

MANAGEMENT OF CHRONIC KIDNEY DISEASE IN PRIMARY HEALTH CARE

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem that is often under-diagnosed and under-treated. CKD is a “silent” disease and goes unnoticed because it may not be “felt.” Yet it affects many more people than we would even imagine: 1 out of 10 adults in the world have some form of kidney damage [1]. However, as many as 90% of those who have CKD remain unidentified. High blood pressure and diabetes are the main causes of CKD. It is projected that diabetes will increase by 70% by 2025. Therefore, early detection and prevention of the progression of CKD for people who also have a very high cardiovascular risk are extremely important challenges and goals for general practitioners/family doctors (GP/FD).

CKD represents a progressive, irreversible decline in glomerular filtration rate [2]. Most chronic nephropathies unfortunately lack a specific treatment and progress relentlessly to end stage renal disease. Progressive renal function loss is a common phenomenon in renal failure irrespective of the underlying cause of the kidney disease [3]. The kidney is able to adapt to damage by adaptive hyperfiltration—increasing the filtration in the remaining normal nephrons. As a result, a patient with mild renal insufficiency often has a normal or near-normal serum creatinine concentration. Adaptive hyperfiltration, although initially beneficial, appears to result in long-term damage to the glomeruli of the remaining nephrons, which is manifest by proteinuria and progressive renal insufficiency. This process appears to be responsible for the development of renal failure among those in whom the original illness is either inactive or cured [4]. The cost of the advanced renal failure and renal replacement therapy is enormous [5, 6]. Therefore, early diagnosis and optimal management of CKD affords many challenges for primary health care in helping to maintain health and life quality among the population at risk.

This position paper is based on published reviews about CKD management in different stages and focuses on key references published since the year 2000. This position statement also provides evidence-based screening recommendations and interventions for shared-care between GP/FD and specialists.

CHRONIC KIDNEY DISEASE: DEFINITION, CLASSIFICATION, EPIDEMIOLOGY

Definition

The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) workgroup has defined CKD as the following [7], which have been accepted internationally with some clarifications [8, 9]:

- 1 The presence of markers of kidney damage for 3 months, as defined by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR), that can lead to decreased GFR, manifest by either pathological abnormalities or other markers of kidney

damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests

- 2 or The presence of $GFR < 60 \text{ mL/min./1.73 m}^2$ for 3 months, with or without other signs of kidney damage as described above.

Based upon representative samples of the United States population [7], the studies have estimated the prevalence of CKD in the general population through measurement of markers of kidney damage, such as elevated serum creatinine concentration, decreased predicted GFR and presence of albuminuria.

According to the Kidney Disease: Improving Global Outcomes (KD:IGO) position statement [9] the use of the term “disease” in CKD is consistent with:

- 1) the need for action to improve outcomes through prevention, detection, evaluation and treatment;
- 2) providing a message for public, physician and patient education programs;
- 3) common usage; and
- 4) its use in other conditions defined by findings and laboratory tests, such as hypertension, diabetes and hyperlipidaemia [9].

Classification of CKD

CKD is classified according to severity, diagnosis, treatment and prognosis [9]. Five-stage classification is based on structural and functional criteria regardless of the cause and accounting for dialysis and transplantation (Table 1). The suffix “T” is used for all transplant recipients, at any level of GFR and, “D” for dialysis, for CKD stage 5 patients treated with dialysis.

Table 1. Classification of chronic kidney disease [10].

Stage	Description	GFR (mL/min. per 1.73 m ²)	Related terms
1	Kidney damage with normal or ↑ GFR	≥ 90	Albuminuria Proteinuria Haematuria
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria Proteinuria Haematuria
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency Early renal insufficiency
4	Severe ↓ GFR	15–29	Chronic renal insufficiency Late renal insufficiency Pre-ESRD
5	Kidney failure	<15	Renal failure Uraemia End-stage renal disease

Epidemiology of CKD

Clinical evaluation for CKD should include elucidation of the cause of disease. However, the cause of the disease cannot be ascertained in all cases. Also, renal function declines normally with age and the exact level of decline at a given age that should be considered pathological is not known. The KDIGO statement considers GFR less than 60 mL/minute pathological at all ages [10]. Cross-sectional studies report a slow decline in GFR after the fourth decade of life ~ 0.75 mL/min./1.73 m²/year. These changes proceed slowly but in the presence of other diseases such as diabetes, hypertension and heart disease, the kidney becomes vulnerable to failure [11].

Very few of the causes of chronic renal failure are completely curable. It is often not necessary to do extensive tests to find a cause especially when symptoms of renal insufficiency already present. However, for determining the stage and specific characteristics of the underlying disease follow-up of patients and thorough diagnostic work-up is needed. Diabetes is one of the commonest causes of kidney failure beside glomerulonephritis in many countries [12–15]. The major groups of diseases leading to end-stage renal disease (ESRD) are glomerulonephritis, diabetic nephropathy, hypertension, chronic pyelonephritis and polycystic kidney disease. In different countries the proportions of these diseases as a cause of renal failure vary: e.g. glomerulonephritis form 22-24% from prevalent renal replacement therapy (RRT) patients in Estonia, Germany, Poland or Finland but only 11-12% in France, Italy or England. Prevalent patients of diabetic nephropathy form from RRT patients in Italy 12%, in Estonia 22%, in Finland and Poland 24%, in Germany 23%, in England 12%, in Japan 30%, and in USA 37%, [16–19].

The use of RRT varies in different countries. There is a rising incidence and prevalence of kidney failure [12–15] and the worldwide epidemic of CKD shows no signs of abating in the near future. The exact reasons for the growth of the end-stage renal disease are unknown. Changes in the demographics of the population, differences in disease burden among different racial groups and under-recognition of earlier stages and of risk factors for CKD may partially explain this growth [8]. Recent trends show that the rate of increase of new cases of both diabetic and all-cause end-stage renal disease (ESRD) has progressively levelled off in many countries [13, 20]. It is therefore currently impossible to predict the long-term trend of RRT in Europe. The prevalence of RRT patients/million inhabitants 2005 was very different worldwide: in Estonia 394, in Finland 722, in Sweden 818, in Germany 1057, in Spain 899, in England 668 or in USA 1590 [16, 17].

It has been shown that CKD affects men more often than women. For example, according to the Finnish Registry for Kidney Diseases the prevalence of RRT in men was 898 and in women 553/million inhabitants in 2006 [17]. Since 1996, the prevalence of RRT has increased faster among men (63%) than among women (44%). The prevalence among the elderly is growing fast: in the age group 75+ years, the prevalence of RRT has increased by almost 250% during the past ten years and 70% during the past five years. In the younger age groups, the prevalence has increased 10–61% in ten years and 4–14% in five years [17].

MANAGEMENT OF CHRONIC KIDNEY DISEASE PATIENTS

Risk groups and screening

Detection of CKD is believed to be a priority for primary care because early treatment of CKD and its complications may delay or prevent the development of ESRD. It would be ideal for GP/FD to carry out screening as the majority of the population visits their GP/FD within a 3-year

period and can be subject to screening. There are reports suggesting that CKD often is not detected, even when patients have access to primary care [21]. There is an overwhelming consensus that screening for CKD should include high-risk groups. Screening for asymptomatic persons beyond the above-mentioned patient groups has not yet found justification. Early detection of diabetes and hypertension as the most important reasons for CKD and their appropriate treatment is a method of avoiding or postponing complications, incl. chronic kidney failure. Screening of hypertension by measurement of blood pressure at office visits has found support in many guidelines [22]. However, systematic diabetes screening of the general population without symptoms or risk factors has not been found effective.

Risk groups of chronic kidney disease are the follows:

- Patients with a family history of diabetes, hypertension
- Diabetics
- Hypertensive patients
- Recurrent urinary tract infections
- Urinary obstruction
- Patients with systemic diseases that affect kidneys
- Patients with past or family history of cardiovascular disease

The most widely used methods for screening for kidney disease are:

1. an analysis of a random urine sample for albuminuria and,
2. a serum creatinine measurement to calculate an estimated GFR, which is an indication of functioning kidney mass.

It is recommendable to use both of these methods as significant kidney disease can present with diminished GFR or proteinuria, or both. [23]. Detecting and quantitation of proteinuria are essential to the diagnosis and treatment of CKD. Albumin, the predominant protein excreted by the kidney in most types of renal diseases, can be detected by urine dipstick testing. The protein-creatinine ratio in an early-morning random urine sample correlates well with 24-hour urine protein excretion and is much easier to obtain [7]. Albuminuria often heralds the onset of diabetic nephropathy, thus this sample is therefore recommended for all patients at risk for kidney disease. The quantitative determination of protein in the urine in the lab is more economical and more correct, than the use of microalbuminuria dipsticks and should be the recommended method to detect proteinuria. The term “albuminuria” should be substituted for the terms “microalbuminuria” and “macroalbuminuria.” These terms are commonly used but should be avoided because they are misleading [10]. Increased urinary excretion of albumin is the earliest manifestation of CKD due to diabetes, other glomerular diseases and hypertensive nephrosclerosis. Also, albuminuria may also accompany tubulointerstitial diseases, polycystic kidney disease and kidney disease in transplant recipients.

Significant kidney dysfunction may be present despite a normal serum creatinine level. An estimated GFR based on serum creatinine level correlates better with direct measures of the GFR and detects more cases of CKD than does the serum creatinine level alone. Clinically useful GFR estimates are calculated from the measured serum creatinine level after adjustments for age, sex and race. [24, 25] The two most commonly used formulas for GFR estimation are the MDRD (Modification of Diet in Renal Disease) study equation and the Cockcroft–Gault equation (Table 2). Validation studies in middle-aged patients with CKD showed the MDRD study equation to be more accurate. [24]. However, the MDRD study equation was found to systematically underestimate the GFR in patients without CKD. It is important to realise that the methodology used for determination of serum creatinine is of great importance in the interpretation of the results obtained with the MDRD formula and that in fact, only the IDMS-corrected serum

creatinine can be used [26]. It should be kept in mind that these formulas do not result in correct GFRs when used in persons with abnormal body composition: the obese, patients with oedema, pregnancy, states of cachexia or amputees. In most situations of family doctors and as long as kidney function is stable, a calculated GFR can replace measurement of a 24-hour urine collection for creatinine clearance, that is still required in pregnant women, patients with extremes of age and weight, patients with malnutrition, patients with musculoskeletal diseases, paraplegia or quadriplegia and patients with a vegetarian diet or rapidly changing kidney function. [27]. Also, creatinine clearance is preferred in predialysis and transplant patients.

Table 2. Estimated glomerular filtration rate mathematical formulas.

Abbreviated MDRD study equation [24]	$\text{GFR (mL per minute per } 1.73 \text{ m}^2) = 186 \times (\text{S}_{\text{Cr}})^{-1.154} \times (\text{age})^{-0.203} \times (0.742, \text{ if female}) \times (1.210, \text{ if black})$
IDMS traceable MDRD formula [26]:	$\text{GFR (mL per minute per } 1.73 \text{ m}^2) = 175 \times \text{standardised } \text{S}_{\text{Cr}}^{-1.154} \times (\text{age})^{-0.203} \times (0.742, \text{ if female}) \times (1.212, \text{ if black})$
Cockcroft–Gault equation [25]	$\text{GFR (mL/min.)} = \frac{(140 - \text{age}) \times \text{weight}}{0.81 \times \text{S}_{\text{Cr}}} \times (0.85, \text{ if female})$

GFR = glomerular filtration rate; *MDRD* = Modification of Diet in Renal Disease; *S_{Cr}* = serum creatinine concentration ($\mu\text{mol/L}$);

Prevention

Screening of risk populations may help to detect kidney disease early by GP/FD and use primary prevention strategies to avoid the development of diabetic or hypertensive nephropathy that may develop over many years and decades.

Primary prevention interventions seek to delay or halt the development of CKD. This involves public health measures to influence smoking cessation, modification of wrong dietary habits and reduce the prevalence of obesity among the population. Secondary and tertiary prevention interventions include prevention strategies for individuals with CKD and seeking to prevent (secondary) or control (tertiary) complications of renal insufficiency.

Primary and secondary prevention of cardio-vascular disease (CVD) and CKD remain the main purpose in modern medicine as the main cause of death in patients with CKD is cardiovascular disease. The risk of death in CKD stage 4–5 patients are 10–20-fold that of the general population [28, 29]. CKD patients belong in the highest risk group for subsequent atherosclerotic complications. Therefore, CKD should be recognised as early as possible and all prevention interventions that may arrest the kidney disease and cardiovascular disease progression should be used [30].

When kidney disease progresses CKD patients become hypertensive, have acquired combined hyperlipidaemia and hyperhomocysteinaemia, increased oxidative stress and decreased physical activity and psychosocial stress. If patients choose to smoke, the additive risk is profound [31]. Diabetes mellitus is a major risk factor for both CVD and CKD progression [32]. Moreover, CKD patients are becoming older and are often menopausal if female [33]. Finally, CKD patients have a dramatic tendency for vascular and cardiac calcification that is related with

hyperphosphataemia and secondary hyperparathyroidism [34]. Therefore, modification of both cardiovascular risk factors, classical and factors associated with renal insufficiency (uraemic toxins, hyperphosphatemia, prolonged oxidative stress, malnutrition, hyperuricemia etc.) should be considered in the management of CKD patients.

Secondary prevention and the management of several renal and CVD risk factors as hypertension, being overweight, hypercholesterolaemia, hypertriglyceridaemia and others should begin early in the course of CKD with reno- and vasoprotective medications [35]. Hypertensive diabetics and those with micro-albuminuria or macro-albuminuria, whether hypertensive or not, should be treated with renin-angiotensin system (RAS) blockers of either an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) [36]. ACE inhibitor therapy also lowers the rate of progressive kidney disease in children and young adults with IgA nephropathy and moderate proteinuria [37]. In addition to classical risk factors patients with CKD have specific risk factors (Table 7). Psychosocial factors, such as environmental stress and responsiveness to stress, should not be unmentioned, especially when referred late to a kidney clinic.

Principles of management of CKD: role of GP/FD and shared care

As the population with chronic renal failure grows, primary care physicians will increasingly be involved in the management of these patients. GP/FD have an important role in detecting CKD early, in taking measures to slow the disease progression and in providing timely referral to a nephrologist [38]. However, who is responsible for CKD patients, whether the GP/FD or the specialist, depends of the stage of CKD and often of the organisation of the health care system. Several models of care of CKD patients are possible: a primary care-based model (conventional shared care between GPs and hospital-based nephrologists), secondary care-based model or a model of specialised kidney centres besides routine primary and secondary care. International evidence indicates that health systems based on well-structured and organised primary care with adequately trained GPs provide both more cost-effective and more clinically effective care than those with a low primary care orientation. However, there is no specific evidence for the cost-effectiveness and clinical effectiveness of primary care in the specific case of CKD [39]. There is only little data about management of CKD in primary care and the data vary a lot from excellent to poor quality of care [40–43]. In addition, high total quality of care was achieved in most of the studies on CKD management in nephrological centres [44, 45]. In the few studies that directly compared primary and nephrological care in advanced CKD supported management of CKD in nephrological centres [42, 46]. In the guidelines of the UK, Canada and Australia, co-management of patients referred to a nephrologist with their primary care physician and other health care providers to enable a shared care model is suggested [47] which defines the roles and the ways of communication, but their implementation may be problematic.

The most important role of GP/FD in the management of CKD patients is detecting and treating possible reversible causes of renal dysfunction and preventing the progression of CKD and CVD [4]. It is important to consider the patient’s renal function in prescribing and nowadays more importantly- in planning radiologic investigations with contrast media. However, when symptoms of renal insufficiency become more pronounced referral to and shared-care with a nephrologist is essential (Table 3).

Table 3. Principles of management of CKD patients

Management of CKD	Symptoms	Treatment of CKD medicamentous/non-	Monitoring of CKD patient by GP/FD/internist	Monitoring of CKD patient
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		medicamentous	endocrinologist/cardiologist/other)	by nephrologist
Treatment of reversible causes of renal dysfunction	Decreased renal perfusion (vomiting, diuretic use, diarrhoea, hypotension, etc.) Administration of nephrotoxic drugs (aminoglycosides, NSAIDs, etc.) Urinary tract obstruction	Diagnosis and treatment of prerenal causes of renal dysfunction The administration of nephrotoxic drugs should be avoided or used with caution Urinary tract obstruction should always be considered in the patient with unexplained worsening renal function.	Diagnosis and treatment by GP Urologic consultation if needed	If CKD progresses nephrologist consultation may be needed
Preventing or slowing the progression of CKD	Hypertension Proteinuria Diet Hyperlipidaemia Metabolic acidosis Anaemia Smoking Being overweight Low physical activity	RAS blockade Diet: low-protein, low-salt and low-fat Exclusion of risk factors (smoking, being overweight, low physical activity)	Diagnosis and treatment mostly by GP/FD when GFR>60 mL/min. If GFR<60 mL/min. referral to nephrologist GFR<60–30 mL/min.—equal shared-care with GP/FD	Nephrologist consultation if needed for diagnosis clarification or when GFR<60 mL/min.
Treatment of the complications of renal dysfunction Pre-dialysis care	Hypertension Hyperphosphataemia Osteodystrophy Anaemia Disorders of fluid and electrolyte balance (volume overload) Hyperkalaemia Metabolic acidosis Dyslipidaemia Hormonal dysfunction	RAS blockade and other antihypertensive drugs if needed Diet Phosphate binders Iron, erythropoietin Statins Pre-dialysis care	GP visits rarely, shared-care with nephrologist Identification, referral and adequate preparation of the CKD patient in whom RRT will be required	GFR<30 mL/min.—pre-dialysis care at kidney centre
Adequate preparation of the patient in RRT	Uraemic pericarditis, neuropathy, Bleeding, Malnutrition Thyroid dysfunction	Haemodialysis Peritoneal dialysis Kidney transplantation	GP visits very rare, only if acute problems arise	Nephrologist—leader the treatment

The gradual decline in function in patients with CKD is initially asymptomatic. Different signs and symptoms may be observed with advanced renal dysfunction, including volume overload,

hyperkalaemia, metabolic acidosis, hypertension, anaemia and bone disease. A shared care, including involvement of a nephrologist, primary care physician, renal dietician, nurse and social worker, should be initiated early in the course of CKD, with close patient follow-up.

Management should include: measurements of serum creatinine concentration and estimated GFR, haemoglobin, calcium, phosphate, potassium, bicarbonate and PTH concentrations, dietary assessment, treatment of anaemia with intravenous iron \pm erythropoiesis stimulating agents, treatment of hyperparathyroidism and phosphate retention, correction of acidosis, counselling and education about the options for RRT and conservative (non-dialytic) management. Conservative (palliative) treatment may still include drug treatment of hypertension, anaemia, phosphate retention, hyperparathyroidism and acidosis if the patient chooses not to undergo RRT.

Early referral to nephrologist

Patients with CKD stage 1 and 2 should be treated in primary care, while the nephrologist's task is seen in providing RRT. Late referral to specialist care for renal failure is associated with increased morbidity, mortality and cost. The criteria for referral to a nephrologist are in Table 4 [48, 49].

Table 4. Criteria for referral to specialist

<p><u>Services depending on GFR</u> Estimated GFR less than 15 mL/min./1.73 m²: immediate referral Estimated GFR 15–29 mL/min./1.73 m²: urgent referral (routine referral if known to be stable)</p>
<p>Estimated GFR 30–59 mL/min./1.73 m²: routine referral if: progressive fall in GFR/increase in serum creatinine, microscopic haematuria present, urinary protein to creatinine ratio greater than 45 mg/mmol, unexplained anaemia (Hb below 11 mg/L), abnormal potassium, calcium or phosphate, suspected systemic illness, uncontrolled BP (above 150/90 mm/Hg on 3 agents), estimated GFR 60–89 mL/min./1.73 m²: referral not required unless other problems present.</p>
<p><u>Services irrespective of GFR</u> Immediate referral for: malignant hypertension, hyperkalaemia. (potassium >7.0 mmol/l) Urgent referral for: proteinuria with oedema and low serum albumin (nephrotic syndrome). Routine referral for: dipstick proteinuria present and urine protein/creatinine ratio above 100 mg/mmol, proteinuria and microscopic haematuria present, macroscopic haematuria but urological tests negative</p>

Pre-dialysis, renal replacement therapy—role of primary care and nephrologists

The availability of RRT forces the nephrologist to consider its application in every patient in whom it might be indicated. As kidney disease progresses patients cannot get help only from GP/FD because of pre-dialysis activities and preparations to RRT, which takes several months. Patients often feel that the nephrologist is the only doctor who should manage all medical problems.

There are many clinical problems in patients with CKD during the pre-dialysis and RRT period that can be associated with CKD, but not always. Therefore, nephrologists often provide primary care or non-renal related medical care to pre-dialysis patients or to patients undergoing chronic haemodialysis because these patients visit the centre often. Patients also often feel that the nephrologist should manage even their acute illness because the nephrologist is the first who

makes the diagnosis of acute illness. On the other hand, comparison of haemo- and peritoneal dialysis (HD, PD) patients showed that PD patients depended upon their nephrologists less [50].

A paucity of objective data exist concerning the nephrologist's role as a primary care provider: the volume and type of practice provided by the nephrologist for patients with ESRD may be similar to that of the GP/FD [51–54]. During predialysis period and especially during RRT patients visit the kidney center more often than the GP/FD office. Therefore, nephrologists have to deal beside the RRT also with other general health problems (infections, traumas, drug prescription, social problems etc.), which may or may not associate with the CKD. For example, predialysis diabetic patient with CKD and leg ischemia, peritoneal dialysis patient with abdominal pain, transplanted patient with fever or haemodialysis patient with oedema.

The results of a recent study that estimates the annualised cost of implementation of the guidelines on newly identified CKD cases among family doctors show significant increases in nephrology referral and additional investigation. The projected cost per practice of investigating stable stage 3 CKD patients was lower compared with nephrology referral [54]. More studies should be performed to compare long-term life quality and economic aspects in different managed care practices. It is possible that although in the first year CKD patient management costs are higher in specialised care settings, the long-term costs may be lower because of the better care.

Some nephrologists feel that GP/FD should be the first to encourage the use of home-based dialysis therapies, like peritoneal dialysis. In practice, however, most GP/FDs seem to be afraid of such modalities. Once a patient is already undergoing dialysis therapy the part of GP/FDs differs from country to country. In the UK, haemodialysis patients are seen by their nephrologist only once every month, so here the GP/FD might have an important role. In other countries, for example Belgium, haemodialysis patients are seen 3 times a week by their nephrologist.

Social support

Social support is an understudied, yet important, modifiable risk factor in a number of chronic illnesses, including CKD and ESRD. Increased social support has the potential to positively affect outcomes through a number of mechanisms, including decreased levels of depressive affect, increased patient perception of quality of life, increased access to health care, increased patient compliance with prescribed therapies and direct physiological effects on the immune system. Higher levels of social support have been linked to survival in several studies of patients with and without renal disease [55]. CKD patient education during the pre-dialysis period involves also management of future social needs. Usually, in patients who are students or still working, a suitable RRT modality will be considered.

CKD occurs in patients with complex medical and social problems. CKD management requires that multidisciplinary professionals provide patient education, disease management and psychosocial support. To remain cost-efficient, many physicians are training and supervising midlevel practitioners in the delivery of specialised health care [56]. In the US and other countries the CKD clinics have been organised to better meet the specific needs of CKD patients. Multidisciplinary collaboration among physicians (GP/FD, nephrologist, cardiologist, endocrinologist, vascular surgeons and transplant physicians) and participating caregivers (nurse, pharmacist, social worker and dietician) is critical as well. There are several potential barriers to the successful implementation of a CKD/ESRD program, including lack of awareness of the disease state among patients and health care providers, late identification and referrals to a

nephrologist, and complex fragmented care delivered by multiple providers in many different sites of care [57]. It is a question of the health care system whether the multidisciplinary team is built around specialist services or primary care. However, primary care is an environment permitting better coordination of medical and social care.

CONCOMITANT MAJOR HEALTH PROBLEMS IN CKD PATIENTS

Infection

Different infections are associated with CKD. Occurrence of urinary tract infections (UTI) is frequent and may complicate the course of CKD. Despite the frequency of renal impairment as a result of diabetes, the management of UTI in patients with CKD or renal failure has not been a focus of published literature [58]. Hepatitis and human immunodeficiency virus (HIV) infected patients can develop different types of CKD. All patients at the time of HIV diagnosis should be assessed for existing kidney disease with a screening urine analysis for proteinuria and a calculated estimate of renal function [20, 59, 60]. Infectious diseases are the second most common cause of death in ESRD patients [61]. Hepatitis C is a complicating factor among patients with ESRD. The source of HCV infection in these patients can be nosocomial. Screening and careful attention to infection control precautions are mandatory for dialysis units to prevent the spread of hepatitis C [62].

Regardless of age and the presence of other comorbid illnesses, it is recommended that patients with CKD receive regular vaccinations. Responsiveness to vaccination in patients with CKD can be diminished, but adequate seroresponse with standard or augmented regimens for vaccinations against influenza, hepatitis B, pneumococcus and other infections have been documented (Table 5) [63]. Live vaccines (yellow fever, polio, varicella and MMR vaccines) are generally avoided because they present a theoretical risk of vaccine-induced infection [63].

Table 5. Recommended vaccines for CKD patients

Infection	Vaccine	Existing evidence and recommendations for CKD patients
Hepatitis B virus	Non-infectious recombinant DNA hepatitis B vaccine (Engerix B®)	Seroconversion rates were found in 60–91% of ESRD patients with higher doses of vaccine with 40 µg on a four-shot schedule.
Hepatitis A virus	Inactivated non-infectious hepatitis A vaccine (Havrix®)	HAV vaccination in ESRD patients is well tolerated and immunogenic
Influenza	Inactivated influenza vaccines (Vaxigrip®, Influvac®)	Influenza vaccination was safe and effective in patients with CKD despite an impaired antibody response.
Diphtheria and tetanus	Diphtheria and tetanus toxoids	Diphtheria and tetanus vaccine can be used in ESRD patients, but monitoring of antibody levels is recommended and a booster may be used in non-responding patients.
Haemophilus influenzae	Haemophilus influenzae type B conjugate vaccine	ESRD patients should receive the same doses as for healthy subjects.
Pneumococcal infection	23-valent pneumococcal polysaccharide vaccine (Pneumo 23®)	Vaccination is recommended standard doses of 23-valent pneumococcal polysaccharide vaccine, but revaccination should be performed within 3–5

Nutrition

Dietary recommendations are important in the management of CKD and the maintenance of broader health in CKD patients. In early stages of CKD dietary protein restriction is the first recommendation to prevent its progression [64, 65]. However, the effects of dietary protein restriction in humans are controversial [66–69]. Guidelines suggest that the protein content of the diet should not be lower than 0.75 g/kg/day and should not exceed 0.8–1.0 g/kg/day [70]. The desire to maintain adequate nutrition among patients with chronic renal failure clearly competes with attempts to slow the progression of renal dysfunction with the use of a low protein diet, since this level of restriction avoids protein malnutrition and may slow progressive disease [4]. All patients with stage 4–5 CKD should undergo regular nutritional screening by a dietician. Nutritional assessment should include a minimum of a record of body weight prior to the onset of sickness, current body weight and ideal body weight; body mass index (weight/height²) and subjective global assessment. Other measures of nutritional state are: serum creatinine, serum lipids, serum albumin and handgrip strength. [65, 71]. The dietary recommendations are different in all countries, but all guidelines agree that the energy intake in CKD patients of 30–35 kcal/kg/day may be sufficient. Sodium, total fat, cholesterol, carbohydrate, protein, phosphorus and potassium are restricted for all CKD patients.

Anaemia

Anaemia is an early and common complication of CKD [72]. GP/FD's role should involve measurement of haemoglobin (Hb) concentration, MCV and MCH to assess the type of anaemia, absolute reticulocyte count to assess erythropoietic activity, plasma/serum ferritin concentration to assess iron stores, plasma/serum CRP to assess inflammation and assessment of occult gastrointestinal blood loss. GPs usually can treat most causes of anaemia. [73]. Patients with a GFR < 60 mL/min/1.73 m² should have their Hb level checked and if found to be low then their anaemia should be further investigated and treated [73], usually by a nephrologist. The recommended Hb levels at which therapy with an erythropoietic agent should be initiated is <110 g/l [74].

EDUCATION AND QUALITY OF CARE

Education

Education about the CKD, risk factors of the CKD progression and treatment with RRT should be viewed in different levels: medical professionals (nephrologists, internists, primary care doctors, nurses), patients, relatives and public health professionals. A modern approach to CKD and the concept that CKD is a risk factor for cardiovascular disease and needs to be managed (as does diabetes and dyslipidaemia) should be included in the under- and postgraduate curriculum of physicians everywhere. The free movement of doctors throughout the European Community has led to harmonisation of medical education to ensure common standards of care. [75].

Awareness of CKD risk factors among GP/FDs who treat high-risk populations, such as persons with diabetes, persons with hypertension and family members of dialysis patients, should be excellent. Only GP/FDs can diagnose the disease early and give advice to patients about the management of the risk factors that may lead to CKD progression. Primary care physicians and nurses need targeted education to increase awareness of populations at high risk for CKD [76].

Timely education of CKD patients, their family members and close friends and/or primary care

providers is critical for both HD and PD. Studies have shown that this can both improve outcomes and reduce costs. Nephrology nurses are often crucial for educating patients with CKD, patients with ESRD, family members and caregivers.

Hypertension and diabetes care guidelines have been recently updated. Many guidelines also have been worked out exceptionally for nephrologists [48]. A nephrologist's conformity to guidelines has been shown systematically better than that of non-nephrologists. Published analyses reveal that a large number of patients with advanced CKD are being treated solely by non-nephrologists and that nephrologists treat patients with more advanced disease [77].

In order to improve patient outcomes, there is a need to take a more holistic approach to the problem, by coordinating the efforts of policymakers, those involved in health care system redesign, clinicians and researchers. In doing so, there should be an improvement in both identification and management of patients with impaired kidney function, whether cared for by primary care physicians, specialists, or nephrologists and irrespective of the health care system [78].

Quality of care in CKD

Monitoring quality, particularly when clinically detailed measures are combined with appropriate incentives, may be one of the most effective ways to improve performance on targeted measures [79]. However, quality monitoring is only one aspect of quality management. Training of health staff, promoting use of guidelines, having a database of chronically ill patients, call/recall systems, early recognition and referral, improved information systems, etc., are other very important tools in improving the quality of care of chronic patients [80]. Wagner and his co-partners worked out the widely accepted model of improvement of chronic disease management, which includes several components and which are also important when talking about CKD management [81].

Training of health staff: Several studies have shown that there is a lack of awareness of evidence-based guidelines of CKD, a large variability in the treatment of complications of CKD and uncertainty of timing for referral to a nephrologist. The need for targeted training to raise the awareness of clinical practice guidelines and recommendations for patients with CKD among primary care physicians is emphasised [43, 82, 83].

Existence and implementation of evidence-based guidelines for management of CKD patients: For optimal management of patients with CKD in primary care good guidelines are needed including identification of those who would benefit from referral to specialist services. Formulating and implementing specific treatment strategies are key factors in the success of achieving quality patient outcomes. Evidence-based guidelines for management of CKD have been developed in several countries [47, 48, 84]. As a variety of models have been proposed and implemented to improve CKD care, careful evaluation of what works and what does not work in the current clinical environment is needed. Guidelines need to be adapted to local situations in order to be acceptable and implemented.

Information system facilitating the development of disease registries, tracking systems and reminders. Early identification of CKD is important as it allows appropriate measures to be taken to slow or prevent the progression to more serious CKD and also to combat the major risk of illness or death due to cardiovascular disease. Studies of general practice computerised medical records show that it is feasible to identify people with CKD [85] and that computer records are a valid source of data [86]. The UK Quality and Outcomes Framework has a very good example in

having a valuable database of chronic patients and improving the quality of care. This system also consists of indicators for monitoring CKD, e.g. the percentage of patients on the CKD register in whom the last blood pressure reading, recorded in the previous 15 months, is 140/85 or less; the percentage of patients in the CKD register with hypertension who are treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker [22].

Reorganising team function and practice systems to meet the needs of CKD patients. Ensuring access to services that are proven to improve outcomes. Recognition of CKD by the treating physician and timely nephrology referral are shown to be essential components for providing adequate care to patients with CKD [27, 84]. Several authors believe that patients with CKD require a multidisciplinary team approach that focuses on early diagnosis of CKD, identifying and managing the complications of CKD, co-morbid conditions and smoothing transition to RRT. There should be integrated services with primary care, specialist services (nephrologist, endocrinologist, cardiologist, surgeon), nurses, a dietician and a palliative care team [47, 57, 87, 88].

Recommendations, issues for policymakers

1. Health systems should guarantee the access of the population to primary care and with referral to secondary care, if needed.
2. Primary care should have a leading position in implementing the screening programs of CKD in risk groups, and health systems should provide resources for this.
3. Primary care is in an ideal position to implement primary and secondary prevention of CKD. It is important to realise that CKD adds significantly to the overall cardiovascular risk; therefore, the prevention should be looked at in the framework of cardiovascular prevention.
4. Optimal cooperation between primary and secondary care should be developed for CKD patients. Shared-care models permit better coordination of services and are more cost-effective.
5. In primary health care teams of GPs and other specialists should be involved. It is important to collect evidence of the role of primary care in prevention and care for patients with CKD. For advanced CKD cases when renal replacement therapies are used, nephrology teams have a major role. Even in this phase good cooperation between primary and secondary care permits the best results for patients and for society. Educational programs for different levels of patients, nurses and doctors are of utmost importance for achieving the best outcomes.

Appendices

1. Consensus Statements of the ISN (International Society of Nephrology) 2004 Consensus Workshop on Prevention of Progression of Renal Disease, Hong Kong, June 29, 2004 (http://www.nature.com/isn/education/guidelines/isn/full/ed_051027_4.html)

The International Society of Nephrology recommends reference to these statements when formulating policy and guidelines for tackling chronic kidney disease, a disease with significant global impact.

1. It is recommended to establish a global surveillance center (ISN Kidney Disease Data Center

or ISN KDDC) to coordinate worldwide standardized screening studies with standardized screening techniques in appropriate target groups to allow for the collection of clearly comparable data.

2. It is recommended that patients diagnosed with diabetes and hypertension should have regular screening for development of kidney disease.

3. It is recommended that close relatives of patients with nephropathy due to diabetes, hypertension and glomerulonephritis should also be the primary targets for screening to detect clinically silent kidney disease.

4. No consensus was made on an exact age "cut-off" for initiating chronic kidney disease (CKD) screening.

5. It is recommended to develop standardized region- (or nation-) specific guidelines. It is envisaged that the "tailor-made" tools for a particular region should provide reproducible and comparable results.

6. It is asserted that kidney disease is already a significant public health concern. There should be national policies for both public health and medical professionals to educate their societies on the importance of screening and early detection of kidney disease on prevention.

7. It is recommended to validate the current glomerular filtration rate (GFR) estimation formulas based on ethnicities in different parts of the world.

8. It is recommended to use albumin-creatinine ratios (ACR) to quantify proteinuria and allow for follow-up. However, it is probably cost prohibitive to use ACR as a tool for primary renal disease screening (except in diabetic patients).

9. It is strongly recommended to have the relevant screening for the development of CKD, recognizing its close interrelationship with cardiovascular, diabetic, and chronic metabolic diseases. Traditional cardiovascular disease risk factors should be screened in all patients with CKD. These include documentation of smoking history, measurement of blood pressure, body weight, body mass index, fasting plasma glucose, fasting lipid profile, serum uric acid level, and 12-lead electrocardiogram (ECG).

10. With the validation of GFR formulas in different ethnic groups, it is endorsed that GFR should be estimated from serum creatinine concentration at least yearly in patients with CKD. This should be done more often in patients with GFR below 60 mL/min/1.73 m², GFR decline greater than 4 mL/min/1.73 m², risk factors for faster progression, or exposure to risk factors for acute GFR decline, and in those undergoing treatment to slow progression.

11. It is endorsed that CKD patients should be encouraged to reduce their body weight if overweight, adopt a healthy eating habit, restrict their dietary salt intake, cease smoking, moderate their alcohol consumption, and increase physical activity.

12. It is endorsed to achieve the target for blood pressure control in CKD patients of below 130/80 mm Hg. It is recommended that adjunctive dietary salt restriction is invariably required. Diuretics and multiple medications in addition to angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) may also be used to achieve the blood pressure targets.

13. It is endorsed that glycemic control in diabetic patients with CKD should be optimized to achieve a target fasting plasma glucose of <7.2 mmol/L and a hemoglobin A_{1c} (HbA_{1c}) level of <7%. Hypertensive diabetics and those with micro-albuminuria or macro-albuminuria, whether hypertensive or not, should be treated with either an ACE inhibitor or ARB.

14. It is recognized that further large scale studies to substantiate the combined use of ACE inhibitor and ARB are needed, but that the cost of such combined therapy may be prohibitive for some countries.

15. It is recommended that patients with CKD should be referred to a nephrologist for evaluation when their creatinine clearance is $< 30 \text{ mL/min/1.73 m}^2$, or earlier in patients at risk of rapid progression or in whom doubt exists as to their diagnosis and prognosis.

Guidelines

2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension:

ESH-ESC Task Force on the Management of Arterial Hypertension.

http://www.escardio.org/knowledge/cardiology_practice/ejournal_vol6/vol6n9.htm

[89]

European Renal Association – European Dialysis and Transplantation Association guidelines: <http://www.era-edta.org/guidelines.htm>

International Society of Nephrology web site guidelines:

<http://www.nature.com/isn/education/guidelines/guidelines.html>

Chronic kidney disease in adults. UK guidelines for identification, management and referral. RCP publications.: http://www.rcplondon.ac.uk/pubs/books/kidney/ckd_clinical_guide.pdf

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