REVIEW

CHRONIC KIDNEY DISEASE (CKD): THE SILENT EPIDEMIC. THE IMPORTANCE OF EARLY DETECTION AND TREATMENT ON THE PREVENTION OF CKD

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ABSTRACT

The incidence and prevalence of end-stage renal disease (ESRD) is increasing worldwide. Despite the absence of precise epidemiological data, it is known that there are a great many patients in the conservative phase of chronic kidney disease (CKD). In this context, any medical intervention that may prevent the progression of CKD towards ESRD is extremely important. Improving the patients’ cardiovascular status is also a major objective in the management of this population, as cardiovascular disease is the leading cause of morbidity and mortality for dialysis patients.

Keywords: Chronic Kidney Disease, Epidemiology, Prevention, Cardiovascular Disease

INTRODUCTION

1. Epidemiology of Chronic Renal Disease (CRD)

1.1. Definition and Detection of Kidney Damage

Chronic kidney damage is defined as structural abnormalities of the kidney that can lead to decreased kidney function. The level of glomerular filtration rate (GFR) is accepted as the best measure of overall kidney function in health and disease. Pathologic studies show that substantial kidney damage can be sustained without decreased GFR. Albuminuria is widely accepted as a marker of glomerular damage, and excretion of even small amounts of albumin (microalbuminuria) is the earliest manifestation of diabetic kidney disease. In addition to its importance as a marker of kidney damage, albuminuria is also an important prognostic factor for the progression of kidney disease and development of cardiovascular disease. Other examples of markers of kidney damage in chronic kidney disease include abnormalities in the urine sediment and abnormalities on imaging studies of the kidney. High blood pressure was not defined as a marker of kidney damage because high blood pressure has other causes. The relationship between high blood pressure and kidney disease is complex, as high blood pressure is both a cause and a consequence of kidney disease.

As a rule, kidney failure due to chronic kidney disease is preceded by a stage of variable length during which GFR is decreased. GFR is affected by a number of factors in addition to kidney disease, not all individuals with decreased GFR have CRD. Mild reduction in GFR was defined as CRD only in the presence of kidney damage. However, because of the risk of complications, moderate to severe reduction in GFR and kidney failure (ESRD) were defined as chronic kidney disease, irrespective of the presence of kidney damage. Other than kidney disease, the most important factor affecting GFR is age. After approximately age 20 to 30 years, the normal mean value for GFR declines with age in both men and women, with a mean decrease of approximately 1 ml/min/1.73 m² per year. Therefore, mild reduction in GFR may be normal at the extremes of age and, in the absence of
kidney damage, is not considered to be CRD. GFR is slightly lower in young women than in young men and this difference appears to persist at older ages.  

1.2. Prevalence of Proteinuria in Adults

Table I shows the prevalence of albuminuria estimated from the albumin-to-creatinine ratio in a single spot urine collection in 14,836 adults studied in NHANES III. Based on these results, it is estimated that approximately 20.2 million adults have abnormal urine excretion. Among adults, the prevalence of albuminemia varies by age and presence or absence of diabetes. The prevalence is approximately 30% in adults with age ≥70 years: 26.6% with microalbuminuria and 3.7% with albuminuria. At all ages, the prevalence is higher among individuals with diabetes. Among individuals with a history of diabetes, the prevalence of microalbuminuria and albuminuria is 43.2% and 8.4%, respectively, at age ≥70 years. Among individuals without a history of diabetes the prevalence of microalbuminuria and albuminuria is 24.2% and 3%, respectively, at age ≥70 years.

Table I: Prevalence of Albuminuria in Adults: NHANES III

<table>
<thead>
<tr>
<th>Albumin/Creatinine Ratio</th>
<th>n</th>
<th>US Adult Prevalence (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12,478</td>
<td>88.4% (0.4)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>2,040</td>
<td>10.6% (0.4)</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>318</td>
<td>1.1% (0.1)</td>
</tr>
<tr>
<td>Totals</td>
<td>14,836</td>
<td>100%</td>
</tr>
</tbody>
</table>

Abbreviation: SE, standard error

In the KEEP 2.0 program when six thousand seventy-one persons with hypertension or diabetes or a first-order relative with hypertension, diabetes, or kidney disease, were screened, microalbuminuria was found in 29% of the participants, with 96% of those cases occurring in participants without a reported history of kidney disease. Among participants with microalbuminuria, 34% met the definition for diabetes. Among individuals with EGFR=89 ml/min/1.73m², the prevalence of microalbuminuria was %27.9. Persons of African-American, Native-American, or Asian/Pacific Islander race compared with whites and those with systolic or diastolic hypertension, diabetes, or an estimated GFR (eGFR) less than 60 ml/min/1.73 m² were significantly more likely to have microalbuminuria.

In another study aimed to designate the impact of microalbuminuria in the general population approximately 7% of 41,000 subjects had microalbuminuria. Of this group of 3000 patients with microalbuminuria, 75% were not known to have either diabetes or hypertension. Although the prevalence of microalbuminuria was higher in diabetic (16%) and hypertensive (%11) subjects, still 6.6% of subjects without known risk factors appeared to have microalbuminuria. Whereas the percentage was fairly stable over all ages in woman, it greatly increased in men over 50 years of age.

As most of the subjects with microalbuminuria were not known to have diabetes and hypertension, what caused microalbuminuria in these subjects? Besides male gender and age, obesity and smoking were found to be important predictors for a higher risk of having microalbuminuria.

These studies focused primarily on Caucasian populations. Extremely limited data are available in literature for the identification of risk factors for the development of urinary abnormalities among Asians, particularly among the Chinese population. In an epidemiological data on proteinuria aimed to identify the determinants of proteinuria for Chinese, Malays, and Asian Indians in Singapore proteinuria of ≥1+ was observed for 1.1% (2014 subjects) of the young adult working population. Among subjects with proteinuria of ≥1+, 0.79% of the total population exhibited isolated proteinuria and the remaining 0.27% of the total population exhibited proteinuria with hematuria. Subjects with a history of diabetes, hypertension or renal disease were more likely to exhibit proteinuria and each increase in age beyond 30 years was observed to be associated with a progressively greater likelihood of proteinuria. In addition, increasing BMI, systolic and diastolic blood pressure, familial history of diabetes, hypertension and kidney disease was associated with proteinuria.

1.3. Prevalence of Urinary Sediment Abnormalities in Adults

In the KEEP 2.0 program, the prevalence of pyuria was found to be much greater in women
The increased prevalence of pyuria might mark a specific risk for kidney progression; namely, the presence of asymptomatic urinary tract infections, which appears to be of greater prognostic and pathological significance for women with diabetes and increases the risk for progressive kidney failure.

1.4. Incidence and Prevalence of Kidney Disease

Both the incidence and prevalence of treated ESRD are increasing. Reasons for this are likely to be an actual increase in the occurrence of CRD. Data on ESRD are quite extensive, due to the availability of registries covering a large percentage of patients on RRT. However, epidemiological data regarding CKD in the predialytic phase may be unreliable because of an increasing tendency to extrapolate data obtained from RRT population. Available data shows that CKD is a significant epidemiological problem even in its conservative phase.

A French epidemiological study of a large urban area indicated an overall annual incidence of CKD of 260 pmp, with a striking increase in incidence with age. The incidence in patients aged >75 years was almost seven times higher than that of patients 20-39 years and more than twice that of patients aged 40-59 years.

The most comprehensive source of epidemiological data on CKD in the predialytic phase is the Third National Health and Nutrition Examination Survey (NHANES III), which collected epidemiological data in the USA from 1988 to 1994. NHANIS III reported that 4.98% of the male population and 1.55% of the female population had serum creatinine (Scr) >2.0 mg/dl and 0.64% and 0.33% respectively. The same report also found that older age and male sex were associated with higher Scr levels. More than 25% of American males aged >70 years had Scr levels >1.5 mg/dl.

Eleven percent of the adult population has varying stages of CKD, according to researchers from the John Hopkins Bloomberg School of Public Health. Four percent of the USA adults, approximately 8 million people, have less than half of the normal kidney function of a young adult. This low level of kidney function is estimated to be present in one out of every five Americans over the age of 65. Another 11 million adult Americans have a persistent presence of at least a small amount of albumin in their urine.

Researchers used the recently developed National Kidney Foundation Clinical Practice Guidelines which provide a standardized definition of CKD and its stages to a nationally representative sample of 15625 non-institutionalized adults who participated in the NHANES III. CKD stages are based on estimated kidney function measured as GFR. A healthy young adult has a GFR of 130 ml/min/1.73 m². The researcher found an estimated 5.9 million individuals (3.3%) had stage 1/normal kidney function with protein found in urine on two occasions; 5.3 million (%) had stage 2/mildly decreased kidney function with protein found in urine on two occasions; 7.6 million had stage 3/moderately decreased kidney function (GFR 30-59 ml/min/1.73 m²); 400000 (0.2%) had stage 4/severly decreased kidney function (GFR 15-29 ml/min/1.73 m²); and 300000 (0.2%) had stage 5 or kidney failure. Older age was strongly associated with a higher prevalence of moderately or severely decreased kidney function.

The prevalence of reduced kidney function was greater in KEEP than in other studies. In KEEP, 5.4% of the subjects were identified as having elevated serum creatinine levels, including 8.3% of the men and 4.0% of the women. In addition, older age, male sex, African-American race, and presence of diabetes, anemia, and/or microalbuminuria had a significant association with EGFRs less than 60 ml/min/m². Using the stages of kidney disease defined in the K/DQOI guidelines, it was estimated previously that 3.7% of Americans have an EGFR less than 60 ml/min/1.73m², in the KEEP study that targeted those at high risk for kidney disease, 16% of subjects had reduced EGFRs. 93% of these subjects with an EGFR less than 60 ml/min/1.73 m² had no history of kidney disease. Consequently, KEEP follow-up data showed the effectiveness of community-based targeted health screening programs in increasing awareness of kidney disease among high-risk groups.

There have been many studies focusing on African-American/white differences in CKD. All of these studies have documented an excess risk for African Americans, compared with whites, with estimates of the association ranging from 1.9 to 7.4. In a population-based study, the age-adjusted incidence of kidney disease attributable to diabetes mellitus or hypertension was found to be almost 12 times higher among
African-American adults, compared with whites. Higher blood pressure, lower income, and higher prevalence of diabetes mellitus and hypertension among African-American adults explained some of the racial differences in CKD risk. However, most of the excess risk of CKD experiences in African Americans cannot be explained by traditional risk factors. A potential explanation for the unexplained excess risk among African Americans might be unmeasured environmental, behavioral, sociocultural, or developmental factors.

Undernutrition in fetal life imparts a higher risk of CKD in adulthood. Because African Americans exhibit much higher rates of low birth weights, compared with whites, and low birth weights are associated with kidney underdevelopment, the low birth weight theory has been advanced to help explain the racial differences in CKD rates. Additionally, African Americans are more likely to be exposed to occupational and environmental toxins, to experience viral infections, and to have less access to preventive medical care, as well as being referred to treatment for CKD late in the course of their disease. Enhanced susceptibility of African-American kidneys to injury resulting from hypertension and racial differences in renal vascular hemodynamics have also been reported as explanations for the racial disparity in CKD risk.

1.5. Risk Factors for Chronic Kidney Disease (CKD)

A risk factor is defined as an attribute that is associated with increased risk of an outcome. In principle, there are four kinds of risk factors for adverse outcomes of CKD which were defined by the Work Group as “CKD risk factors” (Table II).

**Table II: Types of Risk Factors for Adverse Outcomes of CKD**

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Susceptibility</strong></td>
<td></td>
</tr>
<tr>
<td>Factors</td>
<td>Increased susceptibility to kidney damage</td>
</tr>
<tr>
<td><strong>Initiation</strong></td>
<td>Directly initiates kidney damage</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Cause worsening kidney damage and decline in kidney function after initiation of kidney damage</td>
</tr>
<tr>
<td><strong>End-stage</strong></td>
<td>Cause complications in patients with kidney failure</td>
</tr>
</tbody>
</table>

ESRD is disproportionately high among older individuals, certain ethnic minorities, and individuals with hypertension, diabetes, and autoimmune diseases. This observation suggests that demographic and clinical factors may be risk factors for the development or progression of CKD. In addition, individuals with a family history of kidney disease appear to be at higher risk of developing kidney disease. This appears to be true for most types of kidney disease, suggesting the presence of genes coding for susceptibility factors for the development or progression of kidney disease in general, as well as genes coding for specific kidney diseases, such as autosomal dominant polycystic kidney disease or Alport’s syndrome.

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1.6. Notion of Renoprotection

Most renal diseases progress to renal failure as a consequence of functional adaptations intervening in the kidney, after the original disease prices causes a critical loss of nephron units. Renoprotection is a strategy that aims to interrupt or reverse this process.

1.6.1. Renoprotection by Dietary Management

The efficacy of dietary protein restriction in slowing progression of CKD is still controversial despite a large number of studies over the last decades. Although reduction of the amount in the diet prevents disease progression in most animal models, several large-scale randomized clinical studies reported minor benefits of low-protein diets but failed to demonstrate a major effect. In an Italian controlled study, the effect of a low-protein diet (0.6 g/kg daily) on cumulative renal survival was only of borderline significance compared with a normal controlled protein diet (1.0 g/kg daily). In the Modification of Diet in Renal Disease (MDRD) study, the benefit of a low-protein diet (0.58 g/kg daily) in the delaying dialysis was not substantial. A recent meta-analysis showed that a restricted protein intake was associated with a 39% reduction in the relative risk of death or need for RRT compared with normal protein intake. However, because...
low-protein diets decrease serum-urea levels, and the decision to start RRT is often based on these levels, patients with a reduced intake would be expected to start RRT later than patients with higher protein intake. Therefore, it is difficult to understand from the data whether low-protein diets effectively reduce the progression of CKD or simply provide better metabolic control, which in any case is of major importance for phosphate control.

1.6.2. Renoprotection by Blood Pressure and Proteinuria Control

Other than treatment of the primary disease, control of blood pressure and proteinuria are the only interventions to date that have definitively demonstrated the ability to slow the progression of CKD. Hypertension came to be recognised as a strong, independent risk factor for ESRD.

The results of the MDRD study showed that patients assigned to target mean arterial pressures of 92 and 107 mmHg had a decline in GFR of -3.56 and -4.10 ml/min year, respectively. The MDRD study also indicated that patients with higher levels of proteinuria had faster declines in GFR and that the beneficial effect of lowering blood pressure on the progression of CKD was associated with the severity of baseline proteinuria.

For this reason, proteinuria level should always be taken into account when defining the target blood pressure for patients with CKD.

Some antihypertensive drugs themselves display renoprotective effects that appear to be partially independent of the blood pressure control. Several clinical trials have shown that drugs blocking the renin-angiotensin system ACE (angiotensin-converting enzyme) inhibitors and AT-II (angiotensin receptor) antagonists are more effective in reducing CKD progression than other antihypertensive drugs, and this effect could be partially independent of an increased blood pressure control.

Whenever proteinuria is decreased, progression to ESRD is reduced. Results of the MDRD study established that a reduction of proteinuria was associated with a decrease in the rate of decline in GFR, and that the protection of renal function achieved by lowering blood pressure was dependent on the extent of the initial proteinuria. The Ramipril Efficacy In Nephropathy (REIN) study identified that a sustained reduction in proteinuria prevented or slowed long-term GFR decline. Patients who had more proteinuria to start with, benefited more from blood-pressure-lowering treatment than those who had less proteinuria.

Table III summaries results from 11 trials (2387 patients). Reduction of proteinuria was invariably associated with improved outcome, whereas no effect on proteinuria predicted no long-term benefit. A worsening proteinuria was never associated with improvement.

Table III: Change in proteinuria from baseline and renal disease outcome in 11 trials in non-diabetic chronic nephropathy

<table>
<thead>
<tr>
<th>Reduced proteinuria</th>
<th>Improved renal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes  No</td>
</tr>
<tr>
<td>Trials</td>
<td>7  2</td>
</tr>
<tr>
<td>Patients</td>
<td>1710 39</td>
</tr>
<tr>
<td>No</td>
<td>0  2</td>
</tr>
<tr>
<td>Trials</td>
<td>0  2</td>
</tr>
<tr>
<td>Patients</td>
<td>0  638</td>
</tr>
</tbody>
</table>

The studies in which proteinuria, but not outcome, improved were small and too short to detect a treatment effect on glomerular filtration rate decline or renal events because follow-up was short.

In patients with type 1 and type 2 diabetes with microalbuminuria it was established that ACE inhibitors significantly reduced albuminuria, slowed GFR decline, and prevented progression to overt nephropathy. Subsequently two large randomised controlled clinical trials, the reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan Diabetic Nephropathy Trial (IDNT), have high-lighted that angiotensin II antagonists are renoprotective in Patients with type 2 diabetes. These drugs seem to be able to slow the progression of diabetic nephropathy, to some degree independently of their capacity to lower blood pressure.

1.6.3. Smoking Cessation

Over the last few years, smoking has emerged as an important risk factor for progression of CKD. Smokers with type 1 or type 2 diabetes are at higher risk of developing microalbuminuria, of progressing to develop gross proteinuria (i.e. overt diabetic nephropathy and above all, accelerated progression of diabetic nephropathy towards ESRD than non-smokers with diabetes. Even in non-diabetic patients (eg, with IgA nephropathy...
or adult polycystic kidney disease), the risk of progression to ESRD is much increased in smokers.\(^{37}\)

### 1.6.4. Lipid Lowering

Dyslipoproteinemia of chronic renal insufficiency presents from the early stages of renal functional impairment. These lipid changes, besides accelerating atherosclerosis, could promote progression of renal disease.\(^{30}\) Experimental studies suggest that circulating lipoproteins play a direct part in the pathogenesis of glomerulosclerosis and tubulointerstitial changes.\(^{38,39}\) In a prospective study of non-diabetic patients with primary CKD, raised plasma concentration of apoB and LDL cholesterol were correlated with faster progression of renal insufficiency.\(^{40}\) In a meta-analysis that included 13 controlled trials of lipid reduction in the context of renal disease, drugs such as statins decreased proteinuria and preserved GFR in patients with CKD.\(^{41}\)

### 1.6.5. Glycaemic Control

The value of blood-glucose control in the prevention of onset of microalbuminuria has been established in two major studies.\(^{42,43}\) Indeed, the risk of nephropathy is low provided that glycaemic control corresponds with HbA1c concentrations of less than 8% (88%). Intensified glycaemic control is recommended by most authorities, since this intervention is safe and limits the other microvascular and macrovascular complications of diabetes.\(^{42,43}\)

### 1.6.6. Weight Loss

Severe obesity is associated with increased systemic arterial pressure,\(^{44}\) high plasma flow,\(^{45}\) increased GFR,\(^ {45}\) and enhanced albumin excretion rate.\(^ {46}\) The prevalence of obesity-related glomerulopathy, morphologically defined as glomerulomegali with or without focal segmental glomerulosclerosis, has increased tenfold over 15 years.\(^ {47}\) A recent study demonstrated that IgA nephropathy progresses more rapidly in obese subjects than in lean patients.\(^ {48}\) Weight loss improves the glomerular haemodynamic abnormalities associated with severe obesity in a subject without overt renal disease.\(^ {49}\) These findings suggest that weight loss may delay the progression of renal insufficiency in obese patients with glomerular disease.

In conclusion, to reduce the prevalence and incidence of ESRD, we need to intensify our efforts to prevent the development and progression of CKD. Future objectives should be focused on diagnosis and treatment of complications of earlier stages of kidney disease, ameliorating its complications, retarding the progression of the disease, reducing the morbidity and mortality of cardiovascular disease, and reducing the morbidity and mortality of ESRD.

### REFERENCES


