THE ROLE OF ALTERNATIVE MARKERS IN THE DIAGNOSIS OF CHRONIC KIDNEY DISEASE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Elena Bolotova¹, Anna Dudnikova²

¹First Department of Therapy, Kuban State Medical University of the Ministry of Healthcare of the Russian Federation,
²Regional Clinical Hospital No 2 of the Ministry of Healthcare of the Krasnodar region, Russian Federation

ABSTRACT

INTRODUCTION: It is considered that the main comorbid diseases in chronic obstructive pulmonary disease (COPD) are cardiovascular disease, osteoporosis, anxiety and depressive illness. However, there are few reports of chronic kidney disease (CKD) as a comorbidity of COPD.

MATERIALS AND METHODS: The study included 198 patients with a diagnosis of COPD. The patients were divided into four groups according to the degree of COPD severity. In all the patients, calculation of glomerular filtration rate (GFR) based on formulas of CKD-EPI with serum creatinine and serum cystatin C was performed.

RESULTS: GFR calculation by creatinine showed that the frequency of individuals with normal GFR>90 ml/min/1.73 m² was significantly higher than that of cystatin C (48% versus 12.6%, \(\chi^2=52.97, p<0.05\)). For the group of patients with decreased GFR in the range of 59–45 ml/min/1.73 m², there were opposite results: the frequency of patients with calculation of GFR by cystatin C (34.3% versus 1%, \(\chi^2=48.87, p<0.05\)) was significantly higher. Similar data were obtained comparing the methods in groups with GFR of 44–30 ml/min/1.73 m² (12.1% versus 0%, \(\chi^2=28.97, p<0.05\)) and GFR of 29-15 ml/min/1.73 m² (5.0 versus 0%, \(\chi^2=5.13, p<0.05\)). In the interval from the reduced GFR of 89–60 ml/min/1.73 m² there was no significant difference between these methods used (51% versus 35.8%, \(\chi^2=2.95, p>0.05\)).

CONCLUSION: Systemic effects of COPD induce the development of protein-energy malnutrition and muscle loss. A close relationship between creatinine and muscle tissue condition lowers the creatinine level and results in overestimation of the real GFR and underdiagnosis of CKD in these patients. Scr Sci Med. 2017;49(4):47-52

Keywords: CKD, COPD, creatinine, muscle dysfunction, cystatin C

INTRODUCTION

In recent decades, chronic kidney disease (CKD) is in the spotlight not only among nephrologists, but also of physicians of other specialties. The patients with diabetes mellitus (DM), arterial hypertension (AH), primary renal disease and older people are considered high-risk CKD groups (1). However, in recent years, there is evidence of the development of renal dysfunction among patients with chronic obstructive pulmonary disease (COPD). It can be explained by the accumulation and cumula-
tive effects of risk factors for CKD in these patients, on the one hand, and by the influence of the systemic manifestations of COPD on renal function, on the other hand (2-4). Currently, the magnitude of glomerular filtration rate (GFR) is widely used in the diagnosis of CKD using serum creatinine values. However, the creatinine concentration may not serve as an ideal marker of kidney function as it depends on many factors, and, in particular, on muscle status (5). Therefore, given the high incidence of muscular dystrophy among COPD patients the standard formula for calculating GFR based on serum creatinine may be insufficiently informative (6). In this connection, the search for alternative markers is extremely important, i.e., for markers that do not depend on the state of the muscular tissues, for the timely diagnosis of renal dysfunction in COPD patients.

The aim of our study was to evaluate the frequency of CKD in COPD patients based on standard and alternative laboratory markers.

**MATERIALS AND METHODS**

The study included 198 patients of Regional Clinical Hospital No 2 with a diagnosis of COPD (69.6% of men at a mean age of 65.9±10.8 years and average length of illness of 17.2±2.2 years, and 30.3% of women at a mean age of 62.1±6.9 years and average length of disease of 8.7±2.1 years) as well as 28 healthy age- and sex-matched volunteers. COPD diagnosis was made in accordance with Report GOLD recommendations of 2014 (7). Assessment of respiratory function was carried out on EasyOne Pro spirograph of Ultrasound Spirometry Lab (Switzerland).

The patients were divided into four groups: groups A and B - non-exacerbators (0-1 events per year) and groups C and D - exacerbators (≥2 events per year). Groups A and C presented with mild symptoms (CAT <10 points; mMRC 0-1) and groups B and D did with severe ones (CAT ≥10; mMRC ≥2), according to the Report GOLD recommendations of 2014 (7). In accordance with the recommendations of experts in any patients, GFR calculation was performed on the basis of formulas CKD-EPI: CKD-EPIcreat - based on serum creatinine (2009) and CKD-EPIcyst - based on serum cystatin C (2012) (8).

Serum cystatin level was determined by immuno-turbidimetric method (Cystatin C-FS, DiaSys, Germany), and creatinine one estimation was based on Jaffe reaction. Laboratory tests were performed on AU640 automatic clinical chemistry analyzer in Fresenius Medical Care Kuban centralized laboratory of LLC. Besides body mass index (BMI) was calculated for all the patients. In order to study body composition, namely muscle, a bio-impedance body composition analysis (BIA) was carried out by means of ABC-01 ‘Medass’ device (Russia). The indicator of skeletal muscle mass (SMM) (in %) was used for the analysis of the nutritional and muscular tissue status.

The study was performed in accordance with the standards of good clinical practice and the principles of Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of Kuban State Medical University (Protocol of Meeting No 32 from October 21, 2014). All the patients signed written informed consent prior to entering the study.

Statistical data processing was performed by the methods of variation statistics using the package of statistical program Statistica 10.0 for Windows. The significance of differences between two average values of the normal distribution was performed using Student’s t-test, as in case of deviation from normal, Mann-Whitney criterion was applied. To assess the statistical significance of differences between two or more relative indicators, $\chi^2$ criterion was made use of. The difference was considered significant at a level of $p<0.05$. Data were presented as mean±SD.

**RESULTS**

General patients’ characteristics are presented in Table 1.

The average creatinine levels amounted to 1.15±0.02 mg/dL in the control group, slightly higher than the corresponding figures for COPD patients of 0.93±0.03. However, this difference was not statistically significant ($p>0.05$). Thus, increased creatinine levels (≥1.2 mg/dL for men and >1.0 mg/dL for women) were observed in 16 COPD patients (in 8.1% of the cases), while lower ones (<0.5 mg/dL for men and <0.3 mg/dL for women) were found in in 23 COPD patients (in 11.6% of the cases). Control group of individuals with reduced creatinine levels was not identified. Using a linear Pearson correlation coefficient, a medium-strength correlation between BMI and creatinine (r=0.242, $p<0.05$) as well as between SMM percentage and creatinine (r=0.504, $p<0.05$) was established. No significant correlation between BMI
Table 1. Clinical and laboratory findings of COPD patients (n=198) and healthy volunteers (n=28)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Infrequent exacerbations (0-1/year)</th>
<th>Frequent exacerbations (≥2/year)</th>
<th>Control group, n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A n=36</td>
<td>B n=54</td>
<td>C n=66</td>
<td>D n=42</td>
</tr>
<tr>
<td>CAT-test, scores</td>
<td>&lt;10</td>
<td>≥10</td>
<td>&lt;10</td>
<td>≥10</td>
</tr>
<tr>
<td>mMRS, scores</td>
<td>0-1</td>
<td>≥2</td>
<td>0-1</td>
<td>≥2</td>
</tr>
<tr>
<td>Age, years</td>
<td>59.1±2.6</td>
<td>63.6±4.1</td>
<td>65.7±7.6</td>
<td>64.2±5.9</td>
</tr>
<tr>
<td>Smoker index, packs-years</td>
<td>18.6±2.3</td>
<td>21.6±4.7</td>
<td>33.4±5.1</td>
<td>34.2±3.9</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>67.3±8.5</td>
<td>66.3±6.3</td>
<td>44.1±4.6</td>
<td>33.4±5.7*</td>
</tr>
<tr>
<td>COPD duration, years</td>
<td>7.9±3.6</td>
<td>10.1±3.4</td>
<td>10.8±4.7</td>
<td>11.8±5.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.8±5.3</td>
<td>26.7±7.4</td>
<td>25.6±5.2</td>
<td>23.2±5.1</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.8±0.06</td>
<td>0.9±0.06</td>
<td>0.7±0.04</td>
<td>0.7±0.01</td>
</tr>
<tr>
<td>Cystatin C, mg/l</td>
<td>0.7±0.03</td>
<td>1.1±0.2</td>
<td>1.3±0.1</td>
<td>1.5±0.3**</td>
</tr>
<tr>
<td>GFRcreat, ml/min/1.73 m²</td>
<td>84.5±2.3</td>
<td>85.4±3.9</td>
<td>89.7±6.1</td>
<td>90.6±5.9</td>
</tr>
<tr>
<td>GFRcyst, ml/min/1.73 m²</td>
<td>79.9±3.9</td>
<td>77.1±5.6</td>
<td>69.6±7.8</td>
<td>60.2±5.7</td>
</tr>
<tr>
<td>SMM, %</td>
<td>52.6±7.8</td>
<td>46.6±6.8</td>
<td>39.6±7.3</td>
<td>36.7±5.4</td>
</tr>
</tbody>
</table>

*p<0.05 reliability of differences between control group and group A  
**p<0.05 reliability of differences between groups A and D

and SMM for cystatin C was found out (p>0.05). Cystatin C average levels in the control group amounted to 0.79±0.07 mg/L, which was lower than the same parameter for COPD patients amounting to 1.31±0.2 mg/L. However, these differences were not statistically significant (p>0.05). There were significant differences when comparing cystatin C average levels between group A and group D (p<0.05).

The average GFRcreat levels in the control group were 90.5±9.5 ml/min/1.73 m², which was comparable to GFRcreat level in COPD patients, where its value was 89.4±5.7 ml/min/1.73 m². Normal GFR levels of >90 ml/min/1.73 m² were found out in 95 COPD patients (in 48.0% of the cases), there was a slight GFR decrease of 89-60 ml/min/1.73 m² in 101 COPD patients (in 51.0% of the cases), and a moderate GFR decrease of 59-45 ml/min/1.73 m² - in two COPD patients (in 1.0% of the cases). A more pronounced GFR decrease was not revealed at all (Fig. 1).

The average GFRcyst levels in the control group amounted to 102.1±10.5 ml/min/1.73 m², being higher for similar data among COPD patients at 63.5±8.7 ml/min/1.73 m². No reliability of differences could be achieved (p>0.05). GFR calculation by cystatin C showed the following results: the levels were normal (GFR>90 ml/min/1.73 m²) in 25 COPD patients (in 12.6% of the cases), there was a slight GFR decrease of 89-60 ml/min/1.73 m² in 71 COPD patients (in 35.8% of the cases), a moderate GFR decrease of 59-45 ml/min/1.73 m² in 68 COPD patients (in 34.3% of the cases), a significant GFR reduction of 44-30 ml/min/1.73 m² - in 24 COPD patients (in 12.1% of the cases), as well as a sharp GFR decline of 29-15 ml/min/1.73 m² - in 8 COPD patients (in 5.0% of the cases) (Fig. 1).

Fig. 1. The frequency of reduced GFR in the calculation of cystatin C and creatinine

The comparison of the data obtained for the $\chi^2$-criterion demonstrated that with GFR calculation by creatinine, the percentage of individuals with normal GFR>90 ml/min/1.73 m² was significantly higher than that by cystatin C (48% versus 12.6% for creat-
inine and cystatin C, respectively, $\chi^2=52.97$, $p<0.05$). For the group of patients with decreased GFR in the range between 59 and 45 mL/min/1.73 m², there were opposite results: the percentage of patients with GFR calculation by cystatin C was significantly higher (34.3% versus 1% for cystatin C and creatinine, respectively, $\chi^2=48.87$, $p<0.05$). Similar data were obtained when comparing the methods in the groups with GFR of 44-30 mL/min/1.73 m² (12.1% versus 0% for cystatin C and creatinine, respectively, $\chi^2=28.97$, $p<0.05$) and with GFR of 29-15 mL/min/1.73 m² (5.0% versus 0% for cystatin C and creatinine, respectively, $\chi^2=5.13$, $p<0.05$). In the interval of a slight estimated GFR (eGFR) decline of 89-60 mL/min/1.73 m², there was no statistically significant difference between the two methods (51% versus 35.8% for creatinine and cystatin C, respectively, $\chi^2=2.95$, $p>0.05$).

In the group of healthy volunteers, there was a significant difference between the methods concerning eGFR of 89-60 mL/min/1.73 m² (17.8% versus 14.2% creatine and cystatin C, respectively, $\chi^2=0.13$, $p>0.05$). The rest of the volunteers presented with GFR >90 mL/min/1.73 m². For further analysis of the frequency and characteristics of renal dysfunction in COPD patients, we have chosen the method of calculation of GFR by cystatin C, as it doesn’t depend on the magnitude of muscle mass, which is important for patients with this pathology.

Based on reducing GFRcyst <60 mL/min/1.73 m² that is the basis for CKD diagnosis even without imaging methods and the presence or absence of proteinuria, CKD diagnosis is made in 88 COPD patients (in 44.4% of the cases). In this case, CKD incidence rate was significantly higher in groups C and D (13.6% in group C and 18.8% in group D versus 4% in group A and 8.0% in group B, $\chi^2=21.12$, $p<0.05$). In addition, in the group with common exacerbations of CKD at III-IV stage, these events were significantly more frequent (in 6.5% in group C and 9.2% in group D versus in 0% in group A and 1.5% in group B; $\chi^2=22.21$, $p<0.05$) (Fig. 2).

**DISCUSSION**

Our study showed a low informative value of creatinine in CKD diagnosis in COPD patients. This is demonstrated by the high frequency of serum creatinine level reduction (11.6%), the close correlation between BMI, SMM and creatinine, and the comparable average GFRcreat levels between the control group and the examination one. This low informative creatinine value is explainable by the fact that it is, in fact, a byproduct of muscle metabolism completely depending on the amount of muscle tissue. In addition, it is capable of being displayed due to extrarenal mechanisms, tubular secretion and elimination in the intestine (6). Under the influence of systemic inflammation in COPD patients, muscle dysfunction often develops up to ‘pulmonary cachexia’, so the use of formulas to calculate GFR in this group of patients leads to CKD underdiagnosis (9). In this context, cystatin C usage is optimal as it is a low-molecular weight protein freely filtered through the glomerular membrane. It is not affected by tubular secretion and metabolized exclusively in the kidney (10). In addition, it is distinguished from creatinine as a marker of renal dysfunction by a constant rate of synthesis and excretion, depending only on renal function, without influence of age and anthropometric indicators (10). The data about the frequency reduction at GFRcyst <60 mL/min/1.73 m² amounting to 51.4% are comparable to results of similar recent studies. Yoshizawa et al. (3) examined 108 COPD patients with a similar index based on GFRcyst of 53%.

In this study, low informative value of creatinine use for CKD diagnosis in COPD patients was also shown, however, analysis of the impact of the frequency of exacerbations on the development of renal dysfunction in this group of patients was not carried out.

The results of several similar studies using GFRcreat showed a lower frequency of renal dysfunction. In the study of Incalzi et al. (11), CKD incidence in COPD patients was 22.2%. In this case like in our present study, a high proportion of ‘hid-
den CKD in COPD patients was identified, i.e. persons with normal creatinine, but reduced GFRcreat (11). Not all studies include the underestimation of true GFR calculated according to creatinine. In a recent study involving patients with DM, the difference in frequency was not significant (16.5% versus 22% for creatinine and cystatin C, respectively) (12). This confirmed the role of muscle dysfunction evolving under the action of the system of COPD occurrence, as a result, creatinine level of these patients was underestimated (6,9).

In our study, the effect of COPD exacerbations on the incidence and severity of renal dysfunction was found out. It is understandable that this aggravation is manifested by increased levels of inflammatory mediators in combination with the deterioration of respiratory parameters, the exacerbation of the imbalance of ventilation-perfusion ratio leading to severe hypoxemia and increased systemic COPD manifestations (13). Obviously, recurrent exacerbations are extreme not only in relation to underlying disease forecast, but also for renal dysfunction development. In a 11-year study, the influence of inflammation and hypoxia in COPD patients on kidney function with CKD was demonstrated (14). This study showed that COPD patients were at risk for developing CKD by 1.6 times higher than the general population. According to other authors (15,16), hypoxia, hypercapnia, vascular stiffness and administration of nephrotoxic drugs play a role in the pathophysiology of renal dysfunction in COPD patients.

Systemic effects of COPD induce the development of protein-energy malnutrition and muscle loss. A close relationship between creatinine and muscle tissue status lowers creatinine level, and results in overestimation of the real GFR and underdiagnosis of CKD in these patients where calculations based on creatinine are used. In this respect, we need to monitor kidney function with alternative markers that do not depend on muscular tissue status, such as cystatin C.

CONCLUSIONS

1. Our data demonstrate a high CKD frequency in COPD patients, reaching up to 51.4%.
2. The use of formulas using the serum creatinine leads to CKD underdiagnosis in COPD patients because of its high dependence on muscular tissue status.
3. The application of GFR calculation based on serum cystatin C is preferable in COPD patients, because of the fact that cystatin does not depend on muscular tissue status and anthropometric indices as well.
4. The impact of exacerbations on the incidence and degree of GFR reduction in COPD patients was revealed.

Conflict of interests

The authors declare that they have no conflict of interests.

REFERENCES


