Association between chronic obstructive pulmonary disease and chronic kidney disease in vascular surgery patients

Yvette R. M. van Gestel1, Michel Chonchol2, Sanne E. Hoeks1, Gijs M. J. M. Welten3, Henk Stam4, Frans W. Mertens4, Ron T. van Domburg5 and Don Poldermans3

1Department of Anaesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands, 2Division of Renal Diseases and Hypertension, University of Colorado Denver Health Sciences Center, Aurora, CO, USA, 3Department of Vascular Surgery, 4Department of Pulmonology and 5Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence and offprint requests to: Don Poldermans; E-mail: d.poldermans@erasmusmc.nl

Abstract

Background. Chronic obstructive pulmonary disease (COPD) is recognized as a source of systemic inflammation and is associated with the development of cardiovascular disease. However, little is known about the association between COPD and chronic kidney disease (CKD). Therefore, we investigated the relationship between COPD and CKD and the association between COPD and mortality in patients with CKD.

Methods. We conducted a cohort study of 3358 vascular surgery patients between 1990 and 2006. CKD was defined according to the Modification of Diet in Renal Disease equation as an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m². In addition, the patients were divided into three categories based on the baseline estimated GFR: ≥ 90 mL/min/1.73 m²; 60–89 mL/min/1.73 m² and < 60 mL/min/1.73 m². Multivariable logistic regression analysis was used to evaluate the independent association between prevalent COPD and CKD.

Results. The prevalence of COPD was inversely related to kidney function. COPD was present in 47, 38 and 32% of patients with an estimated GFR < 60, 60–89 and ≥ 90 mL/min/1.73 m², respectively. COPD was independently associated with CKD (OR 1.22; 95% CI 1.03–1.44; P = 0.03). This association was strongest in patients with moderate COPD (OR 1.33; 95% CI 1.07–1.65; P = 0.01). Both moderate and severe COPD were associated with increased long-term mortality in patients with CKD (HR 1.27; 95% CI 1.03–1.56; P = 0.03 and HR 1.61; 95% CI 1.10–2.35; P = 0.01, respectively), compared to patients without COPD.

Conclusions. Our findings indicate that COPD is moderately associated with CKD in a large cohort of vascular surgery patients. In addition, moderate and severe COPD are related to increased long-term mortality in patients with CKD.

Keywords: chronic kidney disease; chronic obstructive pulmonary disease; vascular surgery

Introduction

Chronic kidney disease (CKD) is a growing public health problem and affects a large number of individuals, ~13% of the US adult population [1]. This is mainly due to the increased prevalence of traditional cardiovascular risk factors such as diabetes, hypertension and obesity [1,2]. In addition, the presence of cardiovascular disease is also important in the development and deterioration of kidney disease [3]. Previous studies have found underlying atherosclerosis, an inflammatory process [4], to be associated with the pathogenesis of kidney disease [5,6]. Hence, the relationship between cardiovascular disease and kidney function could also be due to an increased prevalence of other less well-examined cardiovascular risk factors, such as chronic obstructive pulmonary disease (COPD).

As with kidney disease, COPD is a major health care problem worldwide and is associated with cardiovascular disease as well. COPD is characterized by an abnormal inflammatory response of the lungs to noxious particles and gases [7]. However, the inflammation is not only restricted to the lungs but also extends systemically. Previous studies showed that this systemic inflammation might be the missing link between COPD and the development and progression of atherosclerosis and cardiovascular disease [8]. Consequently, given that a number of investigators [9–11] have shown that COPD is associated with cardiovascular disease in people with normal kidney function, it seems reasonable to propose that COPD in patients with vascular disease may also be associated with CKD independent of other covariates that might influence kidney function loss. Therefore, we investigated the relationship between COPD and CKD in a large cohort of vascular surgery patients with peripheral arterial disease. Moreover, we assessed the association between COPD and mortality in patients with kidney disease.
Methods

Study population
The study included 3358 patients of an original cohort of 3371 patients who underwent elective vascular surgery (abdominal aortic surgery (AAA), carotid endarterectomy (CEA) or lower limb arterial reconstruction procedures (LLR)) between January 1990 and December 2006 in the Erasmus Medical Center, Rotterdam, The Netherlands.

Exposures and outcomes
The primary exposure variable was a diagnosis of COPD at baseline. This diagnosis was based on a post-bronchodilator pulmonary function test, which was performed by 82% of the patients with a clinical diagnosis of COPD at baseline. Those participants without a pulmonary function test were given a clinical diagnosis of COPD according to a history of cough, dyspnkea, sputum production and their pulmonary medication use. The severity of COPD was categorized according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria using the forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio and the percentage of the predicted FEV1 [7]. This approach is suggested by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [12]. Further details of our study design have been previously described [13].

The primary outcome variable was CKD. Serum creatinine was assessed in approximately all patients (n = 3358, 99.6%) who were included in the analysis. CKD was defined as estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m² using the equation of the Modification of Diet in Renal Disease (MDRD) [14]: 186.3 × (serum creatinine−1.154 × (age−0.203) × 0.742 (if female). Serum creatinine was measured in mg/dL, age in years and estimated GFR was expressed as mL/min/1.73 m². This cutoff was chosen on the basis of the National Kidney Foundation’s (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [15]. In addition, patients were divided into three categories based on the baseline estimated GFR: ≥90 mL/min/1.73 m²; 60–89 mL/min/1.73 m² and <60 mL/min/1.73 m².

Secondary end points included short-term (within 30 days after surgery) and long-term (within 10 years after surgery) mortality. Survival status was complete in 96% of all patients and ascertained from the municipal civil registry. The median follow-up was 5 years (interquartile range 2.0–9.1 years).

Other variables
In all patients, we recorded the following cardiovascular risk factors: age, gender, hypertension (defined as a blood pressure ≥140/90 mmHg), diabetes mellitus (presence of fasting blood glucose of ≥140 mg/dL or treatment with insulin or oral hypoglycaemic agents), hypercholesterolaemia (total cholesterol of ≥200 mg/dL) and current smoking status. The patients’ cardiovascular history was assessed including ischaemic heart disease (previous myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention and/or angina pectoris), heart failure (defined according to the New York Heart Association classification) and stroke and/or transient ischaemic attack.

Statistical analysis
The baseline characteristics between the patients with and without CKD are described as means ± SD and percentages. Continuous variables were compared using Student’s t-test and dichotomous variables using chi-square tests. Univariable and multivariable logistic regression analyses were used to investigate the association between COPD and kidney disease. In addition, logistic regression analysis was used to examine the relationships between COPD and short-term mortality in a subgroup analysis including only patients with CKD (estimated GFR <60 mL/min/1.73 m²). Furthermore, Cox regression analysis was used to investigate this association during a 10-year period. In the multivariable analysis, adjustments were made for age, gender, type surgery, current smoking, previous heart failure, hypertension, diabetes and hypercholesterolaemia. The final variables were chosen on the basis of biological plausibility. Odds ratios (ORs) and hazard ratios (HR) are provided with their 95% confidence intervals (CI). Testing was two-sided and P-values <0.05 were considered statistically significant. Data were analysed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

Baseline characteristics
The characteristics of the 3358 patients are presented in Table 1 based on the presence or the absence of CKD. The mean serum creatinine concentration and estimated GFR in this population were 1.22 ± 1.15 mg/dL and 76 ± 30 mL/min/1.73 m², respectively. In total, 918 (27%) patients had CKD defined by an estimated GFR <60 mL/min/1.73 m² (mean estimated GFR 43 ± 15 mL/min/1.73 m²) (Table 1). Patients with CKD were older, were more likely to be female and had significantly higher proportions of hypertension, diabetes, COPD and cardiovascular disease. Importantly, CKD patients were less likely to be smokers and had a lower proportion of hypercholesterolaemia. COPD was present in 1307 (39%) patients.

In addition to the 918 patients with an estimated GFR <60 mL/min/1.73 m², 1500 and 940 patients had an estimated GFR level of 60–89 and ≥90 mL/min/1.73 m², respectively. The distribution of the prevalence of COPD according to kidney function is presented in Figure 1. Across decreasing estimated GFR groups 32%, 38% and 47% had COPD (P < 0.001).

Cross-sectional relationship between COPD and CKD
Table 2 shows that COPD was associated with a higher risk of prevalent CKD. After adjustment for age, gender, type of surgery, current smoking, previous heart failure, hypertension, diabetes and hypercholesterolaemia, patients with COPD had increased odds of CKD (adjusted OR 1.22 95% CI: 1.03–1.44; P = 0.03). This relationship was further explored by examining the association between COPD severity and CKD. A borderline significant relationship was observed for mild COPD while moderate COPD was independently associated with kidney disease (OR 1.23; 95% CI 0.99–1.53; P = 0.06 and OR 1.33; 95% CI 1.07–1.65; P = 0.01, respectively). No significant association was found between severe COPD and kidney disease (OR 0.80; 95% CI 0.54–1.20; P = 0.29) (Table 2).

Short- and long-term outcome in patients with CKD
In total, 178 (5%) patients died within 30 days after surgery and 80 (9%) of those with CKD. No relationship between COPD and short-term mortality was observed in patients with CKD (adjusted OR 0.94 95% CI: 0.58–1.54; P = 0.82). During 10 years of follow-up, 1555 (46%) patients died. COPD was associated with a higher risk of long-term mortality (Table 3). After adjustments for demographics, type of surgery, current smoking, previous heart failure, hypertension, diabetes and hypercholesterolaemia, moderate and severe COPD remained significantly associated with all-cause mortality in patients with CKD (HR 1.27; 95% CI 1.03–1.56; P = 0.03 and HR 1.61; 95% CI 1.10–2.35; P = 0.01, respectively).

Discussion
To date, several risk factors have been identified for the development and progression of CKD, e.g. older age,
hypertension, diabetes, body mass index and cigarette smoking [16]. However, to our knowledge, the relationship between COPD and kidney disease as assessed in this study has not been previously reported. We demonstrate that the presence of COPD is moderately associated with CKD. Tobacco smoking plays an important role in both the development and progression of COPD and kidney disease [17]. However, the association between COPD and CKD persisted even after adjusting for smoking status. In addition, moderate and severe COPD were found to be independently associated with an increased risk of long-term mortality in patients with peripheral arterial disease and CKD.

COPD is generally recognized as a cause of systemic inflammation [18]. Pro-inflammatory cytokines, especially tumour necrosis factor-alpha (TNF-α), play an important role in the disease process [19,20]. This systemic inflammatory state in patients with COPD is associated with the increased risk of cardiac injury [8]. In addition to pulmonary inflammation, several other parts of the body are affected resulting in muscle wasting, weight loss, diabetes, osteoporosis and importantly atherosclerosis [19,20]. A recent study by Iwamoto and colleagues found airflow limitation to be associated with increased mean carotid intima-media thickness in smokers compared to control smokers and never-smokers [21]. This suggests that airflow limitation, instead of smoking status, is independently related to subclinical atherosclerosis. Subsequently, atherosclerosis might affect the vasculature in the kidneys leading to kidney dysfunction. So the systemic inflammation seen in patients with COPD might explain the associations observed in our study. Moreover, it has been previously demonstrated that increased inflammation levels are present...
in patients with kidney dysfunction. The Cardiovascular Health Study found kidney dysfunction to be independently associated with elevated levels of high-sensitivity C-reactive protein (hsCRP), fibrinogen and interleukin-6 in participants of 65 years and older [22]. This might suggest that the inflammatory response observed in patients with kidney disease might be exacerbated by concomitant COPD.

Another possible explanation of our findings might be pulmonary hypertension secondary to COPD, which has been associated with the progression of kidney disease. Patients with COPD have severe retention of salt and water, reduction in renal blood flow and glomerular filtration and neurohormonal activation [23]. However, as our study was not designed to examine the mechanisms responsible for the association between COPD and kidney disease, further studies are needed to elucidate the rationale behind these relationships.

The fact that we did not find severe COPD associated with kidney disease might be explained by the following: first, only those patients who underwent vascular surgery were included in our study, so it might be possible that surgery was cancelled in those patients with a poor pulmonary function. Moreover, cardiovascular disease and cancer are major comorbidities in patients with COPD, with the inflammatory state as a possible link. These comorbidities are the leading causes of death in patients with mild and moderate COPD, while in those with severe COPD respiratory failure is the predominant cause [24]. So it might be suggested that patients with severe COPD died because of their respiratory failure before they could develop kidney disease.

Given that early stages of impaired kidney function are associated with increased risk of death, cardiovascular events and hospitalization [25], it is important to identify and consequently treat these patients to improve prognosis. Adequate treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARB) is required in those patients to slow the progression of kidney disease. In addition, a recent meta-analysis of randomized controlled trials demonstrated that statin therapy significantly reduces lipid concentrations and cardiovascular end points in patients with prevalent cardiac disease and CKD [26]. Therefore, an important aspect of the treatment of patients with kidney disease is to control the underlying cause and management of cardiovascular risk factors.

Hence, the observed association between moderate and severe COPD and increased long-term mortality in patients with CKD advocates the importance of the optimal management of COPD in patients with kidney disease as well.

Our study has some limitations as seen with retrospective studies. Unfortunately, we do not have any information on patients who were declined for surgery because of their pulmonary or kidney function that might explain the absence of a relationship between patients with severe COPD and kidney disease. Data on markers of inflammation were not available. Hence, the proposed mechanism that inflammation might be the underlying link between COPD and CKD could not be examined. In addition, due to the cross-sectional design of the study, the results need to be interpreted cautiously. As both pulmonary and kidney functions are assessed at one time point, it is difficult to infer causality as the sequence of COPD and kidney disease could not be ascertained. Consequently, the results of our study need to be interpreted cautiously. Finally, only 5% of the cohort had advanced kidney disease (i.e. estimated GFR ≤30 mL/min/1.73 m²). Hence, the prevalence of COPD in this group of patients could not be examined.

In summary, mainly moderate COPD was found to be associated with kidney disease in vascular surgery patients with peripheral arterial disease. Furthermore, advanced stages of COPD are associated with increased long-term mortality in patients with kidney disease. The presence of COPD might be responsible for the progression of atherosclerosis inducing further kidney disease. Further experimental and longitudinal studies are necessary to elucidate the role of COPD in the pathway by which kidney disease contributes to an increased risk of death.

Conflict of interest statement. None declared.

References
Glomerular filtration rate is related to carotid intima–media thickness in middle-aged adults

Helena Kastarinen, Olavi Ukkola and Y. Antero Kesäniemi

Institute of Clinical Medicine, Department of Internal Medicine and Biocenter Oulu, University of Oulu and Clinical Research Center, Oulu University Hospital, Oulu, Finland

Correspondence and offprint requests to: Helena Kastarinen; E-mail: helena.kastarinen@oulu.fi

Abstract

Background. Severe renal dysfunction is associated with increased cardiovascular risk. The aim of this study was to investigate the association between renal function and carotid intima–media thickness (cIMT) in a middle-aged population-based cohort.

Methods. A total of 247 males and 258 females aged 40–62 years participated in this cross-sectional study. Renal function was assessed with estimated glomerular filtration rate (eGFR) and carotid atherosclerosis with ultrasonography as the mean IMT of the far carotid wall.

Results. The mean eGFR values were 90.2 (SD 16.8) ml/min/1.73 m² for men and 78.0 (SD 14.0) ml/min/1.73 m² for women. There was a significant correlation between cIMT and eGFR. The mean cIMT was 0.84 ± 0.14 mm for men and 0.78 ± 0.14 mm for women. The mean cIMT for men with eGFR < 60 ml/min/1.73 m² was 0.90 ± 0.14 mm and for women it was 0.83 ± 0.14 mm.

Conclusion. The study indicates that renal dysfunction is associated with increased cardiovascular risk.