ORIGINAL PAPERS

Adv Clin Exp Med 2014, **23**, 5, 749–755
ISSN 1899–5276

Erdal Kaysoydu[1, A, B, D], Sulhattin Arslan[1, A, C, F, G], Gürsel Yildiz[2, A–C], Ferhan Candan[3, A, G]

Factors Related to Microalbuminuria in Patients with Chronic Obstructive Pulmonary Disease

[1] Department of Chest Disease, Faculty of Medicine, Cumhuriyet University, Turkey
[2] Department of Nephrology, Atatürk State Hospital, Turkey
[3] Department of Nephrology, Faculty of Medicine, Cumhuriyet University, Turkey

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Chronic obstructive pulmonary disease (COPD) is characterized by inhaled particles and gases inducing chronic inflammation of the airways accompanied by a not fully reversible airflow limitation. Systemic inflammation has an important role in the pathogenesis of COPD. In parallel, several comorbidites can be observed. Microalbuminuria is related to endothelial dysfunction. Microalbuminuria was increased in exacerbation periods of COPD.

Objectives. The aim of the study was evaluate to the presence of microalbuminuria (MA) in patients with chronic obstructive pulmonary disease (COPD) and its relationship to inflammation, arterial blood gas parameters and 24-hour ambulatory blood pressure alterations.

Material and Methods. Seventy COPD patients and 40 healthy volunteers were enrolled in the study. 24-h ambulatory blood pressure monitoring (ABPM) results, including pressure and pulse rates of the subjects were recorded and the cases were classified as "dipper" if a normal fall of more than 10% in blood pressure was observed at night and "non-dipper" if not. Routine renal function tests were performed, C-reactive protein (CRP) values were examined and urine samples were obtained to scrutinize the presence of MA. Patients were allocated into two groups, those with and without MA. The spirometry and arterial blood gas results of the patients were recorded.

Results. The urinary albumin creatinin ratio (64.8 ± 91.8), CRP (21 ± 14.8), nocturnal systolic and diastolic blood pressure (118 ± 14 and 72 ± 10), nocturnal and diurnal pulse (87 ± 17 and 90 ± 14), nocturnal pulse pressure (49 ± 11), mean pulse (89 ± 15), mean pulse pressure (48 ± 10) and the number of non-dipper subjects (65) were found significantly higher in the COPD group than in the control group (10.6 ± 6, 5.4 ± 2.4, 105 ± 6 and 68 ± 7, 70 ± 10 and 78 ± 11, 42 ± 1, 75± 11, 42 ± 7 and 5, respectively); ($p < 0.001$, < 0.001, < 0.001 and 0.041, < 0.001 a nd < 0.001, < 0.001, < 0.001, < 0.001 and < 0.001, respectively). Nocturnal pulse (89 ± 17) and CRP (23.5 ± 14.8) were found to be significantly higher in COPD patients with MA than in COPD patients without MA (78 ± 8 and 8.8 ± 6.3, respectively); ($p = 0.021$ and < 0.001, respectively).

Conclusions. The facts that CRP, a systemic inflammation marker, and mean nocturnal pulse pressure values were significantly higher in the group with MA among COPD patients, and that ambulatory blood pressure values did not differ between COPD patients with and without MA, suggest both a possible role of inflammation in MA development in COPD patients and a relationship between MA and increased heart rate (**Adv Clin Exp Med 2014, 23, 5, 749–755**).

Key words: COPD, arterial blood gas, inflammation, microalbuminuria, non-dipper.

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Airway obstruction is chronic and progressive [1–2].

Systemic inflammation has an important role in the pathogenesis of COPD. Circulating proinflammatory cytokines and C-reactive protein [CRP],

a derivative of these cytokines, are important markers of systemic inflammation [3–4].

Cardiovascular disease is a major cause of mortality in COPD, particularly in patients with mild to moderate severity [5]. Microalbuminuria (MA) is a sensitive marker of cardiovascular risk [6]. A recent study has shown an association between lower FEV1 and emphysema severity with endothelial dysfunction [7]. Microalbuminuria is considered to be related to endothelial dysfunction [8]. Microalbuminuria was observed to increase in exacerbation periods of COPD and this was suggested to be related with increased glomerular filtration and consequent protein leakage due to increased hypoxemia during COPD episodes [9–11].

Blood pressure (BP) normally changes with circadian rhythm. According to ambulatory blood pressure monitoring (ABPM) data, BP reaches the highest level in the morning, gradually declines during the day and stays at the lowest levels during the night [12]. In ABPM, a 10% or more decline in nocturnal blood pressure value compared to diurnal value was defined as "dipper" and a decline less than 10% was defined as "non-dipper" [13]. Cerebrovascular disease, left ventricle hypertrophy, cardiovascular mortality, morbidity and related renal disorders (MA, reduced creatinine clearance) were observed more frequently in non-dipper patients [14–16]. The absence of a normal fall in blood pressure during the night (non-dipping) has been examined previously in normotensive diabetic subjects and was found to be correlated with MA [17, 18]. As far as we know, non-dipping has not previously been studied in COPD patients with or without MA.

The aim of our study was to investigate the presence of MA in patients with COPD, which is a systemic inflammatory disease, and its relationship to inflammation, hypoxia and nocturnal blood pressure alterations.

Methods

Study Design and Patients

The approval of the local ethics committee was obtained before the study. A total of 110 individuals were enrolled in the study, including 70 who were diagnosed with COPD according to spirometry results and GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria 3 and who were treated at the Department of Pulmonology of our hospital, and 40 non-smoking healthy controls. The patients were in stage III or IV of COPD according to GOLD criteria and were receiving similar armamentarium of drugs for their disease. None of the patients were active smokers.

Exclusion criteria were as follows: history of hypertension, symptoms or diagnosis of sleep apnea, angina pectoris, myocardial infarction, ST-T alterations on electrocardiography suggestive for ischemic heart disease, left bundLe branch block, arrhythmia, obesity (body mass index > 30 kg/m^2), renal disease, hyperthermia, permanent posture disorder, diabetes mellitus/hyperglycemia, glucosuria, hematuria and urinary tract infection findings.

Data Collecting

Detailed medical histories and physical examination finding of all the patients were recorded.

Age, gender, BMI, history of smoking, CRP, blood urea nitrogen (BUN), creatinine (Cre), MA in spot urine, ABPM, arterial blood gases (ABG) and spirometry results of the patients and the control group were recorded. The measurements of the patients were performed while they were hospitalized and receiving appropriate treatment for COPD, including oxygen through nasal cannula (2 L/min). Blood samples were obtained for biochemical parameters (Beckman Coulter device) and CRP (with a nephelometric method using an Image device). Spot mid-stream urine was collected in the morning from the patients who had not done heavy exercise in the last 48 h. The levels of albumin and creatinine were studied from the urine specimens using an immunoturbidimetric method. A urine albumin/creatinine ratio (UACR) between 0–20 mg/g for men, 0–30 mg/g for women was accepted as normoalbuminuria and UACR > 20 mg/g for men and UACR > 30 mg/g for women was accepted as microalbuminuria.

COPD patients were allocated into 2 groups, those with and without MA. Oxygen administration was interrupted for 30 min before collecting arterial blood samples and 2 mL of blood was obtained from a radial artery into a heparinized injector when the oxygen percent of the inhaled oxygen (FiO_2) was 21% (at room air). Arterial blood gas analysis was done with a blood gas analyzer (Beckman Coulter device). Spirometric measurements were performed with a dry-type standard SensorMedics Vmax 20C spirometer (Viasys Healthcare, Missouri, USA). Ambulatory blood pressure monitoring was done using a Mobil-Q-Graph New Generation 24-h ABP-Control (I.E.M. GmbH, Staiberg, Germany) device in all cases included in the study. Measurements were done every 30 min during the day (06:00–21:59) and at night (22:00–05:59), and the results were recorded automatically. While a 10% or more reduction in blood pressure in the measurements done at night was accepted as dipper, 10% or less reduction was accepted as non-dipper.

Statistical Analysis

The data from our study was entered into a SPSS (Statistical Package for Social Sciences) 14.0 package program. For the assessment of the data, a significance test of the difference between two mean values in independent samples, a t-test and a Mann-Whitney *U* test were used. A chi-square test was used to investigate the inter-group differences for quantitative data. A p level of < 0.05 was accepted as statistically significant. The data is shown as mean ± standard deviation, number of individuals and percent.

Results

Forty-six (65.7%) of the patients and 23 (57.5%) of the control group were males. A significant difference was not detected between the patients and the control group in terms of age, gender and BMI. CRP value ($p < 0.001$) and mean MA value ($p < 0.001$) were found to be statistically significantly higher in COPD patients. Laboratory and demographic characteristics of the patients and the control group are given in Table 1. While a significant difference was not found between the demographic characteristics of the patients with and without MA, the mean CRP value was found to be significantly higher in patients with MA ($p < 0.001$) (Table 2). A statistically significant difference was not found between the patients with and without MA in terms of spirometric and ABG parameters (Table 3). The mean and daytime SBP and DBP values, other than the parameters of ABPM, were significantly higher in the COPD patients (Table 4). The comparison between the patients with and without MA is given in Table 5. The mean nocturnal pulse rate was found to be significantly higher in the patients with MA ($p = 0.021$).

Table 1. Demographic and laboratory characteristics of patients and the control group

Variables	Patient group (n = 70)	Control group (n = 40)	p
Gender (Male/Female n, %)	46 (65.7)/24 (34.3)	23 (57.5)/17 (42.5)	0.396**
Age (year)	64.1 ±7.2	62.0 ± 10.1	0.267
Non-smoker/history of smoking (n, %)	23 (32.9)/47 (67.1)	11 (27.5)/29 (72.5)	0.294**
BMI (kg/m^2)	27.7 ± 5.9	27.8 ± 4	0.450*
CRP (mg/L)	21 ± 14.8	5.4 ± 2.4	< 0.001*
BUN (mg/dL)	19.3 ± 7.5	17.7 ± 7.4	0.286*
Cre (mg/dL)	0.9 ± 0.2	1.0 ± 0.2	0.224*
UACR (mg/g)	64.8 ± 91.8	10.6 ± 6.2	< 0.001*

Data expressed as mean ± standard deviation and n, %. * Independent Samples t test, ** χ^2 test,
BMI – body mass index; BUN – blood urea nitrogen, Cre – creatinin; CRP – C-reactive protein; UACR – urinary albumin to creatinine ratio.

Table 2. Demographic and laboratory properties of patients with and without microalbuminuria

Variables	Microalbuminuria (+) (n = 58)	Microalbuminuria (–) (n = 12)	p
Gender Male/Female (n, %)	38 (82.6)/20 (83.3)	8 (17.4)/4 (16.7)	0.939**
Age (year)	63.7 ± 7.7	65.5 ± 4.5	0.657*
BMI (kg/m^2)	27.4 ± 6.1	25.4 ± 5.0	0.399*
Non-smoker/history of smoking (n, %)	19 (82.6)/39 (83)	4 (17.4)/8 (17)	0.969**
CRP (mg/L)	23.5 ± 14.8	8.8 ± 6.3	< 0.001*
BUN (mg/dL)	19.2 ± 7.5	19.3 ± 8	0.994*
Cre (mg/dL)	0.9 ± 0.3	0.9 ± 0.2	0.819*

Data expressed as mean ± standard deviation and n, %. * Mann-Whitney *U* test, ** χ^2 test,
BMI – body mass index; BUN – blood urea nitrogen; CRP – C-reactive protein; Cre – creatinine; MA – microalbuminuria.

Table 3. Pulmonary function tests and arterial blood gas parameters of patients with and without microalbuminuria

Variables	Microalbuminuria (+) (n = 58)	Microalbuminuria (–) (n = 12)	p
FEV_1 (L)	0.9 ± 0.4	0.9 ± 0.6	0.657*
FVC (L)	1.6 ± 0.8	1.71 ± 0.6	0.726*
FEV_1/FVC	53.1 ± 13.4	53.1 ± 12.7	0.895*
Respiratory failure, (n, %)	41 (70.7)	7 (58.3)	0.401**
$PaCO_2$ (mm Hg)	43.4 ± 9.2	40.9 ± 6.3	0.399*
PaO_2 (mm Hg)	54.8 ± 9.1	56.6 ± 10	0.601*
SaO_2 (%)	86.8 ± 5.5	87.4 ± 6	0.845*
HCO_3 (mmol/L)	27.6 ± 5.1	25.6 ± 3.9	0.189*

Data expressed as mean ± standard deviation and n, %. * Mann-Whitney *U* test, ** χ^2 test,
ABG – arterial blood gas analysis; FEV1 – forced expiratory volume in one second; FVC – forced vital capacity; HCO_3 – bicarbonate; PaO_2 – partial arterial oxygen pressure; $PaCO_2$ – partial arterial carbon dioxide pressure; SaO_2 – arterial oxygen saturation.

Table 4. Hemodynamic parameters in the patient and control groups

Variables	Patient group (n = 70)	Control group (n = 40)	p
Systolic blood pressure (mm Hg)	117 ± 17	114 ± 8	0.283*
Diastolic blood pressure (mm Hg)	73 ± 8	71 ± 6	0.221*
Heart rate (beat/min)	89 ± 15	75 ± 11	< 0.001*
Pulse pressure (mm Hg)	48 ± 10	42 ± 7	< 0.001*
Daytime systolic blood pressure (mm Hg)	120 ± 13	119 ± 7	0.286*
Daytime diastolic blood pressure (mm Hg)	74 ± 8	72 ± 8	0.388*
Daytime heart rate (beat/min)	90 ± 14	78 ± 11	< 0.001*
Daytime pulse pressure (mm Hg)	48 ± 10	42 ± 7	0.003*
Nocturnal systolic blood pressure (mm Hg)	118 ± 14	105 ± 6	< 0.001*
Nocturnal diastolic blood pressure (mm Hg)	72 ± 10	68 ± 7	0.041*
Nocturnal heart rate (beat/min)	87 ± 17	70 ± 10	< 0.001*
Nocturnal pulse pressure (mm Hg)	49 ± 11	42 ± 1	< 0.001*
Nondipper/Dipper (n, %)	65 (92.9)/5 (7.1)	5 (12.5)/35 (87.5)	< 0.001**

Data expressed as mean ± standard deviation and n, %. * Independent Samples *t* Test, ** χ^2 test.

Discussion

COPD is a multi-component disease in which structural and functional changes are seen in the lungs and extrapulmonary organs [19]. Therefore, systemic involvement in COPD patients should certainly be considered. Some of the few studies investigating the relationship between gender and MA in COPD showed a higher frequency of MA in males, some found the opposite, and some found no difference in terms of gender [19, 20]. In our study, we did not find a significant relationship between MA and gender.

A significant relationship was also not detected between MA and age in most of the studies [9, 20]. Mean age in our study was similar to that in the mentioned studies and a significant relationship was not found between age and MA.

It has been suggested that MA could be high in smokers due to endothelial dysfunction secondary to increased hypoxic stimulation in endothelial cells [21]. Some studies have detected a significant relationship between smoking history and MA in COPD patients while another showed no such relationship [11, 16]. In our study, a significant relationship was not found between MA and a history

Table 5. Hemodynamic parameters of patients with and without microalbuminuria

Variables	Microalbuminuria (+) (n = 58)	Microalbuminuria (–) (n = 12)	p
Systolic blood pressure (mm Hg)	117 ±18	116± 13	0.353*
Diastolic blood pressure (mm Hg)	73 ± 8	3 ± 7	0.853*
Heart rate (beat/min)	90 ± 15	82 ± 8	0.103*
Pulse pressure (mm Hg)	48 ± 9	46 ± 11	0.433*
Daytime systolic blood pressure (mm Hg)	120 ± 13	120 ± 14	0.767*
Daytime diastolic blood pressure (mm Hg)	73 ± 8	76 ± 8	0.404*
Daytime heart rate (beat/min)	91 ± 15	86 ± 9	0.378*
Daytime pulse pressure (mm Hg)	48 ± 10	45 ± 10	0.308*
Nocturnal systolic blood pressure (mm Hg)	118 ± 14	114 ± 15	0.296*
Nocturnal diastolic blood pressure (mm Hg)	72 ± 9	73 ± 11	0.925*
Nocturnal heart rate (beat/min)	89 ± 17	78 ± 8	0.021*
Nocturnal pulse pressure (mm Hg)	49 ± 10	49 ± 14	0.908*
Nondipper/Dipper (n, %)	54 (83.1)/4 (16.9)	11 (80)/1 (20)	0.860**

Data expressed as mean ± standard deviation and n, %. * Mann-Whitney *U* Test, ** χ^2 test.

of smoking. BMI decreases in severe COPD patients. Mortality and morbidity increase in the cases where BMI decreases, the patients are elderly and especially hypoxic [22]. While a relationship was detected between urinary albumin excretion rate and obesity in a limited number of studies carried out in COPD patients and in the general population, a significant relationship could not be found in some other studies as in ours [20, 21, 23, 24]. CRP is an acute phase protein synthesized in response to tissue injury and/or inflammation. In previous studies, it was thought that MA could be related to CRP, which is an inflammatory marker of endothelial dysfunction [5, 21, 23, 25, 26]. In the study by Stuveling et al. that was carried out with a study group without hypertension and diabetes and that investigated whether CRP changed the relationship between blood pressure and microalbuminuria, a significant relationship was detected between MA and CRP and it was concluded that MA elevation was correlated with inflammation [21]. In our study, MA level was found significantly higher in the patient group in which CRP was high. We detected a relationship between elevated MA level and elevated CRP indicating inflammation. In previous studies, patients with COPD and MA were reported to be more hypoxemic and hypercapnic [27, 28]. It is known that COPD is associated with increased atrial natriuretic peptide release and increased glomerular size, facilitating glomerular filtration and ultimately protein leakage [9]. While Komurcuoglu et al. found a negative correlation between MA detected in COPD patients and PaO_2 and SaO_2 levels, they did not detect a significant relationship between MA and pH and $PaCO_2$ levels. In that study, they suggested that the reason for MA development could be increased glomerular filtration due to increased hypoxemia and consequently developing protein leakage [9]. In a recent study, patients with COPD and MA were found to be more hypoxemic and hypercapnic compared to those with only MA, PaO2 was found to be lower in the COPD group and a significant relationship was found between MA level and PaO2 and PaCO2 [20]. As a result of this study, the relationship between MA and hypoxia was suggested to be possibly related to endothelial dysfunction in COPD. It was suggested that the number of endothelial cells increases secondarily to hypoxic stimulation, leading to V/P disproportion [28]. Nonetheless, it was stated that not all subjects with hypoxemia developed MA and other, possibly genetic, factors were suggested [20].

A significant relationship was not found between MA elevation and FEV1, FVC, FEV1/FVC in the studies investigating the relationship between pulmonary functions and MA in COPD patients [9, 20]. As a result of these studies, it was concluded that MA is not related to the degree of airway obstruction. Similarly in our study, a significant difference was not found between MA and spirometric parameters. MA was not previously

studied in COPD patients without hypertension. Most of the studies reported that MA frequency was greater in hypertensive cases whose ABPM pattern was non-dipper [21, 29, 30]. In those studies, the likelihood of MA among the subjects with increased mean arterial pressure was found to be higher in those with higher CRP levels and this finding was suggested to be related to endothelial dysfunction secondary to inflammation. A significant relationship was also detected between elevated pulse pressure and MA in the studies investigating the relationship between MA and blood pressure [31–33]. In a study carried out with hypertensive patients who did not receive antihypertensive treatment, an increased MA ratio was shown to be related to elevated nocturnal systolic, nocturnal diastolic and mean diastolic blood pressures [32]. Clinical studies have indicated that resting tachycardia and bradycardia were associated with increased cardiovascular disease risk. It was suggested that a resting heart rate increase was more closely associated with mortality than a decreased heart rate. There are a limited number of studies investigating the relationship between MA and blood pressure values in COPD patients. Of them, in the study by Casanova et al., a relationship was found only between MA and systolic blood pressure [20]. In our study, a significant difference was not found between MA and ABPM in terms of both dipper/non-dipper classification and other parameters of ABPM. Most of the studies were carried out with hypertensive patients whereas hypertension was not present in the patients or control group in our study. In addition, increased nocturnal heart rate and CRP levels in patients with MA supported the opinion that MA and impaired heart rate variability could arise from inflammation leading to endothelial dysfunction as suggested in some of the studies. In our study, including normotensive COPD patients, lack of an examination for pulmonary hypertension may be considered a limitation.

In conclusion, the urinary albumin creatinin ratio was found significantly higher in the COPD patient than in the control group. Increased CRP level and nocturnal heart rate in MA with COPD patients, ABPM parameters such as mean daytime and nocturnal heart rate, pulse pressure, nocturnal systolic and diastolic blood pressure and nondipper pattern were higher in the patient group compared to the control group.

In view of the fact that there was a significantly higher CRP level and nocturnal heart rate in MA patients with COPD, this situation suggests inflammation and inflammation-induced endothelial dysfunction may be associated with MA development in COPD. Possible causative relations between these parameters warrant further research.

References

[1] The Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2013), the Pocket Guide (updated 2013). Available at: http://www.goldcopd.org.

[2] **Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, Paré PD:** The nature of small airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004, 350, 2645–2653.

[3] **Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG:** Creactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007, 175, 250–255.

[4] **de Torres JP, Cordoba-Lanus E, López-Aguilar C, Muros de Fuentes M, Montejo de Garcini A, Aguirre-Jaime A, Celli BR, Casanova C:** C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. Eur Respir J 2006, 27, 902–907.

[5] **Sin DD, Anthonisen NR, Soriano JB, Agusti AG:** Mortality in COPD: role of comorbidities. Eur Respir J 2006, 28, 1245–1257.

[6] **Diercks GF, Van Boven AJ, Hillege JL, de Jong PE, Rouleau JL, van Gilst WH:** The importance of microalbuminuria as a cardiovascular risk indicator: a review. Can J Cardiol 2002, 18, 525–535.

[7] **Barr RG, Mesia-Vela S, Austin JH, Basner RC, Keller BM, Reeves AP, Shimbo D, Stevenson L:** Impaired flow-mediated dilation is associated with low pulmonary function and emphysema in ex-smokers: the Emphysema and Cancer Action Project (EMCAP) Study. Am J Respir Crit Care Med 2007, 15, 176, 1200–1207.

[8] **Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y:** Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients. Hypertension 2005, 45, 198–202.

[9] **Komurcuoglu A, Kalenci S, Kalenci D, Komurcuoglu B, Tibet G:** Microalbuminuria in chronic obstructive pulmonary disease. Monaldi Arch Chest Dis 2003, 59, 269–272.

[10] **Cogo A, Ciaccia A, Legorini C, Grimaldi A, Milani G:** Proteinuria in COPD patients with and without respiratory failure. Chest 2003, 123, 652–653.

[11] **Polatli M, Cakir A, Cildag O, Bolaman AZ, Yenisey C, Yenicerioglu Y:** Microalbuminuria, von Willebrand factor and fibrinogen levels as markers of the severity in COPD exacerbation. J Thromb Thrombolysis 2008, 26, 97–102.

[12] **Seo WS, Oh HS:** The circadian rhythms of blood pressure and heart rate in the hypertensive subjects: dippers and non-dippers. Yonsei Med J 2002, 43, 320–328.

[13] **Fujii T, Uzu T, Nishimura M, Takeji M, Kuroda S, Nakamura S, Inenaga T, Kimura G:** Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertension. Am J Kidney Dis 1999, 33, 29–35.
[14] **Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Satoh H, Hisamichi S:** Relation between nocturnal decline in blood pressure and mortality. The Ohasama Study. Am J Hypertens 1997, 10, 1201–1207.
[15] **Fagard RH, Van Den Broeke C, De Cort P:** Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. J Hum Hypertens 2005, 19, 801–807.
[16] **Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y:** Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. Hypertension 2006, 47, 149–154.
[17] **Equiluz-Bruck S, Schnack C, Kopp HP, Scherntaner G:** Nondipping of nocturnal blood pressure is related to urinary albumin excretion rate in patients with type 2 diabetes mellitus. Am J Hypertens 1996, 9, 1139–1143.
[18] **Inaba M, Negishi K, Takahashi M, Serizawa N, Maruno Y, Takahashi K, Katayama S:** Increased night:day blood pressure ratio in microalbuminuric normotensive NIDDM patients. Diabetes Res Clin Pract 1998, 40, 161–166.
[19] **Agusti AG:** COPD, a multicomponent disease: implications for management. Respir Med 2005, 99, 670–682.
[20] **Casanova C, de Torres JP, Navarro J, Aguirre-Jaíme A, Toledo P, Cordoba E, Baz R, Celli BR:** Microalbuminuria and hypoxemia in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010, 182, 1004–1010.
[21] **Stuveling EM, Bakker SJ, Hillege HL, Burgerhof JG, de Jong PE, Gans RO, de Zeeuw D; PREVEND Study Group:** C reactive protein modifies the relationship between blood pressure and microalbuminuria. Hypertension 2004, 43, 791–796.
[22] **Phelps DT, Ferro TJ, Higgins PJ, Shankar R, Parker DM, Johnson A:** TNF-alpha induces peroxynitrite-mediated depletion of lung endothelial glutathione via protein kinase C. Am J Physiol 1995, 269, 551–559.
[23] **Forsblom CM, Groop PH, Ekstrand A, Tötterman KJ, Sane T, Saloranta C, Groop L:** Predictors of progression from normoalbuminuria to microalbuminuria in NIDDM. Diabetes Care 1998, 21,1932–1938.
[24] **Thoenes M, Reil JC, Khan BV, Bramlage P, Volpe M, Kirch W, Böhm M:** Abdominal obesity is associated with microalbuminuria and an elevated cardiovascular risk profile in patients with hypertension. Vasc Health Risk Manag 2009, 5, 577–585.
[25] **Lieb W, Mayer B, Stritzke J, Doering A, Hense HW, Loewel H, Erdmann J, Schunkert H:** Association of low-grade urinary albumin excretion with left ventricular hypertrophy in the general population: the MONICA/KORA Augsburg Echocardiographic Substudy. Nephrol Dial Transplant 2006, 21, 2780–2787.
[26] **Arnlöv J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS:** Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation 2005, 112, 969–975.
[27] **Stewart AG, Bardsley PA, Baudouin SV, Waterhouse JC, Thompson JS, Morice AH, Howard P:** Changes in atrial natriuretic peptide concentrations during intravenous saline infusion in hypoxic cor pulmonale. Thorax 1991, 46, 829–834.
[28] **Peinado VI, Pizarro S, Barbera JA:** Pulmonary vascular involvement in COPD. Chest 2008, 134, 808–814.
[29] **Stamm AM, Meinerz G, Silva JC:** Systemic hypertension and microalbuminuria. Arq Bras Cardiol 2007, 89, 415–420.
[30] **Deferrari G, Pontremoli R:** Microalbuminuria, hypertension and cardiovascular risk. Cardiologia 1994, 39, 159–162.
[31] **Farasat SM, Valdes C, Shetty V, Muller DC, Egan JM, Metter EJ, Ferrucci L, Najjar SS:** Is longitudinal pulse pressure a better predictor of 24-hour urinary albumin excretion than other indices of blood pressure? Hypertension 2010, 55, 415–421.
[32] **Wang Y, Hu Y, Li Y, Li H, Chu S, Zhu D, Gao P:** Association of renal function with the ambulatory arterial stiffness index and pulse pressure in hypertensive patients. Hypertens Res 2012, 35, 201–206.
[33] **Kozan O, Ozcan EE, Sancaktar O, Kabakcı G:** The prevalence of microalbuminuria and relevant cardiovascular risk factors in Turkish hypertensive patients. Arch Turk Soc Cardiol 2011, 39, 635–645.

Address for correspondence:

Gürsel Yildiz
Department of Nephrology
Atatürk State Hospital
Zonguldak
Turkey
Tel: + 90 372 400 01 83
E-mail: drgursel@yahoo.com

Conflict of interest: None declared

Received: 11.03.2013
Revised: 16.02.2014
Accepted: 17.09.2014