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Managing patients with chronic kidney disease and cardiovascular comorbidities in primary care

Kudina E.V., Larina V.N., Sheregova E.N.

Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, Russia.

Authors:

Ekaterina V. Kudina *, M.D., associate professor, Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, Russia.

Vera N. Larina, M.D., professor, Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, Russia.

Elena N. Sheregova, M.D., assistant professor, Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, Russia.

Abstract

This paper discusses the ambulatory care approaches to patients with co-existing chronic kidney disease (CKD) and cardiovascular disease (CVD). We provide diagnostic algorithm and evaluation principles in this group of patients. We demonstrate our stage-based treatment approach and principles of prevention on the example of a long-term management of an actual patient with arterial hypertension, atrial fibrillation and CKD. We also discuss nephroprotective and cardioprotective regimens and anticoagulation for the prevention of disease progression.

Key words: *atrial fibrillation, comorbidities, chronic kidney disease, polycystic kidney disease, nephroprotection, albuminuria, cardiorenal syndrome*

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Introduction

Chronic kidney disease (CKD) is a serious medical, social and economic challenge in health care due to the growing prevalence worldwide and close association with chronic disease development, primarily, cardiovascular diseases that lead to worsening of life

* Corresponding author. Tel. +7-916-821-46-34. E-mail: e-kudina@mail.ru

quality, increased mortality and need for dialysis in the majority of patients [1].

Currently the pathogenesis of cardiac and kidney remodeling and early biomarkers of kidney damage and CKD progression are being actively studied. Early biomarkers of kidney damage and CKD progression include NGAL (Neutrophil Gelatinase-Associated Lipocalin), kidney injury molecule-1, liver fatty acid binding protein, fibroblast growth factor 23 and Klotho [2, 3, 4]. Kidney and cardiac remodeling is caused by myofibroblast development and angiofibrogenesis, which is, in turn, is induced by angiotensin II, transforming growth factor beta 1, plasminogen activator inhibitor-1, vascular endothelial growth factor, matrix metalloproteinase and other factors that cause structural and functional changes and heart and kidney fibrosis in CKD patients [5].

The prevalence of CKD varies from 7% to 12.5% according to a number of different sources [6–9]. The National Guidelines "Chronic Kidney Disease: screening, diagnosis, prevention and management" state that CKD is as highly prevalent as hypertension (HTN), diabetes mellitus (DM), obesity and metabolic syndrome [6, 10, 11]. As for 2019, around 30 thousand individuals have stage V CKD and are treated with renal replacement therapy and up to 20 million people have stage I–IV CKD. Moreover, up to 60 million people are currently at risk of CKD. These are the patients with DM, HTN, obesity and heart failure (HF) [12, 13].

CKD risk factors

In order to identify the patients who are at high risk of CKD, the primary physician should be well aware of CKD risk factors [8].

Individuals with coexistent chronic diseases, that affect kidneys such as HTN, DM, congestive heart failure (CHF), connective tissue diseases are at the highest risk of CKD. Clinical guidelines in endocrinology, cardiology and rheumatology recommend routine control of creatinine level.

Moreover, CKD risk increases with age. Individuals over 50 years of age are at high risk of CKD development.

Another group of patients with high risk of CKD development are individuals with harmful exogenous effects on kidneys, such as:

a. Nephrotoxic medications and nutritional supplements, such as nonsteroidal anti-inflammatory drugs (NSAIDs);

b. Occupational hazards (organic solvents, heavy metals, insecticides, etc.)

c. Diets too low or high in protein, such as sport diet.

Patients with a history of acute kidney injury are also at high risk of CKD.

CKD and other chronic non-communicable diseases

CKD not only worsens the patient's prognosis and quality of life but also influences other co-existent chronic diseases and may cause their progression. The high prevalence of both CKD and cardiovascular disease (CVD) in the population led to the introduction of the term "cardiorenal syndrome" [14]. The common mechanisms of these diseases like chronic systemic inflammation and endothelial dysfunction cause the development and progression of cardiovascular and renal dysfunction. Furthermore, kidney disease cause anemia, volume overload and calcium and phosphate metabolic disorders that negatively affect CVD [11, 15]. All patients with stage I and II CKD and A2-A3 albuminuria or with stage III CKD are at a very high cardiovascular risk [6, 9].

According to the PREVEND study, albuminuria, which is one of the CKD markers, is an independent risk factor of CVD mortality [3]. CKD also plays an important role is the development of left ventricle diastolic dysfunction in patients with congestive heart failure (CHF) [16].

The ARIC (Atherosclerosis Riskin Communities Study) study showed that the incidence of cardiovascular complications is twice as high in patients with stage III–IV CKD compared with stage II CKD [17].

Arterial hypertension, which is one of the most prevalent chronic noncommunicable diseases, is also closely connected with CKD. The multicenter, observational study CHRONOGRAPH analyzed 1600 patients with HTN. Of those, CKD markers (decreased glomerular filtration rate (GFR)< 60 ml/min/1.73 m^2 and/or urine albumin/creatinine ratio> 30 mg/g) were identified in 49.4% [18].

One of the most important problems in daily clinical practice is a combination of CKD and atrial fibrillation (AF). Both diseases are highly prevalent, especially in older patients. Around 15–20% of CKD patients have one of the forms of AF [19–20].

The connection between these two diseases can be explained by the pathogenesis of their development — atherosclerosis, chronic inflammation, hypertension, diabetes, obesity. CKD is also an important predictor of atrial fibrillation (AF) relapse after catheter ablation in patients with unstable AF [19]. It is crucial to detect CKD in AF patients, determine its stage and monitor its development, because the worsening of

kidney function affects pharmacodynamics of the most drugs. CKD stage determines the possibility to use the renin-angiotensin-aldosterone system (RAAS) blockers and the dosing of anticoagulants.

Along with CVD, DM is an important cause of CKD. According to the Russian National DM registry (2013–2016), CKD is highly prevalent in this group of individuals. At the same time, the majority of patients with DM had stage I and II CKD, meaning that most care provides follow DM guidelines and diagnose DM early due to annual RFG and albuminuria control [22].

Timely diagnosis and appropriate management of CKD in elderly patients are important goals of outpatient care. Being over the age of 50 is an unmodifiable CKD risk factor and most elderly patients have multiple comorbidities, in particular, HTN, atherosclerosis and DM that increase the risk of kidney damage. Uncontrolled NSAIDs use is another major reason of CKD development in this group of patients [23].

CKD diagnosis

CKD is diagnosed based on the following criteria [11]:

- Laboratory changes over the past 3 months;
- Histological changes in the kidney;
- Structural changes seen in visualization;
- History of kidney transplantation.

As such, the presence of structural changes (nephrolithiasis, multiple cysts, hydronephrosis, etc.), renal disease based on the laboratory changes (pyelonephritis), histological changes on biopsy (glomerulonephritis) or persistent signs of renal dysfunction verify the diagnosis of CKD. The markers of renal dysfunction include:

- Albuminuria (⩾ 30 mg/24 h)
- Albumin/creatinine ratio⩾ 30 mg/g (⩾3 mg/mmol)
- GFR<60 ml/min/1,73 m^2.

Screening of high-risk patients is crucial for prompt diagnosis of CKD at early stages, when preventive measures are most effective. Besides from blood creatinine and GFR, albuminuria is another essential marker for CKD.

In routine outpatient care the presence of excessive protein in urine is assessed with urine dipstick test strips but this diagnostic tool can determine only major proteinuria. In case of severe proteinuria, the level of albuminuria can be determined in the single portion of urine. Albuminuria test is a simple and highly sensitive method that can be used to identify CKD early and, therefore, should be used as a screening tool [5, 16]. It can be used in the following cases:

- Qualitative test is positive;
- Patient is at high risk of CKD;
- Patient has stage I–III CKD but no evident proteinuria.

In patients with CKD, the screening frequency is determined by disease severity and rate of progression. According to the European guidelines on CKD, GFR and albuminuria should be evaluated at least once a year. More frequent control of GFR and albuminuria is recommended in patients at high risk of disease progression and/or when these test results are needed to guide management [25].

Russian clinical guidelines provide the frequency of patient evaluation depending on the GFR and the presence of proteinuria [2]. Evaluation frequency is presented in Table 1.

Table 1. **Evaluation frequency of patients with CKD**

Evaluation frequency	CKD stage
Annually	C1–2, A0-A2
Every 6 months	C 1–2 A3 C 3A-3B A0-A3
Every 3 months	C 4 A0-A2
Every 6 weeks	C 4 A4, C 5

The frequency can be corrected depending on the disease progression rate, presence of co-existent diseases, etc. In case of the secondary CKD, management decisions should be based on existent clinical guidelines on the specific disease, like HTN or systemic diseases [7].

Prevention of CKD progression

Multiple studies have shown that various renoprotective measures slow the rate of the decline in GFR in patients with CKD. These measures include:

- Reaching blood pressure goals;
- Proteinuria reduction;
- Uric acid level reduction;
- Hypercalcemia and hyperphosphatemia management;
- Normalization of hemoglobin level.

Hypertension and proteinuria management with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) improve the prognosis in patients CKD [26]. This is due to the fact that proteinuria is common in early stages of CKD; HTN is usually a cause of kidney dysfunction or accompanies it. Anemia and disturbances in calcium and phosphate homeostasis are usually present in the later stages of CKD, when preventive measures are no more crucial. Therefore, early use of nephropro-

tective agents can improve patient prognosis [18]. It is still unknown if renin-angiotensin-aldosterone system (RAAS) inhibitors are beneficial in patients with stage VI–V CKD. According to the European guidelines on CKD, there is no need to stop these medications if GFR declines to≤ 30 ml/min as they still provide nephroprotection [25]. At the same time, Russian clinical guidelines state that in elderly patients with the late-stage renal disease there is an increased risk of GFR decline and hyperkalemia [23]. Therefore, each case of further ACEIs/ARBs use should be decided individually based on the changes in biochemical markers of kidney function.

Normalization of lipid levels is another important nephroprotective measure. Statins are usually used but the higher the CKD stage is, the lower their effectiveness becomes. Early lipid lowering therapy provides the best prophylactic effect. In stages VI–V, statins do not provide significant improvement in mortality or risk of CVD development [10].

Although these protective measures have proven to be effective, target lipid levels and blood pressure levels are still rarely reached. According to the 2001–2010 NHANES study, blood pressure levels≤130/80 mmHg and low-density lipoprotein (LDL) levels< 100 mg/dl were attained only in 19.5% of cases [8]. Therefore, for effective CKD prevention, clinicians have to follow the specific algorithm.

1. Identify patients at high CKD risk.

2. Regularly evaluate albuminuria and plasma creatinine and calculate GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and also perform urinalysis with albumin/creatinine ratio measurement.

3. The stage of CKD and albuminuria level should be included when indicating the final diagnosis.

4. In patients with HTN, blood pressure goals should be attained with antihypertensive therapy. A required component of this therapy is either an ACEi or an ARB in case of ACEi intolerance. In most cases, antihypertensive therapy should combine several medications including dihydropyridine calcium channel blockers.

5. All patients with stage III CKD independently of the presence of HTN, should receive ACEIs (ARBs) in order to decrease proteinuria. ACEIs (ARBs) should also be given to patients with stage I–II CKD and albuminuria> 30 mg/24 h. In patients with stage VI–V CKD, ACEIs (ARBS) should be cancelled in case of decreasing GFR. ACEIs (ARBs) have similar effects on the level of proteinuria and CKD progression. BRAs cause less side effects such as dry cough, angioedema and hyperkalemia. Some BRAs, however, have some specific features. For instance, only losartan reduces serum uric acid levels and that makes it a preferred choice in patients with HTN and hyperuricemia. Moreover, telmisartan reduces lipoprotein and triglyceride levels and irbesartan is the only ARB that was proven to be effective in all CKD stages [12].

6. The stage of CKD and the presence of other co-existent disease should be taken into account when calculating the cardiovascular risk and lipid goals. Statins should be used if lipid levels are high.

7. Dietary recommendations should be developed based on the patient's specific characteristics such as the stage of CKD, body mass index (BMI) and blood pressure level. The optimal daily salt and protein amount should be determined.

These are some dietary recommendations for patients with CKD:

- Limit the amount of salt to<5 g per day;
- Limit the amount of daily protein depending on the CKD stage: 1.0–1.2 g/kg in CKD stage I–II, 0.6–0.9 g/kg in CKD stage III, 0.3–0.6 g/kg in CKD stage IV.

Multiple studies suggest that limiting protein intake slows the progression of CKD. Low protein diet reduces proteinuria, improves renal perfusion and purine metabolism and increases the efficacy of antihypertensive treatment and corrects hyperkalemia and hyperphosphatemia. On the other hand, low protein diet has some negative effects as well — it leads to the development of protein-energy malnutrition, and, therefore, the diet should be picked based on the CKD etiology and co-existent diseases.

8. It is important to evaluate all the medications that the patient might be taking for other co-existent diseases and to exclude the nephrotoxic drugs. In patients with CKD, preference should be given to medications that are eliminated not only by the kidneys.

Clinical case

In order to illustrate the clinical effectiveness of nephroprotective therapy in a patient with co-existent cardiovascular (AH and AF) diseases and CKD we would like to present a clinical case.

Patient K., 78 y.o. The patient has been visiting our clinic for regular follow ups since 2005. She first came to the clinic due to a history of uncontrolled hypertension (200–210/110–120 mmHg). Before that the patient was regularly seen in another ambulatory clinic. Her medical problems include coronary artery disease (CAD), stable atrial fibrillation (AF),

stage III HTN. Her calculated cardiovascular risk is very high. She also had cerebrovascular disease and had a stroke in 2001. The patient was regularly taking enalapril (20 mg twice daily), nifedipine (20 mg twice daily), bisoprolol (5 mg/daily), acetylsalicylic acid (100 mg/daily). Complete blood count and urinalysis were normal. 24-hour urine collection revealed proteinuria — 250 mg/24 hour. The ECG showed fibrillation and diffuse left ventricular hypertrophy. Lipid panel: total cholesterol 7.8 mmol/l, LDL cholesterol 4.5 mmol/l. Other labs included creatinine 98.7 μmol/l, uric acid 243 μmol/l, iron 17.8 μmol/l, potassium 4.3 mmol/l. Chest x-ray showed no abnormalities. Echocardiography: moderate left atrial dilation, left ventricular hypertrophy, ejection fraction 61%. Renal ultrasound: left kidney 14.2×7.8 cm, right kidney 14.5×7.0 cm., multiple anechogenic round and oval structures, up to 4.1×3.5 cm in both kidneys.

The patient didn't recall if renal ultrasound was ever performed before. Nothing was indicated in the patient's medical records.

As such, according to the results of all tests, we diagnosed the patient with stage 3aA2 CKD, polycystic kidney disease, stage III hypertension, CAD, stable AF, and cerebrovascular disease. She also had a stroke in 2001. We started pharmacologic treatment with perindopril, amlodipine, hydrochlorothiazide, bisoprolol, atorvastatin and warfarin. However, blood pressure goals (130/90 mmHg) weren't attained, and we decided to start a fixed-dose combination of valsartan, amlodipine and hydrochlorothiazide. Target blood pressure level was reached and stabilized at 130–140/80 mmHg. We also managed to reach target total cholesterol and LDL levels in this patient. The patient continued to have stable disease for 11 years. Elevations in blood pressure were rare and were successfully managed by captopril (25 mg). Blood tests were performed twice per year and lipid and creatinine levels were stable. Stable disease in this patient with significant multimorbidity (CAD, AF, history of stroke, stage III HTN, stage 3aA2 CKD) indicates high efficacy of renoprotective therapy. In 2017, at the age of 75 y.o., the patient started to feel fatigued and short of breath after usual activities. Evaluation showed creatinine 215 μmol/l, urea 15.9 mmol/l, potassium 5.6 mmol/l, uric acid 508. Nephrologist was consulted. Due to the CKD progression to stage C4, it was decided to stop valsartan and hydrochlorothiazide. After these medications were cancelled, blood pressure increased and a third additional antihypertensive agent without negative effects on kidneys was added. Although torasimide and moxonidine were both the potential choices, we decided to stop on moxonidine (2 μg) as the patient had no edema and significant CHF symptoms and was reluctant to take diuretics. Moxonidine is an imidazoline receptor agonist in the medulla and doesn't have proven renoprotective activity but it also doesn't have negative on renal function. Some studies suggest that moxonidine decreases sympathetic activity and therefore has some renoprotective effect. Minoxidine is also well-tolerated in elderly patients [27]. As such, it is possible to use it in patients with CKD if there is a need for a tighter blood pressure control.

We also added allopurinol (100 mg) to reduce plasma uric acid levels. Although the prognostic effect of allopurinol on CKD progression prevention is still unknown, positive prognostic effect on normalizing uric acid levels in CKD was shown empirically [17].

We recommended diet low in protein and potassium. Considering that the patient's BMI was in normal range (22 kg/m^2) and she had normal carbohydrate metabolism, we didn't recommend the reduction in fat and carbohydrates in order to satisfy the patient's energy needs. In 2019 the patient was hospitalized for an episode of hemoptysis. She was diagnosed with mild community-acquired pneumonia and received appropriate treatment. Fibrobronchoscopy was performed and showed no pathological findings. The patient recovered and was discharged. Later, she refused to take warfarin because of the hemoptysis episode and was started on apixaban. As such, currently the patient is taking amlodipine 10 mg, minoxidil 2 μg, bisoprolol 5 mg, apixaban 5 mg, atorvastatin 20 mg, allopurinol 100 mg. The patient is stable. In 2019 her laboratory findings were: creatinine 175 μmol/l, uric acid 243 μmol/l. Liver function enzymes were normal throughout all observation period. In 2019 hemoglobin decreased to 108 g/l which corresponds to mild anemia. Serum iron level is normal and anemia treatment was no indicated.

This patient's strong treatment adherence played the major role in the CKD progression slowing. It was achieved by regular follow-ups, patient education and patient's trust. The patient has multiple significant comorbidities and nevertheless she had good quality of life. She lives unassisted and performs all her household chores. Moreover, she has an energy consuming hobby — she enjoys gardening. She works in the garden several hours a day from April to October, watering and planting flowers, pulling out weeds.

Still having the ability to enjoy the activities she likes significantly improves her quality of life.

The patient has two 42-year-old twin daughters. They were evaluated and both were found to have polycystic kidney disease, stage I hypertension and dyslipidemia. Both were educated on their disease, the importance of regular follow-ups and on the renoprotective therapy principles. We provided dietary counselling and explained the need of optimizing their physical activity in detail, determined the right dosages of perindopril and atorvastatin, target blood pressure and lipid levels.

Polycystic kidney disease (PKD) is a genetically determined pathological process that is associated with the formation and progression of multiple kidney cysts that are formed from the tubules and collecting ducts. There are two main types of polycystic kidney disease: autosomal dominant PKD and autosomal recessive PKD.

ADPKD is one of the most common kidney genetic disorder the average prevalence of which is about 1 in 400–1000 newborns.

ARPKD is less prevalent and is diagnosed in 1 in 10000–20000 newborns. PKD causes around 8–10% of all end-stage renal disease that require renal replacement therapy. It is the fourth leading cause of kidney failure after diabetic nephropathy, chronic glomerulonephritis and arterial hypertension.

Currently a number of new treatment approaches that could slow PKD progression is being developed. Tolvaptan, a V2 receptor antagonist, is one of the most promising of them. In two small studies (CRISP — The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; n=202; observation period — 11 years and MDRD — Modification of Diet in Renal Disease) tolvaptan successfully slowed the cyst development and GFR reduction. Moreover, some preliminary trials showed that somatostatin and its analogs as well as mTOR (mammaliantargetofrapamycin — one of the signal pathways that mediates the control of cell growth and proliferation and the protection from apoptosis) inhibitors can also be beneficial in patients with PKD [28, 29].

The case that we presented illustrates two main aspects of primary care physician's work. Firstly, individual approach to each patient based on the latest clinical guidelines should be used. It is also important to provide constant patient education, develop dietary modifications and choose the most appropriate amount of physical activity. Secondly, patients at high risk such as the relatives of patients with CKD should be evaluated for the early signs of kidney dysfunction in order to start preventive measures in advance.

Conclusion

In ambulatory care, patients with chronic kidney disease and co-existent CVD should be managed by a multidisciplinary team that includes a nephrologist and an endocrinologist, cardiologist or rheumatologist depending on underlying disease. Still, the primary care physician should take the leading role in managing these patients. Therefore, the primary practitioner should be well familiar with the assessment algorithm, the principles of dietary modification and stage-wise pharmacologic treatment approaches. The correct choice of medications is also crucial in a comorbid patient. Agents with proven cardio- and nephroprotective effects should be preferred and the dosing should be adjusted according to the kidney function. The primary care provides are responsible for improving the patient's adherence to treatment. Another important component of primary care is screening of individuals at high risk of kidney disease.

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