ABSTRACT:

Chronic Kidney Disease (CKD) is common, harmful and treatable. It is worldwide public health problem, with several adverse outcomes; progressive loss of kidney function and high risk of cardiovascular disease (CVD) and premature death. The asymptomatic nature of CKD needs early detection using laboratory tests. The laboratory approaches to detect CKD include urine examination for protein and urine albumin/creatinine ratio, S. creatinine estimation and measuring blood pressure. Screening is recommended for those who are at increased risk of CKD (diabetics, hypertensive, age above 50 years, family history of renal disease and patients with family history of diabetes, hypertension or coronary artery disease). Screening is useful only when a subject who has been found positive on such a screening can be offered effective treatment. We can slow down the progression of chronic kidney disease by early interventions and changing some of our living habits. Of importance, similar treatment help not only to prevent progressive renal function loss, but they also contribute to prevent the progressive CVD encountered in patients with chronic kidney disease.

Thus, all interventions (lowering blood pressure and lipids, blocking RAA system, cessation of smoking and life style modification) that are necessary to attenuate the progression of CKD are also beneficial for reducing cardiovascular diseases and mortality (what is good for kidney is also good for the heart).

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide medical and public health challenge due to the high risk of progression to end-stage-renal-disease (ESRD), the increased cardiovascular burden and high management cost. Early detection of CKD followed by appropriate clinical management appears the only means by which the increasing burden on the health-care system and affected individual will be reduced. The asymptomatic nature of CKD means that early detection can only occur through laboratory testing of individuals. CKD is defined as glomerular filtration rate <60 ml/minute/1.73m². The patient is not aware of having renal function impairment, because symptoms develop only if GFR decreases below 30 ml/minute/1.73m². Earlier identification of these patients is therefore warranted.

This article will review options/interventions used to prevent the progression of CKD to end-stage-renal-disease. Of importance, similar interventions help not only to prevent progressive renal function loss, but they also contribute to prevent the progressive cardiovascular disease encountered in patients with CKD. The following issues will be addressed:

1. Principles of Screening for CKD.
2. Who should be Screened?
3. How should CKD be Screened?
4. Retarding Progression of CKD.
5. Treating consequences of CKD.
6. Reducing risk of CVD.
7. Conclusion
8. Take Home Message

1. Principles of Screening for CKD

The early recognition of CKD is made difficult by its largely asymptomatic nature. Stage I-3 is known as Early CKD. The detection of CKD early in its course relies on the performance of tests on urine (albumin or protein) and blood (serum creatinine) together with blood pressure measurement. Glomerular filtration rate (GFR) is the best measure of overall renal function and in epidemiological studies this can be best performed using an estimated GFR (eGFR). For this purpose the Cockraft-Gault formula and the Modification of Diet in Renal Disease (MDRD) formula are being used most frequently (Table I).

2. Who should be Screened?

Whole population screening for CKD is impractical and is not cost-effective. Screening of those at increased risk of CKD (diabetes, hypertension, age > 55 years, persons with family history of diabetes, hypertension or chronic kidney disease) is cost-effective. Community screening programmes targeted at known diabetics, hypertensive and
Retarding Progression of Chronic Kidney Disease (CKD)

The two principal outcomes of CKD are progressive loss of renal function and the development & progression of cardiovascular disease (CVD). Although, the rate of progression of CKD is related to some non-modifiable characteristics such as race, baseline renal function, male gender, and increased age, there are a number of modifiable characteristics. It is important to note that three most widely studied interventions; lowering blood pressure (BP), proteinuria reduction and anti-hypertensive drugs are inextricably linked in their effects on glomerular filtration rate (eGFR).

Blood pressure (BP)

Hypertension is both a cause and consequence of CKD. The prevalence of hypertension is inversely related to GFR. Observational and interventional studies show that BP reduction slows the rate of progression of CKD. In a meta-analysis of 11 RCTs including 1860 patients with non-diabetic kidney disease, the lowest risk of CKD progression was seen with systolic BPs of 110-119 mmHg in patients with > 1 gm/day proteinuria (an effect not seen with lower grade of proteinuria). There was a significant increase in the risk of CKD progression at a systolic BP of > 130 mmHg. The modification of diet in renal disease (MDRD) trial showed that there was a linear relation between increasing MAP and the rate of loss of GFR, the effect being greater in patients with higher degree of proteinuria.

Proteinuria

Proteinuria is common in CKD and is a strong independent risk factor for CKD progression. Reducing proteinuria reduces the risk of CKD progression. BP reduction will reduce proteinuria. A meta-analysis of 84 studies demonstrated that proteinuria reduction was proportional to BP reduction in both diabetic and non-diabetic renal diseases. However, some studies are able to show an effect of proteinuria reduction on CKD progression independent of BP control.

Recommendation

Proteinuria reduction should be targeted to slow CKD progression.

Anti-hypertensive drugs

Specific anti-hypertensive drugs may reduce proteinuria and slow CKD progression independent of BP lowering effects, with the most rigorous data supporting the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

In non-diabetic CKD, meta-analysis demonstrate that ACEIs and ARBs can reduce proteinuria. In diabetic CKD, meta-analysis demonstrate that ACEIs in type-2 diabetics, and both ACEIs and ARBs in type-1 diabetics regress microalbuminuria to normoalbuminuria. ACEIs also reduce the rate of progression of microalbuminuria to macroalbuminuria in type-1 and 2 diabetics as do ARB in type-2 diabetics. Finally, two further meta-analyses demonstrate that ACEIs can reduce albuminuria in diabetics. Combination therapy significantly reduced proteinuria independent of BP lowering without causing clinically relevant change in serum potassium level or GFR. In terms of other agents, non-dihydropyridine CCBs significantly reduced proteinuria independent of BP control when compared with dihydropriyridine CCBs. There are also RCTs supporting the use of thiazide diuretic indapamide in type-2 diabetics with hypertension resulting in reduction of microalbuminuria comparable to that achieved by ACEIs enalapril and captopril.

In recent years complete blockade of the rennin-angiotensin-aldosterone (RAA) pathway is suggested to prevent progressive chronic kidney disease. Aldosterone antagonist reduces proteinuria in CKD patients already on ACEIs and ARBs, but increases the risk of hyperkalaemia. Long-term effects of those agents on renal outcomes, mortality and safety need to be established. At present use of complete RAA pathway blockade is not recommended in routine clinical practice.
Recommendation

ACEIs and/or ARBs should be used in all diabetics who tolerate them and in all non-diabetic CKD patients with > 0.5 gm/day proteinuria to reduce proteinuria and slow the rate of progression of CKD. Where RAAS-active drugs cannot be tolerated, non-dihydropyridine CCBs or indapamide can be considered. Further research is needed to clarify the benefit of these drugs beyond BP control alone in patients without proteinuria. Complete blockade of the RAA-pathway to prevent progressive chronic kidney disease is not recommended because of risk of hyperkalemia, hypotension and even worsening of renal function. In theory, complete rennin-angiotensin-aldosterone blockade might be better than partial blockade, but we need more data.

Role of other factors in slowing the progression of chronic kidney disease (CKD):

1. Strict glycemic control (for diabetics only)
2. Lipid-lowering therapy
3. Smoking cessation
4. Dietary modification
5. Regular exercise & weight loss

Strict glycemic control

Several trials (DCCT and UKPDS) suggested that glycemic control with target HbA1C level of ≤ 6.5% is helpful in preventing the onset and progression of diabetic microangiopathy. The Joint British Society guidelines recommend that an HbA1C of ≤6.5% significantly reduce the risk of developing diabetic complications.

Lipid-lowering therapy

Three analyses address the issue of lipid-lowering and CKD progression. One suggested that current evidence for benefit was lacking, whilst another suggested that lipid-lowering may reduce proteinuria and retard the progression of CKD. However, current evidence is insufficient to recommend lipid-lowering therapy to slow the progression of CKD.

Smoking and alcohol

Several observational studies highlighted the nephrotoxic nature of smoking. Chronic smoking increases the risk of proteinuria and accelerates the rate of decline of GFR. Observational studies showed that quitting smoking slowed down CKD progression. The role of alcohol in the development and progression of CKD is less clear. Analysis of NHANES II data did not support a relationship between alcohol consumption and CKD. There are no data on the effects of reducing alcohol consumption on CKD progression.

Recommendation

Smoking must be given up because smoking cessation slow CKD progression. However, there is insufficient evidence that alcohol moderation slows CKD progression.

Dietary modification

The evidence for dietary modification reducing CKD progression is limited to stage 1-3 CKD. Three small RCTs in diabetic patients with stages 2-3 CKD did not show any benefit of protein restriction on CKD progression (0.6 to 0.8 gm/kg/day). One small trial in non-diabetic patients with CKD stage 3 demonstrated a positive effect of protein restriction (0.6 gm/kg/day) on CKD progression, but this was at the expense of an overall deterioration in nutritional status.

Recommendation:

There is insufficient evidence to recommend low protein diet to slow down the progression of early CKD. There is some evidence to support sodium restriction in order to reduce blood pressure.

5. Treating the consequences of CKD

Additionally, anaemia, acidosis and disturbance of calcium and phosphate metabolism should be looked for and treated in patients with CKD stage 3 or above.

Anaemia: “Renal” anaemia is common in CKD and is due to combination of factors; primarily erythropoietin (EPO) deficiency, iron deficiency, hemolysis, and uremic inhibitors of erythropoiesis. In the NHANES III Study, the prevalence of anaemia was 1% at an eGFR of 60 ml/min/1.73m², 9% at an eGFR of 30 ml/min/1.73m² and 33% (men) to 67% (women) at an eGFR of 15 ml/min/1.73m². Whether, the early treatment of anaemia affects CKD progression and cardiovascular morbidity and mortality is currently not clear. However, correction of anaemia predialysis can improve quality of life and exercise capacity.

Recommendation:

CKD patients should maintain a target hemoglobin concentration of > 11 gm/dl using erythropoiesis-stimulating agents (ESA).

Acidosis: The incidence of metabolic acidosis increases with declining renal function, but tends not to occur until CKD stage 4. The detrimental effects of acidosis include muscle wasting, loss of bone mass, exacerbation of β₂-microglobulin accumulation, and impaired insulin sensitivity. The correction of acidosis can result in beneficial effects in terms of bone and muscle metabolism, however, there have been no RCTs investigating acidosis correction on the clinical outcome.
Retarding Progression of Chronic Kidney Disease (CKD)

Recommendation:
There is insufficient evidence to make recommendation on the treatment of metabolic acidosis. However, maintenance of serum bicarbonate level at ≥ 22 mmol/L is reasonable.

Calcium and Phosphate homeostasis: Disturbance in calcium and phosphate metabolism and secondary hyperparathyroidism occur with increasing frequency and severity as GFR declines. Serum phosphate level begins to rise below an eGFR 60 ml/min/1.73m² due to phosphate retention, with serum calcium level falling due to reduced activity of vitamin D (reduced renal 1α-hydroxylation). Parathyroid hormone (PTH) level begins to rise as a consequence of both low calcium and high phosphate below an eGFR 60 ml/min/1.73m². These changes not only affect bone integrity, but also promote soft tissue and vascular calcification over time increasing cardiovascular morbidity and mortality in later CKD stages. Observational data and experimental evidence suggest that early intervention is appropriate. The treatment targets in CKD stage 3 are currently more a matter of opinion than evidence. Initial therapy for hyperphosphatemia includes dietary phosphate restriction and the use of oral phosphate binders. Secondary, hyperparathyroidism is initially treated with the replacement of deficient 1α-calcidol.

6. Reducing risk of cardiovascular diseases (CVD)
Independent of the etiology, the presence of CKD is a strong predictor of CVD. In fact, JNC-7 recognizes an estimated GFR below 60 ml/min as a major cardiovascular risk factor. The K/DOQI guideline suggests that “all patients with CKD should be considered in the “highest risk” group for cardiovascular disease, irrespective of level of traditional CVD risk factor. Hypertension reduction reduces CVD risk in general population. In CKD population specifically, RAAS blockade may reduce cardiovascular risk.39 Combination of lipid lowering agents and aspirin is beneficial in reducing cardiovascular event in patients with CKD.40 The importance of lifestyle modification (diet, exercise, smoking cessation and alcohol moderation) must not be overlooked in CKD patients, because traditional CVD risk factors persist in Chronic Kidney Disease.

Summary of interventions
The current evidence would favor the following treatment goals in order to both slow the progression of CKD and reduce CVD risk:

- **Lowering of Blood Pressure (BP)**: Target BP <130/80 mm Hg (<125/75 mm Hg if > 1 gm/day proteinuria): BP reduction will reduce proteinuria, slow CKD progression and reduce CVD risk.
- **Blocking RAA system**: ACEI and ARBs to reduce proteinuria and slow CKD progression.
- **Glycemic control**: HbA1c < 6.5% in diabetics to reduce microvascular complications.
- **Smoking cessation**: Smoking must be stopped.
- **Lowering lipid**: Total cholesterol < 4 mmol/L.
- **Life style modification**: Encourage regular exercise, weight reduction, alcohol and salt limitation, and avoidance of excess protein intake.

Additionally, acidosis, anaemia, and disturbances of calcium and phosphate metabolism should be looked for and treated in patients with CKD stage 3 or above.

7. Conclusion:
There exist strong evidence that CKD and its progression to ESRD are increasing worldwide. This pose a growing health-care and financial burden. Therefore, there is an urgent need to develop preventive strategies. The asymptomatic nature of CKD means that early detection can only occur through laboratory testing of individuals. Analysis of urine for albumin or protein, S. creatinine level in blood and measurement of blood pressure of individual at increased risk of CKD (diabetics, hypertensives, and aged > 50 yrs) are simple, cheap and easy ways to detect CKD. Institution of early intervention (antihypertensives, ACEI/ARB) will lead to reduction in cumulative incidence of ESRD. It has been observed that screening of population at risk and their treatment is cost effective.

8. Take Home Message:
Early detection of chronic kidney disease (CKD) followed by appropriate clinical management appears the only means by which the increasing burden on the health-care system and affected individuals can be reduced.

REFERENCES:


