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Chronic kidney disease in the elderly

Przewlekła choroba nerek w wieku podeszłym

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S u m m a r y

Chronic kidney disease (CKD) is defined by the reduction of glomerular filtration rate (GFR) to less than 60 mL/min/1.73 m^2 and/or presence of markers of kidney damage such as albuminuria, glomerular- or tubular-based hematuria, abnormal renal imaging and pathologic abnormalities, present for at least 3 months, irrespective of cause. The definition of CKD does not adequately separate the disease from normal renal aging. The formulas used to calculate GFR and to recognize CKD have not been validated in the elderly population and may misclassify many healthy older individuals as having CKD. Traditional formulas based on measurements of serum creatinine concentration are unreliable in the elderly people, particularly those with sarcopenia and multiple co-morbidities. A more accurate marker to reliably assess renal function in the elderly seems to be serum cystatin C concentration, that is not dependent on muscle mass and is only slightly affected by age and gender.

Appropriate treatment applied in patients with CKD allows them to benefit from slower loss of kidney function, better control of metabolic disturbances, lower risk of cardiovascular events as well as extends possibilities of informed choice of renal replacement therapy.

S t r e s z c z e n i e

Przewlekła choroba nerek (PChN) rozpoznawana jest w przypadku stwierdzenia obniżonego przesączania kłębuszkowego (GFR) poniżej 60 ml/min/1,73 m^2 i/lub obecności markerów uszkodzenia nerek, takich jak albuminuria, krwinkomocz pochodzenia kłębuszkowego lub cewkowego oraz nieprawidłowości budowy nerek widoczne w badaniach obrazowych lub histopatologicznych, utrzymujące się przez co najmniej 3 miesiące, niezależnie od ich przyczyny. Definicja PChN nie różnicuje jednoznacznie choroby i fizjologicznego procesu starzenia się nerek. Wzory wykorzystywane do obliczania GFR i rozpoznawania PChN nie zostały dotychczas zweryfikowane w populacji osób starszych i mogą mylnie klasyfikować wiele zdrowych osób w podeszłym wieku jako pacjentów z PChN. Tradycyjne wzory oparte o pomiary stężenia kreatyniny w surowicy krwi są niewiarygodne u osób starszych, szczególnie u pacjentów z sarkopenią i licznymi chorobami współistniejącymi. Bardziej wiarygodnym wskaźnikiem czynności nerek w tej grupie wiekowej wydaje się być stężenie cystatyny C w surowicy krwi, które nie jest zależne od masy mięśniowej i w niewielkim stopniu modyfikowane jest przez wiek oraz płeć.

Właściwa terapia stosowana u pacjentów z PChN pozwala uzyskać spowolnienie pogarszania się funkcji nerek, lepszą kontrolę zaburzeń metabolicznych, zmniejszenie ryzyka wystąpienia powikłań sercowo-naczyniowych, a także poszerza możliwości świadomego wyboru terapii nerkozastępczej.

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INTRODUCTION

People in developed countries live for many years after their retirement age. It is expected that by the year 2030 the number of persons aged ≥ 65 years will account for approximately 1/3 of the global population in Europe (1). It has been known for decades that kidney function declines after 40 years of age at a rate of approximately 1% per year (2). Glomerular filtration rate (GFR) reaches maximum values in the third and fourth decades of life, then drops by about 8 mL/min for every decade of life (3). In several cross-sectional and cohort studies the average GFR reduction ranged from 0.4 to 2.6 mL/min/year. In the Baltimore Longitudinal Study of Aging based on creatinine clearance

measurements in men, and in the Nijmegen Biomedical Study including healthy persons aged > 65 years, the average rate of GFR reduction was 0.7 mL/min/year and 0.4 mL/min/year, respectively. In a population of people aged ≥ 65 years, including individuals with significant co-morbidities, GFR assessed by the Cockroft--Goult formula declined by 2.6 mL/min/year (1).

The age-related decrease in renal function was found to be accelerated in subjects with risk factors and pre-existing diseases. The Italian Longitudinal Study on Aging, including people aged 65-84 years, revealed that the loss of renal function, as defined by an increase in serum creatinine concentration > 2.9 mg/dL, was influenced by current smoking status (OR = 2.3), diabetes (OR = 1.8), and systolic hypertension (OR = 1.6) (4).

The results of Baltimore Longitudinal Study showed that only 2/3 of the adult population developed a decline in GFR with age, whereas 1/3 of the subjects demonstrated a stable GFR over time. It was concluded that age by itself is not necessarily a risk factor for deterioration of kidney function (5). It was suggested that the elderly population was heterogenous: some have GFR reduction connected with co-morbidities such as arteriosclerosis and hypertension, whereas in otherwise healthy people the decline in GFR is not inevitable (6).

RENAL SENESCENCE

Renal senescence is a complex, multifactorial process characterized by anatomical and functional changes accumulating during life span. Renal mass increases from birth to the fourth decade of life, and gradually decreases thereafter at an approximate rate of 10% per decade (1). Till the age of 80 years kidney mass diminishes by 25 to 30%, with the steepest decline after the age of 50 years (7). The reduction process is more pronounced in the renal cortex than in the medulla (8). Physiological aging is associated with diffuse sclerosis of glomeruli reaching 30% of glomeruli that are destroyed by 75 years of age, with the remaining ones exhibiting impaired filtering ability (9, 10). Other features of the aging glomeruli include thickening of the basement membrane, a decrease in the number of podocytes and mesangial expansion (1, 11). The number of renal tubules as well as their length and volume also decrease with age. Functional parenchyma is gradually replaced by fat and fibrous tissue. This process occurs primarily in the renal cortex and preferentially affects nephrons most important for maximal urine concentration (12).

Vascular changes within the kidneys include narrowing of the larger arteries, hypertrophy of intima and media as well as arteriosclerosis and interstitial fibrosis (1). Angiograms and histology studies show narrowing of afferent arterioles and direct shunts between afferent and efferent arterioles, allowing blood to bypass the glomeruli (13). Renal plasma flow (RPF) steadily declines with age and in healthy older men it is 40% lower than in young men. Reduction in RPF occurs mainly in the renal cortex and is disproportionate relative to GFR reduction resulting in increase in filtration fraction in individuals aged ≥ 60 years (14).

The kidneys of elderly people are able to maintain homeostasis of body fluids and electrolytes under steady-state conditions. However, their response on alterations in fluid volume or acid-base status are much slower. Enhanced proximal sodium reabsorption together with reduced distal fractional reabsorption, being the result of inadequate activation of the renin--angiotensin-aldosterone system (RAAS), reduce the ability to conserve sodium in response to low salt intake and makes elderly people exposed to volume depletion and acute kidney injury (15). On the other hand, aged individuals reveal a relative inability to excrete excessed sodium that predispose to salt retention, hypertension and cardiac insufficiency (1). Decreased capacity of concentrating urine results in nocturia and frequency, while impaired urine diluting capacity expose elderly people to an increased risk of hyponatremia after water load (16). Reduced proton pump activity in the collecting tubules and impaired capacity of generating ammonia make older people susceptible to develop acidosis in response to acid load (1). Diminished Na-K ATPase activity together with reduced GFR, dehydration, hyporeninemic-hypoaldosteronism, and metabolic acidosis enhance the tendency to hyperkalemia and may precipitate serious clinical events (14). Elderly people may develop signs and symptoms of vitamin D deficiency due to the impaired capacity of the aging kidneys to convert 25-hydoxy vitamin D (25OHD) to its active metabolite 1,25-dihydroxy vitamin D as well as due to insufficient availability of native vitamin D. It was shown that reduced serum 25OHD concentration increased the risk of bone fractures and was an independent predictor of kidney failure and death (14). It should be also remembered that older kidneys are more prone to nephrotoxicity related to medications or intravenous contrast, as well as more vulnerable to ischemic insult (17).

EVALUATION OF CHRONIC KIDNEY DISEASE

The current definition of chronic kidney disease (CKD) was proposed in 2002 by the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (KDOQI). CKD was defined as the reduction of GFR to less than 60 mL/min/1.73 m^2 and/or presence of markers of kidney damage such as albuminuria > 30 mg/day, glomerular- or tubular-based hematuria, abnormal renal imaging and pathologic abnormalities, present for ≥ 3 months, irrespective of cause (3). Kidney failure was defined as GFR < 15 mL/min/1.73 m^2, with or without signs and symptoms of uremia, while end stage renal disease (ESRD) was determined as kidney failure treated with renal replacement therapy (18).

The incidence of CKD with GFR < 60 mL/min/1.73 m^2, was shown to be markedly higher in elderly than in young population. According to three large databases:

the Kidney Early Evaluation Program, Medicare, and the National Health, Nutrition Examination Survey the prevalence of CKD among people aged > 65 years was approximately 44%, with the highest representation observed in persons aged ≥ 80 years (19). Recent data reveal that around 45% of that subjects should be attributed to diabetes mellitus (20).

The current definition of CKD does not adequately separate the disease from normal renal aging. The formulas used to recognize CKD have not been validated in the elderly population and may misclassify many older individuals as having CKD. Serum creatinine concentration, as a marker of kidney function, is markedly influenced by muscle mass. Sarcopenia that is often found in elderly people diminishes the daily generation of creatinine and significantly decreases serum creatinine concentration (21). As the result the reference range for creatinine considered as normal in the young individuals can be found inappropriately high in the elderly persons and serum creatinine concentration in the high normal range may actually reflect a reduction in kidney function in older patients (1, 6). It was determined that a concentration of 1 mg/dL in 20 years-old people could correspond to a GFR of 120 mL/min/1.73 m^2 while the same value in 80 years-old persons could reflect a GFR of 60 mL/min/1.73 m^2 (22).

GFR may be determined with 24-hour urine creatinine clearance, that is cumbersome and often inaccurate, or can be estimated by a formula. Traditional formulas based on serum creatinine concentration (Scr) are unreliable in elderly people, particularly those with multiple co-morbidities (15). In old individuals GFR determined by the Cockroft-Gault formula: GFR = [(140 – age) x weight] / (72 x Scr) x 0.85 (if patient is female) is systematically underestimated. Currently GFR is most often calculated using the Modification of Diet in Renal Disease (MDRD) formula: GFR = 186 x $(Scr)^{-1.154}$ x $(age)^{-0,203}$ x 0.742 (if patient is female). This equation was developed from a population of 1628 patients enrolled in the MDRD study, with a GFR < 60 mL/min/1.73 m^2. It is considered more accurate in older persons but neither Cockroft-Gault nor MDRD formulas have been validated in the elderly (23). A newer formula for assessment of GFR, known as the CKD-EPI equation, uses the same variables as the MDRD equation but was developed using a more diverse cohort of patients: white women GFR = 144 x $(Scr/0.7)^{-1.209}$ x $(0.993)^{age}$; for patients with Scr > 0.7 mg/dL, white men GFR = 141 x $(Scr/0.9)^{-1.209}$ x $(0.993)^{age}$; for patients with Scr > 0.9 mg/dL (24). It was found that CKD-EPI formula, as the MDRD formula, tends to classify more individuals > 70 years of age as having CKD. In people with GFR in the range of 45-59 mL/min/1.73 m^2, the MDRD equation underestimates GFR by 25% and the CKD-EPI formula by 16% (25).

A more accurate marker to reliably assess renal function in the elderly seems to be serum cystatin C concentration (26). Cystatin C is an endogenous protein produced by all nucleated cells, filtered in kidney glomeruli, and both reabsorbed and catabolized in the proximal tubules (27). Serum cystatin C concentration is not dependent on muscle mass, less affected than serum creatinine concentration by age and gender, but may be influenced thyroid disease, steroid use, and inflammation (18).

There are several formulas developed to estimate GFR based on serum cystatin C concentration: GFR = 76.7 x $(cystatin\ C)^{-1.18}$; GFR = 127.7 x $(cystatin\ C)^{-1.17}$ x $(age)^{-0.13}$ x 0.91 (if patient is female).

THE SEVERITY OF CHRONIC KIDNEY DISEASE

The severity of CKD was classified in 5 stages with stage 1 being evidence of kidney damage without a decrease in estimated GFR and stage 5 being ESRD (tab. 1) (18).

Table 1. KDIGO classification of chronic kidney disease.

Stages of CKD	GFR [mL/min/1.73 m^2]	Kidney function	Marker of kidney damage
Stage G1	≥ 90	Normal to high	Present
Stage G2	60-89	Mildly decreased	Present
Stage G3a	45-59	Mildly to moderately decreased	Not required
Stage G3b	30-44	Moderately to severely decreased	Not required
Stage G4	15-29	Severely decreased	Not required
Stage G5	< 15	Kidney failure	Not required

Many elderly people who have normal serum creatinine concentration, no albuminuria, and GFR values in the range of 45-59 mL/min/1.73 m^2, may actually represent misclassification of CKD (28). The approach that may help define who really has CKD is to use cystatin C as a confirmation measure. KDIGO suggested that in persons with stage 3a GFR but without any markers of kidney damage, a cystatin-based GFR should be calculated – its value ≥ 60 mL/min/1.73 m^2 should be considered as a lack of confirmation of CKD (18).

Both decreased GFR and albuminuria (expressed in mg/day or as albumin-creatinine ratio) are known as independent risk factors for progression of CKD. It was found, however, that patients with severe albuminuria but normal GFR are at significantly greater risk of progression of CKD than most individuals with stage 3 disease. The KDIGO guidelines recommend urinary albumin-creatinine ratio (ACR) determined in spot urine samples as the preferred, sensitive and specific measure of kidney damage. ACR ≥ 30 mg/g on a random untimed urine should be verified with a subsequent assessment of ACR in the early morning urine sample, which correlates well with 24-hour albumin

excretion and has relatively low intra-individual variability (tab. 2) (18).

Table 2. KDIGO classification of albuminuria.

Stages of albuminuria	ACR [mg/g]	Terms
A1	< 30	Normal to mildly increased
A2	30-299	Moderately increased
A3	≥ 300	Severely increased

ACR – albumin-creatinine ratio

RISK FACTORS FOR PROGRESSION OF CKD

Progression of CKD is defined as decline in GFR category accompanied by a 25% or greater reduction in GFR from baseline. Rapid progression of the disease is determined as a sustained decline in GFR of ≥ 5 mL/min/year (29).

The most common and most important risk factors for development and progression of CKD are diabetes and hypertension (30). Other risk factors include proteinuria, obesity, cigarette smoking, dyslipidemia, cardiovascular diseases and exposure to nephrotoxic agents (31). Diabetes, severe albuminuria, and poorly controlled hypertension are strongly associated with more rapid progression of CKD and therefore management should be focused on these issues (32).

CLINICAL CONSEQUENCES OF IMPAIRED KIDNEY FUNCTION

CKD is a significant risk multiplier in patients with diabetes, hypertension, stroke, and heart diseases that are main causes of death and disability in elderly people (33). The early stages of CKD progress asymptomatically and first signs of kidney disease may be found on a screening urine analysis (14). KDIGO guidelines suggest that GFR < 60 mL/min/1.73 m^2 should be considered as impaired renal function. However, this values do not take age into account so it is debated whether healthy elderly subjects with stage G3a, particularly in the absence of urine abnormalities should considered as "diseased". As no classification system is perfect clinical judgment is extremely important (31).

Even mild degrees of renal dysfunction increase the risk of cardiovascular (CV) morbidity and mortality (34). It was shown that patients with CKD of stage ≥ G3 had more than twice the prevalence of coronary artery disease and heart failure and were above 50% more likely to have hypertension compared with individuals without CKD (35, 36). In the CKD-EPI consortium meta-analysis, people aged > 65 years with a GFR 45-59 mL/min/1.73 m^2 had 44% increased risk of CV death as compared to those with normal renal function (34). On the other hand an analysis conducted on more than 2 500 000 US veterans revealed that a reduction in GFR of stage 3a (GFR 45-59 mL/min/1.73 m^2) was not associated with an increase in CV mortality in persons over 65 years of age (37). The results have been confirmed in a study of community based elderly population aged ≥ 75 years that showed no differences in all-cause and cardiovascular mortality between people with GFR of 45-59 mL/min/1.73 m^2 and individuals with a GFR > 60 ml/min/1.73 m^2 (38).

Patients with advanced CKD and a GFR of < 15 ml/min/1.73 m^2 have 5 times increased all-cause mortality as well as high prevalence of cognitive impairment, additionally intensified by albuminuria (34, 39).

Individuals with ESRD reveal high fracture rates. Early signs of metabolic bone disease include increase in serum FGF-23 concentration, followed by decline in 1,25$(OH)_2$ vitamin D concentration. Elevated serum parathyroid hormone and phosphorus concentrations are later findings. In most of older individuals with stage 3a CKD and in many with stage 3b CKD, the predominant bone disease is osteoporosis (18).

REFERRAL TO NEPHROLOGIST

Not everyone with CKD needs to be seen by nephrologist, and this is particularly true for the older people with multiple comorbidities and low expectation of progressing to ESRD.

The KDIGO guidelines suggest that a nephrologist should be consulted in the following situations:

- nephrotic syndrome or significant albuminuria > 300 mg per day or ACR > 300 mg/g creatinine,
- sustained hematuria (RBC >20 per high power field, red cell casts), not readily explained,
- rapid progression of CKD and/or progression of CKD with a reduction of GFR by 25%,
- GFR < 30 mL/min/1.73 m^2,
- persistent hyperkalemia,
- severe hypertension,
- recurrent or extensive nephrolithiasis,
- hereditary kidney disease,
- nephropathy of unclear cause (18).

PREVENTION OF CKD PROGRESSION

With appropriate management, patients with CKD may benefit from slower loss of kidney function, better control of metabolic disturbances, lower risk of cardiovascular events and a more conscious choice of renal replacement modality (40).

In people with CKD both GFR and albuminuria should be assessed at least annually, and more often in persons at higher risk of progression (29). To diagnose anemia (Hb concentration < 13.0 g/dL in males and < 12.0 g/dL in females) hemoglobin concentration should be determined when clinically indicated in people with GFR ≥ 60 mL/min, at least annually in individuals with GFR 30-59 mL/min, and not less than twice per year in persons with GFR < 30 mL/min. Measuring serum concentrations of calcium, phosphate, PTH, and alkaline phosphatase activity should be performed at least once in adults with GFR < 45 mL/min. Measuring of bone mineral density routinely in people with GFR < 45 mL/min is not justified (2).

Long-term, moderate and individualized caloric restriction allows to retard age-related structural

changes in kidneys, including glomerulosclerosis, atherosclerosis, ischemic injury, vascular wall thickening and tubular-interstitial fibrosis (41). Lowering protein intake to 0.8 g/kg of body weight/day in patients with diabetes or individuals without diabetes but with GFR < 30 mL/min/1.73 m^2 (stages G4-G5) should be recommended, as well as avoiding high protein intake (> 1.3 g/kg/day) in adults with a risk of CKD progression. It is also suggested for patients with CKD to reduce sodium intake to 90 mmol (2 g) per day, corresponding to 5 g of sodium chloride (31).

People with CKD should be encouraged to undertake physical activity compatible with cardiovascular health and tolerance, aiming for at least 30 minutes 5 times per week, as well as to achieve a healthy weight (BMI 20-25 kg/m^2) and stop smoking (31).

Recent KDIGO guidelines recommend a target blood pressure (BP) of ≤ 140/90 mmHg if ACR is less than 30 mg/g of creatinine and a BP of ≤ 130/80 mmHg if ACR is ≥ 30 mg/g. In hypertensive patients with diabetes and albuminuria ≥ 30 mg/day, as well as in nondiabetic persons with albuminuria ≥ 300 mg/d, angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) should be preferred (42). In elderly patients treatment regiments have to be tailored by considering age, co-morbidities and coexisting therapies. Treatment should be gradually escalated with close attention to adverse events such as electrolyte disorders, orthostatic hypotension, and acute deterioration of kidney function. A randomized controlled study of losartan (the RENAAL study) including persons with type 2 diabetes and proteinuria, showed that the use of losartan decreased the risk of ESRD by 50% in patients older than 65 years without significant exacerbation of side effects (43). By contrast, a retrospective cohort study of people with GFR < 60 mL/min/1.73 m^2 revealed that the risk of hyperkalemia in patients treated with lisinopril increased with their age (44).

Large control clinical trials showed that tighter glycemic control was associated with less frequent development and progression of albuminuria but with more frequent episodes of hypoglycemia and higher mortality rate. Compared with persons without CKD or diabetes, the relative risk for hypoglycemia was found to be 1.62 in patients with CKD without diabetes, and 8.43 in patients with both CKD and diabetes (45, 46). To prevent or delay progression of diabetic kidney disease, the recommended hemoglobin A1c level should be approximately 7%. However, in individuals with significant co-morbidities and an increased risk of hypoglycemia it should be maintained above 7% (18, 29). In diabetics with CKD glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of ACE-I or ARB, statins, and antiplatelet therapy if clinically indicated (47).

Elderly people are at increased risk for the development of acute kidney injury (AKI). The major identifiable risk factors of AKI include: age > 75 years, CKD, hypovolemic states, heart failure, diabetes, certain medications, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, ACE-Is, ARBs, as well as radio-contrast examinations, and cardiac bypass surgeries. KDIGO guidelines suggest to discontinue nephrotoxic agents when possible and ensure good volume status and adequate renal perfusion pressure. If iodine-based contrast is to be used medications, such as NSAIDs, loop diuretics, ACE-Is and ARBs should be held or diminished, and oral N-acetyl cysteine as well as isotonic saline should be given on the day of examination and a day before (14).

In people with GFR < 45 mL/min/1.73 m^2 serum phosphate concentration should be maintained within the normal range, while the optimal serum parathormone (PTH) level remains unknown. Serum PTH concentration above the upper normal limit may be the result of hyperphosphatemia, hypocalcemia, and vitamin D deficiency. Vitamin D should be prescribed in patients with vitamin D deficiency and its permanent supplementation should be considered. It has to be remembered that most osteoporosis medicines including bisphosphonates can be used only when the GFR is ≥ 30 mL/min/1.73 m^2 (18, 48).

Treatment of older patients with CKD needs special attention with taking into account impaired renal function, multiple co-morbidities and drug side effects. Cautionary notes for prescribing drugs in people with CKD are presented in table 3.

The default management strategy for elderly patients with kidney failure appears to have shifted from conservative management to early initiation of dialysis (49). It should be realized, however, that life expectancy after initiation of dialysis remains relatively short and a large proportion of patients die within 6 months of commencing dialysis, mainly due to preexisting diseases. A United Kingdom and United States studies of people with advanced kidney failure suggested that initiation of dialysis was associated with increased mortality for patients aged over 65-75 years and with 2 or more comorbid conditions. These data indicate that dialysis is an appropriate treatment option for well-informed older patients with ESRD and good baseline quality of life (50, 51).

It is generally accepted that older age alone does not preclude kidney transplantation in otherwise suitable candidates. Elderly patients with ESRD, however, are more likely to have absolute or relative contraindications to transplantation (2). It was shown that 5-year patient and graft survivals are lower among kidney transplant recipients aged ≥ 65 years as compared to people aged 35 to 49 years (patient survival 67.2 vs. 89.6% and graft survival 60.9 vs. 75.4%, respectively) (52). Transplantation appears to reduce mortality by 33% among patients aged 74 years as compared to remaining on dialysis, but benefits associated

Table 3. Cautionary notes for prescribing drugs in people with CKD.

NSAIDs	Avoid in people with GFR < 30 mL/min/1.73 m^2 Avoid prolonged therapy in persons with GFR 30-59 mL/min/1.73 m^2 Avoid in patients taking RAAS blocking agents and dehydrated
RAAS antagonists (ACE-Is, ARBs, aldosterone antagonists, direct renin inhibitors)	Start at lower doses in people with GFR < 45 mL/min/1.73 m^2 Do not routinely discontinue in patients with GFR < 30 mL/min/1.73 m^2 Avoid in persons with suspected renal artery stenosis Assess GFR and serum potassium concentration within 1 week of starting or dose escalation Temporarily suspend during intercurrent illness, prior to planned iv radio-contrast administration, major surgery or bowel preparation before colonoscopy
β-blockers	Reduce dose by 50% in people with GFR < 30 mL/min/1.73 m^2
Statins	In people with GFR < 60 ml/min no increase in toxicity was found for: simvastatin dosed 20 mg per day, atorvastatin dosed 20 mg per day, rosuvastatin dosed 10 mg per day, combined treatment with simvastatin dosed 20 mg per day and ezytimide 10 mg per day
Fenofibrat	Increases serum creatinine concentration
Sulfonylureas	Avoid agents mainly renally excreted (e.g. glyburide, glibenclamide) Reduce agents mainly metabolized in the liver (e.g. gliquidone) in patients with GFR < 30 mL/min/1.73 m^2
Metformin	Safe in people with GFR ≥ 45 mL/min/1.73 m^2 Review its use in persons with GFR 30-44 mL/min/1.73 m^2 Discontinue in patients with GFR < 30 mL/min/1.73 m^2
Insulin	Reduced dose may be needed in people with type 2 diabetes with GFR < 30 mL/min/1.73 m^2
Macrolides	Reduce dose by 50% in persons with GFR < 30 mL/min/1.73 m^2
Fluoroquinolones	Reduce dose by 50% in people with GFR < 15 mL/min/1.73 m^2
Aminoglycosides	Reduce dose and/or increase dosage interval in patients with GFR < 60 mL/min/1.73 m^2 Avoid concomitant ototoxic agents such as furosemide
Tetracyclines	Reduce dose in people with GFR < 45 mL/min/1.73 m^2
Low-molecular heparins	Reduce dose by 50% in persons with GFR < 30 mL/min/1.73 m^2
Bisphosphonates	Avoid in patients with GFR < 30 mL/min/1.73 m^2
Warfarin	Use lower doses and monitor closely in persons with GFR < 30 mL/min/1.73 m^2 (increased risk of bleeding)

with the procedure are restricted to patients with reasonable baseline life expectancy, without significantly increased perioperative risk (52, 53).

CONCLUSIONS

Chronic kidney disease is defined as the reduction of glomerular filtration rate to less than 60 mL/min/1.73 m^2 and/or presence of markers of kidney damage. As GFR declines gradually after 40 years of age at a rate of approximately 1% per year and this age-related decrease in renal function can be markedly accelerated by pre-existing diseases, the considerable part of elderly population may be classified as having CKD. The most important risk factors for development and progression of CKD are diabetes, hypertension and severe albuminuria.

Appropriate treatment applied in patients with CKD allows them to benefit from slower loss of kidney function, better control of metabolic disturbances, and lower risk of cardiovascular events. Therapy of older patients with CKD, however, needs special attention as it has to take into account both impaired renal function and multiple comorbidities, polypharmacy, and drug side effects.

BIBLIOGRAPHY

1. Bolignano D, Mattace-Raso F, Sijbrands EJG et al.: The aging kidney revisited: a systematic review. Ageing Res Rev 2014; 14: 65-80.
2. Tonelli M, Riella M: Chronic kidney disease and the aging population. Iranian J Kidney Dis 2014; 8: 87-92.
3. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (suppl. 1): S1-266.
4. Baggio B, Budakovic A, Perissinotto E et al.: Atherosclerotic risk factors and renal function in the elderly: the role of hyperfibrynogenemia and smoking. Results from the Italian Longitudinal Study on Ageing (ILSA). Nephrol Dial Transplant 2005; 20: 114-123.
5. Lindeman RD, Tobin J, Shock NW: Longitudinal studies on the rate of decline in renal function with age J Am Geriatr Soc 1985; 33: 278-285.
6. Fliser D: Ren Sanus in Corpore Sano: the myth of the inevitable decline of renal function with senescence. Nephrol Dial Transplant 2005; 20: 482-485.
7. Epstein M: Aging and the kidney. J Am Soc Nephrol 1996; 7: 1106-1122.
8. Gourtsoyiannis N, Prassopoulos P, Cavouras D et al.: The thickness of the renal parenchyma decreases with age: a CT study of 360 patients. Am J Rentgenol 1990; 155: 5541-5544.
9. Rule AD, Amer H, Cornell LD et al.: The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med 2010; 152: 561-567.
10. Nyengaard JR, Bendsen TF: Glomerular numberand size in relation to age, kidney weight, and body surface in normal man. Anat Rec 1992; 232: 194-201.
11. Musso CG, Oreopoulos DG: Aging and physiological changes of the kidneys including changes in glomerular filtration rate. Nephron Physiol 2011; 119 (suppl. 1): 1-5.
12. Abrass CK, Adcox MJ, Raugi GJ: Aging-associated changes in renal extracellular matrix. Am J Pathol 1995; 146: 742-752.

13. Long DA, Mu W, Price KL et al.: Blood vessels and the aging kidney. Nephron Experiment Nephrol 2005; 101: e95-99.
14. Velasquez KMR, Hames E, Masri H: Evaluation and management of the older adult with chronic kidney disease. Prim Care Clin Office Pract 2014; 41: 857-874.
15. Fliser D, Franek E, Joest M et al.: Renal function in the elderly: impact of hypertension and cardiac function. Kidney Int 1997; 51: 1196-1204.
16. Sands JM: Urine concentrating and diluting ability during aging. J Gerontol A Biol Sci Med Sci 2012; 67: 1352-1357.
17. Schmith R, Cartley LG: The impact of aging on kidney repair. Am J Physiol Renal Physiol 2008; 294: F1265-1272.
18. Maw TT, Fried L: Chronic kidney disease in the elderly. Clin Geriatr Med 2013; 29: 611-624.
19. Nitta K, Okada K, Yanai M et al.: Aging and chronic kidney disease. Kidney Blood Press Res 2013; 38: 109-120.
20. Fox CS, Larson MG, Leip EP: Predictors of new-onset kidney disease in a community-based population. JAMA 2004; 291: 844-850.
21. Fliser D: Assessment of renal function in the elderly patients. Curr Opin Nephrol Hypertens 2008; 17: 604-608.
22. Musso CG, Michelangelo H, Vilas M et al.: Creatinine reabsorption by the aged kidney. Int Urol Nephrol 2009; 41: 727-731.
23. Levey AS, Bosch JP, Lewis JB et al.: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461-470.
24. Levey AS, Stevens LA, Schmid CH et al.: CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): a new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604-612.
25. Murata K, Baumann NA, Saenger AK et al.: Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. Clin J Am Soc Nephrol 2011; 6: 1963-1972.
26. Ognibene A, Mannuci E, Caldini A et al.: Cystatin C reference values and aging. Clin Biochem 2006; 39: 658-661.
27. Randers E, Erlandsen EJ: Serum cystatin C as an endogenous marker of the renal function – a review. Clin Chem Lab Med 1999; 37: 389-395.
28. Rule AD, Larson TS, Bergstrath EJ et al.: Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med 2004; 141: 929-937.
29. Inker LA, Astor BC, Fox CH et al.: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014; 63: 713-735.
30. Collins AJ, Foley RN, Chavers B et al.: United States renal data system 2011 Annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. Am J Kidney Dis 2012; 59 (suppl. 1): A7, e1-420.
31. Levin A, Stevens PE: Summary of KDIGO 2012 CKD guideline: behind the scenes, need for guidance, and framework for moving forward. Kidney Int 2014; 85: 49-61.
32. Young JH, Klag MJ, Muntner P et al.: Blood pressure and decline in kidney function: findings from the Systolic Hypertension in the Elderly Program (SHEP). J Am Soc Nephrol 2002; 13: 2776-2782.
33. Couser WG, Remuzzi G, Mendis S et al.: The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int 2011; 80: 1258-1270.
34. Go AS, Chertow GM, Fan D et al.: Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. N Eng J Med 2004; 351: 1296-1305.
35. Fried LF, Shlipiak MG, Crump C et al.: Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. J Am Coll Cardiol 2003; 41: 1364-1372.
36. Manjunath G, Tighiouart H, Coresh J et al.: Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int 2003; 63: 1121-1129.
37. O'Hare AM, Berthental D, Covinsky KE et al.: Mortality risk stratification in chronic kidney disease: one size for all ages? J Am Soc Nephrol 2006; 17: 846-853.
38. Roderick PJ, Atkins RJ, Smeeth L et al.: CKD and mortality risk in older people: a community-based population study in the United Kingdom. Am J Kidney Dis 2009; 53: 950-960.
39. Weiner DE, Bartolomei K, Scott T et al.: Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. Am J Kidney Dis 2009; 53: 438-447.
40. Zhang L, Wang F, Wang L et al.: Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet 2012; 379: 815-822.
41. McKiernan SH, Tuen VC, Baldwin K et al.: Adult-onset calorie restriction delays the accumulation of mitochondrial enzyme abnormalities in aging rat kidney tubular epithelial cells. Am J Physiol Renal Physiol 2007; 292: F1751-1760.
42. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and the management of chronic kidney disease. Kidney Int Suppl 2013; 3: 1-150.
43. Winkelmayer WC, Zhang Z, Shahinfar S et al.: Efficacy and safety of angiotensin II receptor blockade in elderly patients with diabetes. Diabetes Care 2006; 29: 2210-2217.
44. Johnson ES, Weinstein JR, Thorp ML et al.: Predicting the risk of hyperkalemia in patients with chronic kidney disease starting Lisinopril. Pharmacoepidemiol Drug Saf 2010; 19: 266-272.
45. Duckworth W, Abraira C, Moritz T et al.: Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360: 129-139.
46. Gerstein HC, Miller ME, Byington RP et al.: Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545-2559.
47. Cooper M: Pathogenesis, prevention, and treatment of diabetic nephropathy. Lancet 1998; 352: 213-219.
48. Płudowski P, Karczmarewicz E, Bayer M et al.: Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe – recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokr Pol 2013; 64: 319-327.
49. Thorsteinsdottir B, Montori VM, Prokop JL et al.: Ageism vs. the technical imperative, applying the GRADE framework to the evidence on hemodialysis in very elderly patients. Clin Interv Aging 2013; 8: 797-807.
50. Chandna SM, Da Silva-Gane M, Marshall C et al.: Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. Nephrol Dial Transplant 2011; 26: 1608-1614.
51. Murtagh FE, Marsh JE, Donohoe P et al.: Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transplant 2007; 22: 1955-1962.
52. Knoll GA: Kidney transplantation in the older adult. Am J Kidney Dis 2013; 61: 790-797.
53. Gill JS, Tonelli M, Johnson N et al.: The impact of waiting time and comorbid conditions on the survival benefit of kidney transplantation. Kidney Int 2005; 68: 2345-2351.

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