
Original article

Article history:
Received: 20 May 2014
Revised: 5 Sep 2014
Accepted: 13 Sep 2014

Keywords:
Chemical Warfare Patients
COPD
Metabolic Syndrome
Sulfur Mustard

ABSTRACT

Introduction: Sulfur mustard (SM), a toxic alkylating gas, can cause serious long-term pulmonary complications such as chronic obstructive pulmonary disease (COPD). Metabolic syndrome (MetS) is one of the important comorbidities of COPD. This study was designed to evaluate the frequency of metabolic syndrome in Iranian chemical warfare patients (CWPs) with COPD.
Materials and Methods: Thirty CWPs with a mean age of 46.93±6.8 were enrolled in this study. The following parameters were studied in: complete pulmonary function tests, health-related quality of life, serum triglycerides (TG), high density lipoprotein (HDL) and fasting blood sugar (FBS) levels. Additionally, 32 COPD patients and 56 healthy persons were considered as control groups who were matched to CWPs.
Results: We found a statistically significant difference in the frequency of MetS between the COPD patients and the healthy control group (P=0.04). Additionally, we observed a statistically significant difference in the mean HDL levels among these groups (P=<0.001). In the CWPs, the frequency of MetS was significantly decreased in severe to very severe stages (P<0.001).
Conclusion: Our data indicate that metabolic syndrome is frequent in chemical warfare patients, and special attention to this condition in mild to moderate stages is recommended.

►*Please cite this paper as:*
Lari SM, Attaran D, Rokni Yazdi H, Towhidi M, Shadkam O, Asadi A, Khajehdaluee M, Ayatollahi H, Ghayour-Mobarhan M. Metabolic Syndrome in Chemical Warfare Patients with Chronic Obstructive Pulmonary Disease. J Cardiothorac Med. 2014; 2(4):231-237.

Introduction

Sulfur mustard (SM) is a toxic alkylating gas that was used as an agent of chemical warfare in World War I and the Iran-Iraq conflict between 1983 and 1988 (1). Currently, there are a considerable number of CWPs in Iran who suffer from important late organ complications (2). SM can cause serious ocular, neurologic, dermatologic, and pulmonary complications in the late phase (1, 3). Pulmonary problems, including chronic obstructive pulmonary disease (COPD), chronic bronchitis, bronchiolitis obliterans, and bronchiectasis, are the most common late complications in CWPs (4-7).

COPD is characterized by a poorly reversible limitation to airflow that is usually progressive (8). COPD, which is a leading cause of morbidity

**Corresponding author:* Davood Attaran, COPD Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +98 511 8012742; Fax: +98 511 8431252; Mobile: +98 915 310 7871; E-mail: attarand@mums.ac.ir

and mortality, is predicted to be the third leading cause of death by 2020 (9, 10). It is now well documented that COPD is a systemic inflammatory condition and is considered to be a "chronic systemic inflammatory syndrome" (8). Numerous important comorbidities are associated with COPD, including hypertension, diabetes, pulmonary vascular disease, ischemic heart disease, and skeletal muscle abnormalities 8. Systemic inflammation and physical inactivity are correlated with the severity of the disease (9, 13). It has also been shown that higher levels of systemic inflammation are associated with lower levels of physical activity in COPD patients (1-13).

The prevalence of metabolic syndrome (MetS), which is defined as the accumulation of several cardiovascular risk factors (hypertension, abdominal obesity, insulin resistance, and dyslipidemia), has significantly increased throughout the world. Approximately 40-50% of people over 60 years of age have MetS in industrialized countries (9, 15). Furthermore, countries in the Middle East are not exempt from this high incidence of MetS (16, 17).

Because frequent metabolic abnormalities are found in COPD patients, the evaluation of these abnormalities seems necessary (9). Watz and colleagues reported that approximately half of all COPD patients have coexisting MetS and that the frequency of MetS was slightly lower in severe stages of COPD (9).

Therefore, it has been proposed that clinical and laboratory abnormalities beyond the respiratory system be evaluated in older COPD patients who smoke (8).

The relationship between the severity of pulmonary disease and MetS in CWPs with COPD is unknown. This study was performed to determine the frequency of MetS in CWPs with COPD and to evaluate the correlation of pulmonary parameters in the presence of MetS.

Materials and Methods

Study population

We performed a cross-sectional, single-center study involving chemical warfare patients with stable COPD. All patients suffered from pulmonary complications as a result of SM exposure and had validated documentation of SM poisoning. CWPs with all levels of COPD, which were defined according to the GOLD (Global initiative of Obstructive Lung Disease) classification (18), were entered in this study if they had a post-bronchodilator FEV1/FVC (forced expiratory volume/forced vital capacity) <0.7 after 400 μg of inhaled albuterol based on the definition of the American Thoracic Society (ATS) (19). The patients were excluded based on the following criteria: their FEV1 increased more than 12% and 200 ml after administration of the bronchodilator; they were taking systemic steroids, antihypertensives, or lipid or glucose lowering agents; they had COPD exacerbations or hospitalizations during the previous 2 months; or they were current or ex-smokers.

Thirty-two COPD patients were entered as control group 1 and were matched with CWPs according to sex, age, and severity of the disease (based on the GOLD classification). Control group 1 met the inclusion and exclusion criteria.

Additionally, 56 age- and sex-matched healthy volunteers were enrolled as control group 2. Control group 2 was selected from the previous MetS cohort study (20).

This study was approved by the ethics committee of Mashhad University of Medical Sciences (MUMS). All patients provided written informed consent.

Anthropometric measurements

Each participant underwent a detailed medical interview and complete physical examination. The body weight (with clothes on) and height (without shoes) of each patient were recorded. The body mass index (BMI) was calculated as weight (kg) divided by height (m).

The waist circumference was measured using an elastic tape at the midpoint between the lower rib and the iliac crest (21). The blood pressure of the patients was measured from both arms after 15 minutes of rest, and the higher measurement was considered for analysis.

Metabolic syndrome

The metabolic syndrome was assessed according to the National Cholesterol Education Program, Adult Treatment Panel III (NCEP: ATPIII) (22). MetS was diagnosed if three or more of the following criteria were present: central obesity, waist circumference (WC) >102 cm (for men) or >88 cm (for women), hypertriglyceridemia [triglycerides (TG) >150 mg/dL or specific medication], low high density lipoprotein (HDL) cholesterol (<40 mg/dL (for men) and <50 mg/dL (for women) or specific medication), hypertension (blood pressure >130 mmHg systolic or>85 mmHg diastolic or specific medication), and fasting blood sugar (FBS) (>110 mg/dL or specific medication or previously diagnosed Type 2 diabetes).

Pulmonary function tests

To assess the severity of the airway disease, spirometry (Multi-Functional Spirometer HI-801, Chest M.I., Inc., Tokyo, Japan) was performed according to the American Thoracic Society (ATS)

guidelines (19). The forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC were measured using standard spirometric techniques. The best of three consecutive spirometry recordings was used.

Based on the global initiative for chronic obstructive lung disease (GOLD) guidelines (18), the severity of COPD was determined as follows: Stage1 (FEV1/FVC<70%, FEV1>80%), Stage 2 (FEV1/FVC<70%, 50%≤FEV1<80%), Stage 3 (FEV1/FVC<70%, 30%≤FEV1<50%), and Stage 4 (FEV1/FVC<70%, FEV1<30%).

The severity of dyspnea was assessed by the modified medical research council (MMRC) scale (23). Additionally, for determining the exercise capacity of the subjects, the 6 minute walk distance (6 MWD) test was performed according to the ATS guidelines (24). The BODE (body mass index, obstruction, dyspnea, and exercise capacity) index was calculated for the patients (23). The BODE stages were defined as stage 1 (BODE index: 0-3), stage 2 (BODE index: 4-6), and stage 3 (BODE index: 7-9).

Additionally the quality of life was assessed using a validated Farsi version of the St. George Respiratory Questionnaire (SGRQ) 25. The SQRQ stages were categorized according to the total score as follows: Stage 1 (0-29), Stage 2 (30-44), Stage 3 (45-59) and Stage 4 (≥60).

Blood samples

Blood samples were obtained after 14 hours of fasting. The serum FBS, TG and HDL levels were measured using enzymatic methods. The serum was stored at -70°C prior to analysis.

Statistical analysis

Descriptive statistics were used to summarize the demographic characteristics of the CWP, COPD, and healthy control groups. The continuous data are presented as percentages and means ± SDs. The normality of continuous variables was verified using the one-sample Kolmogorov-Smirnov test. For continuous and categorical variables, independent Student's t tests and chi-square tests were used to evaluate the statistical significance of any difference or relationship between parameters, respectively. Pearson and Spearman correlation coefficients were calculated. A P-value of less than 0.05 was considered significant. The data were analyzed using the statistical package for social sciences (SPSS, version 11.5).

Results

Clinical characteristics of the study population

Thirty CWPs and the aforementioned control groups were entered into this study. The demographic and clinical parameters are shown in Table 1. All of the participants were male.

There were statistically significant differences in the frequencies of MetS among the groups (P=0.04), as shown in Figure 1. The frequency of MetS was not significantly different between the CWP and COPD groups (P=0.8). We observed a statistically significant difference in the HDL cholesterol level among the groups (P<0.001). In Table 2, the mean values of other MetS parameters are shown. The frequencies of the MetS components in the different groups are shown in Figure 2.

Table 1. The demographic data of chemical warfare patients, COPD patients, and the healthy control groups

	Chemical warfare*	COPDs*	Controls*	P value
Age (years)	46.93± 6.8	47.5±4.50	46.5±6.16	0.80
BMI (kg/m2)	26.32±3.66	26.4±5.65	26.52±4.55	0.60
Smoking (Pack/year)	No	22.0±5.5	No	0.001
Waist circumference (cm)	96±12.06	93.16±13.50	90.29±11.50	0.11
Cholesterol (mg/dl)	193±34.5	49 ± 191	181.12±32.40	0.32
Triglyceride (mg/dl)	181.27±141.84	151±94.30	136.25±64.50	0.12
HDL (mg/dl)	46.23±4.98	44.55±8.35	31.68±9.01	0.001
LDL (mg/dl)	112.17±30.26	118.12±34.50	123.48±30.56	0.10
FBS (mg/dl)	90.60±38.60	63 ± 103	87.48±23.60	0.09
SBP (mmHg)	131.5±19.43	128±25.25	124.58±17.8	0.31
DBP (mmHg)	85±12.3	12± 80.50	81.62±12.17	0.10

*Data are shown as the mean ± SD.
BMI: Body Mass Index, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, FBS: Fasting Blood Sugar, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

Table 2. Lung function parameters in the CWP and COPD groups

Parameter*	CWPs	COPD patients	P value
FEV1 % pred. (%)	66.50±21.00	62.00±26.70	0.55
BODE index	2.70±2.40	3.25±2.70	0.34
Total SGRQ score	50.28±17.30	48.69±13.45	0.68
6 MWD (m)	353.10±101.25	346.60±109.15	0.81
SpO2 (%)	95.90±3.25	95.55±2.80	0.63

*Data are shown as the mean ± SD.
FEV1: forced expiratory volume in one second; BODE: Body Mass Index (BMI), Obstruction, Dyspnea, Exercise; SGRQ: St. George Respiratory Questionnaire; 6 MWD: 6-Minute Walk Distance; SpO2: oxygen saturation by pulse oximeter.

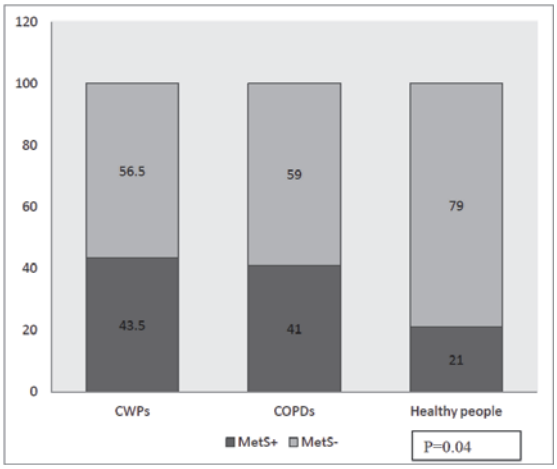

Figure 1. The frequency of metabolic syndrome in CWP, COPD patients, and healthy control individuals
CWP: Chemical Warfare Patient, COPD: Chronic Obstructive Pulmonary Disease

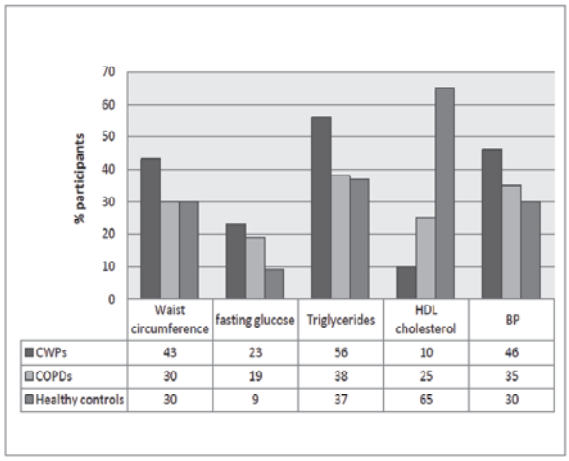

Figure 2. The frequency of metabolic syndrome components among participants
(CWPs: chemical warfare patients, COPD: chronic obstructive pulmonary disease, BP: Blood Pressure)

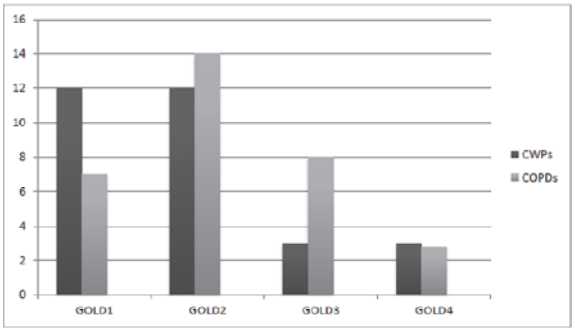

Figure 3. The frequency of the different GOLD stages in chemical warfare and COPD patients
COPD: Chronic Obstructive Pulmonary Disease, GOLD: Global initiative of Obstructive Lung Disease

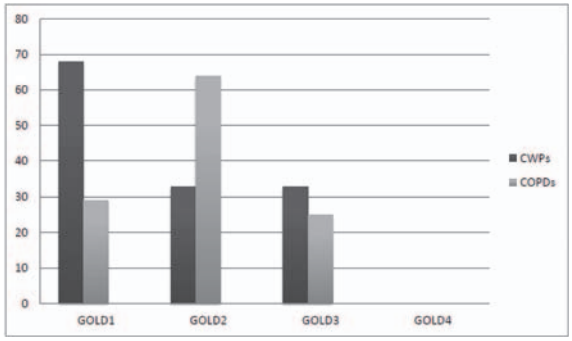

Figure 4. The presence of metabolic syndrome in CWPs and COPD patients at different disease stages, as determined using GOLD staging
CWP: Chemical Warfare Patient, COPD: Chronic Obstructive Pulmonary Disease, GOLD: Global initiative of Obstructive Lung Disease

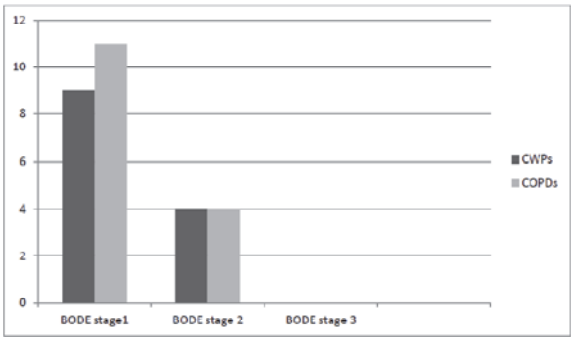

Figure 5. The presence of metabolic syndrome in different stages of the BODE index in chemical warfare patients (CWPs) and COPD patients
BODE: Body Mass Index (BMI), Obstruction, Dyspnea, Exercise, COPD: Chronic Obstructive Pulmonary Disease

Table 3. The frequency of different stages of the BODE index and SGRQ in CWPs and COPD patients

	CWPs	COPD patients
BODE index		
Stage 1	22	20
Stage 2	6	7
Stage 3	2	5
SQRQ score		
Stage 1:	1	2
Stage 2:	3	11
Stage 3:	6	11
Stage 4:	20	8

BODE: Body Mass Index (BMI), Obstruction, Dyspnea, Exercise, SGRQ: St. George Respiratory Questionnaire, CWPs: Chemical warfare patients, COPD: Chronic Obstructive Pulmonary Disease

Lung function parameters in CWPs and COPD patients

The lung function parameters in the CWP and COPD groups are shown in Table 2. The frequencies of the different stages of COPD (according to the GOLD classification) in the different subject groups are shown in Figure 3.

The frequencies of the different stages of the BODE index and SGRQ in CWPs and COPD patients are shown in Table 3.

The frequency of MetS in different stages of lung disease in CWPs and COPD patients

There were statistically significant differences in the frequency of MetS in the different stages of COPD in the chemical warfare patients (P<0.001) but not in the COPD patients (P=0.06), as shown in Figure 4. Additionally, differences in the frequencies of MetS in the different stages of the BODE index were significant in the CWPs and COPD patients (P<0.001, P=0.001, respectively,

Figure 5). These differences suggest that the frequency of MetS was significantly decreased as a function of the disease severity.

According to the BODE index, the frequency of MetS was not different between the CWPs and COPD patients (P=0.3).

We found a statistically significant difference in the frequency of MetS in the different stages of SQRQ exclusively in the CWPs (P=0.001).

Discussion

To the best of our knowledge, there are no studies documenting MetS in chemical warfare patients with COPD. In this study, we evaluated the frequency of metabolic syndrome in these patients. We observed a statistically significant difference in the frequency of MetS between the CWPs and the members of the healthy control group, but the difference between the CWPs and COPD patients was not significant. Additionally, in the CWPs, the frequency of MetS decreased significantly with COPD severity.

Systemic inflammation is considered to be an important underlying mechanism in COPD. Other potential mechanisms of systemic inflammation in COPD are the spillover of inflammatory cytokines from the lungs to the systemic circulation, smoking, genetic and constitutional predisposing factors, and tissue hypoxia (9, 26-28). The role of systemic inflammation in COPD due to sulfur mustard is a matter of debate 3. Some studies have shown increasing levels of inflammatory markers, such as hs-CRP or IL-6, in the stable phase of COPD in CWPs (3, 4). Alternatively, other studies have demonstrated opposing findings (29). While the presence of systemic inflammation has been established in COPD, its role in the pathogenesis of COPD due to sulfur mustard has not been evaluated.

Numerous studies have reported that MetS is associated with increased levels of inflammatory markers, suggesting that MetS has an inflammatory basis (9). The association between COPD and MetS has been described previously (9). It has been proposed that COPD patients often have some components of MetS (30). In addition to its underlying inflammatory basis in COPD, a sedentary lifestyle and deconditioning have been proposed as contributing factors in the pathogenesis of MetS in these patients (21). In our study, 43.5% of CWPs and 41% of COPD patients had 3 or more components of MetS compared to 21% in the healthy group. This comparison between patients and the healthy group was statistically significant; however, the difference between CWPs and COPD patients was not significant. These findings resemble the study by Watz and colleagues, which showed an average MetS frequency of 47.5% in patients with chronic bronchitis and COPD (9).

By evaluating the various components of MetS in participants, we found that the mean HDL levels were elevated in disease patients (CWPs and COPD patients) compared to those in the healthy group. Marquis (21) and Tisi (31) reported the same results in COPD patients. Some potential mechanisms underlying these findings are increased HDL production due to chronic respiratory muscle contractions, drug effects, and other unknown mechanisms (21, 31, 32). The mean levels of HDL were not different between the CWPs and COPD patients.

The frequency of MetS was significantly lower in the chemical warfare patients, which corresponded with the severity of the disease, as assessed using GOLD classifications. This finding is consistent with a study by Watz and colleagues (9). Their proposed hypothesis was that in severe stages of COPD, fewer patients are obese, resulting in lower inflammatory markers and, therefore, lower frequencies of MetS (9). We did not find a significant difference in the frequency of MetS in different GOLD stages in the COPD patients.

An evaluation of the disease severity using the BODE index stages also showed similar results, emphasizing the idea that an increased disease severity is associated with a significant decline in the frequency of MetS in CWPs and COPD patients.

Interestingly, our results showed that the frequency of MetS and its associated symptoms were not different in the CWPs and COPD patients. Because smoking was an excluding factor for CWPs in this study, similar frequencies of MetS in CWPs and COPD patients emphasize the role of systemic inflammatory factors in the pathogenesis of MetS in CWPs.

This study has some limitations. First is the small sample size. If it was possible to expand the number of chemical warfare patients, the analysis of our data would be more precise.

Secondly, it would be better to evaluate the important serum inflammatory markers in the context of MetS components. Finally, the assessment of the physical activity levels of the patients seems reasonable.

Conclusion

Chemical warfare patients with COPD, like other COPD patients, are prone to systemic inflammation and accompanying conditions. MetS is one of the most important comorbidities of COPD. We showed that a considerable number of chemical warfare patients have MetS, which is more common in mild to moderate stages of COPD. Therefore, special attention to this condition is highly recommended in chemical

warfare patients, particularly those with less severe forms of the disease.

Acknowledgements

This study was financially supported by the research council of Mashhad University of Medical Sciences, Mashhad, Iran. The authors wish to thank M. Aalami for his valuable assistance in data collection.

Conflict of interest

The authors declare no conflicts of interest.

References

1. Balali-Mood M, Hefazi M. Comparison of early and late toxic effects of sulfur mustard in Iranian veterans. Basic Clin Pharmacol Toxicol. 2006; 99: 273-82.
2. Ghanei M, Adibi I. Clinical review of mustard lung. IJMS. 2007; 32: 58–65.
3. Attaran D, Lari SM, Khajehdaluee M, Ayatollahi H, Towhidi M, Asnaashari A, et al. Highly sensitive C-reactive protein levels in Iranian patients with pulmonary complication of sulfur mustard poisoning and its correlation with severity of airway diseases. Hum Exp Toxicol. 2009; 28:739-45.
4. Attaran D, Lari SM, Towhidi M, Marallu HG, Ayatollahi H, Khajehdaluee M, et al. Interleukin-6 and airflow limitation in chemical warfare patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2010; 5:335-40.
5. Ghanei M, Amiri S, Akbari H, Kosari F, Khalili A, Alaeddini F, et al. Correlation of sulfur mustard exposure and tobacco use with expression (immunoreactivity) of p53 protein in bronchial epithelium of Iranian "mustard lung" patients. Mil Med. 2007; 172:70–74.
6. Balali-Mood M, Hefazi M, Mahmoudi M, Jalali E, Attaran D, Maleki M, et al. Long-term complications of sulfur mustard poisoning in severely intoxicated Iranian veterans. Fundam Clin Pharmacol. 2005; 19:713–21.
7. Khateri S, Ghanei M, Keshavarz S, Soroush M, Haines D. Incidence of lung, eye, and skin lesions as late complications in 34,000 Iranians with wartime exposure to mustard agent. J Occup Environ Med. 2003; 45:1136–43.
8. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet. 2007; 370:797-9.
9. Watz H, Waschki B, Kirsten A, Müller KC, Kretschmar G, Meyer T, et al. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. Chest. 2009; 136:1039-46.
10. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007; 370: 741-50.
11. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J. 2006; 27: 627-43.
12. Fabbri LM, Rabe KF. Multiple chronic diseases. In: Proceedings of a European Respiratory Society Research Seminar. Rome, Italy; Feb 11-12, 2007. Available at: http://www.ersnet.org/ers/browse/default.aspx?id=31439.
13. Groenewegen KH, Postma DS, Hop WC, Wielders PL, Schlösser NJ, Wouters EF, et al. Increased systemic inflammation is a risk factor for COPD exacerbations. Chest. 2008; 133: 350-7.
14. Watz H, Waschki B, Boehme C, Claussen M, Meyer T, Magnussen H. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. Am J RespirCrit Care Med. 2008; 177: 743-51.
15. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002; 287:356-9.
16. Sahebari M, Goshayeshi L, Mirfeizi Z, Rezaieyazdi Z, Hatef MR, Ghayour-Mobarhan M, et al. Investigation of the association between metabolic syndrome and disease activity in rheumatoid arthritis. Scientific World Journal. 2011; 11:1195-205.
17. Nezhad MA, Ghayour-Mobarhan M, Parizadeh SM, Safarian M, Esmaeili H, Khodaei GH, et al. Metabolic syndrome: its prevalence and relationship to socio-economic parameters in an Iranian population. Nutr Metab Cardiovasc Dis. 2008; 18: e11-2.
18. Pauwels RA, Buist AS, Caleverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global initiative for Obstructive Lung Disease (GOLD) workshop summary. Am J Respir Crit Care Med. 2001; 163:1256–76.
19. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J RespirCrit Care Med 1995; 152:S77–121.
20. Ebrahimi M, Kazemi-Bajestani SM, Ghayour-Mobarhan M, Moohebati M, Paydar R, Azimi-Nezhad M, et al. Metabolic syndrome may not be a good predictor of coronary artery disease in the Iranian population: population-specific definitions are required. Scientific World Journal. 2009; 9:86-96.
21. Marquis K, Maltais F, Duguay V, Bezeau AM, LeBlanc P, Jobin J, et al. The metabolic syndrome in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil. 2005; 25:226-32.
22. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004; 109:433-8.
23. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004; 350:1005-12.
24. American Thoracic Society. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166: 111–7.
25. Halvani A, Pourfarokh P, Nasiriani K. Quality of life

and related factors in patients with chronic obstructive pulmonary disease. Tanaffos. 2006; 5: 51–6.
26. Agusti A. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). Proc Am Thorac Soc. 2007; 4:522-5.
27. Wouters EF. Local and systemic inflammation in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005; 2: 26-33.
28. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. Chest. 2007; 131: 1557-66.
29. Pourfarzam S, Ghazanfari T, Yaraee R, Ghasemi H, Hassan ZM, Faghihzadeh S, et al. Serum levels of IL-8 and IL-6 in the long term pulmonary complications induced by sulfur mustard: Sardasht-Iran Cohort Study. Int Immunopharmacol. 2009; 9:1482–8.
30. Rogliani P, Curradi G, Mura M, Lauro D, Federici M, Galli A, et al. Metabolic syndrome and risk of pulmonary involvement. Respir Med. 2010; 104: 47-51.
31. Tisi GM, Conrique A, Barrett-Connor E, Grundy SM. Increased high density lipoprotein cholesterol in obstructive pulmonary disease (predominant emphysematous type). Metabolism. 1981; 30:340-6.
32. Bolton CH, Mulloy E, Harvey J, Downs LG, Hartog M. Plasma and lipoprotein lipids and apolipoproteins AI, AII, and B in patients with chronic airflow limitation. J R Soc Med. 1989; 82:91-2.