Nondiabetic Kidney Disease

Andrew S. Levey, M.D.

A 66-year-old man without diabetes has worsening high blood pressure, to 160/100 mm Hg. He has a serum creatinine level of 1.8 mg per deciliter (159 µmol per liter), an estimated glomerular filtration rate of 40 ml per minute per 1.73 m² of body-surface area, proteinuria (2+), and a total protein level of 84 mg per deciliter and a creatinine level of 30 mg per deciliter (265 µmol per liter) in a random, untimed (“spot”) urine sample (a ratio of 2800 mg of total protein per gram of creatinine). Ultrasonography reveals small, symmetric kidneys without hydronephrosis or cysts. After an overnight fast, the patient’s serum low-density lipoprotein cholesterol level is 140 mg per deciliter (3.6 mmol per liter), and he smokes half a pack of cigarettes per day. How should this patient be evaluated and treated to slow the progression of kidney disease?

The Clinical Problem

Chronic kidney disease is a worldwide public health problem. In the United States, the incidence and prevalence of kidney failure have doubled in the past 10 years, and the condition is associated with poor outcomes and high costs, especially in the elderly.1 Diabetes mellitus is the leading cause of kidney failure in the United States; an earlier Clinical Practice article discussed kidney disease due to type 2 diabetes.2 This article reviews strategies for the early detection of nondiabetic kidney disease in adults, not including kidney-transplant recipients, and interventions to reduce the risk of progression to kidney failure. Only brief mention will be made of other outcomes of chronic kidney disease, such as complications of a decreased glomerular filtration rate3 and an increased risk of cardiovascular disease.4

Strategies and Evidence

Table 1 shows a recently proposed classification of the stages of chronic kidney disease, irrespective of the cause.3 Chronic kidney disease is defined by either kidney damage or a glomerular filtration rate of less than 60 ml per minute per 1.73 m² for three months or more. On the basis of data from the Third National Health and Nutrition Examination Survey,3 an estimated 19.2 million adults in the United States have stage 1, 2, 3, or 4 kidney disease and 300,000 have stage 5 disease (kidney failure).

Proteinuria as a Marker of Kidney Damage

Albuminuria is an early and sensitive marker of kidney damage in many types of chronic kidney disease.7,8 Measurement of the excretion of total protein or albumin in a timed urine sample is the gold standard for the quantitative assessment of proteinuria (Table 2). An alternative method for the detection and monitoring of proteinuria is measurement of the ratio of protein or albumin to creatinine in an untimed “spot” urine specimen. This method corrects for variations in urinary protein levels that are due to hydration, is more convenient than timed urine collections, and provides a reasonably accurate estimate of the rate of excretion of protein.3,8,10

Glomerular Filtration Rate

The glomerular filtration rate is the best measure of overall kidney function. The normal level in young adults (age, 20 to 30 years) is approximately 125 ml per minute per 1.73 m² and declines by approximately 1 ml per minute per 1.73 m² per year thereafter.3,11,12 A decreased glomerular filtration rate in the elderly is often considered to be normal for age but is associated with an increased risk of drug-induced toxicity. In addition, the age-related decline in kidney function may contribute to the rising incidence of kidney failure.

In clinical practice, the glomerular filtration rate is usually estimated from the creatinine clearance or serum creatinine level. Measurement of creatinine clearance requires the collection of a urine sample for a specific period of time, an approach that is inconvenient and frequently inaccurate. The serum creatinine level is affected by factors other than the glomerular filtration rate, making it difficult to detect earlier stages of chronic kidney disease.13 The accuracy of estimates of the glomerular filtration rate that are based on the serum creatinine levels can be improved by the use of prediction equations that also take into account age, sex, race, and body size (Table 3).3,5,6,14 However, be-

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cause of differences among laboratories in creatinine calibration, estimates of the glomerular filtration rate can be off by as much as 20 percent, a result that could be clinically important in persons with nearly normal kidney function.\(^5\) The use of a timed urine collection to measure creatinine clearance and thus estimate the glomerular filtration rate is usually not more accurate than the use of a prediction equation and an appropriately calibrated serum creatinine measurement.

### The Clinical Plan of Action

Defining the stage of chronic kidney disease facilitates the formulation of a clinical plan of action (Table 1). Specific treatment depends on proper diagnosis, and a thorough search for reversible causes of kidney disease should be carried out in each patient. The remainder of the action plan is based on the stage of kidney disease, irrespective of the diagnosis.

The term “nondiabetic kidney disease” is not a diagnosis. It includes a variety of diseases that are often grouped together in epidemiologic studies and clinical trials but that differ widely in terms of the patient’s history, the clinical presentation (Table 4), the risk of progression, and the response to treatment. After the exclusion of diabetes, measurement of urinary protein is the first step in the differential diagnosis. Proteinuria is also an important prognostic factor, since a higher rate of excretion of protein is associated with a faster progression of kidney disease\(^2\) and an increased risk of cardiovascular disease.\(^4\)

Glomerular diseases, especially those that decrease the glomerular filtration rate, are characterized by a ratio of urinary protein to creatinine of more than approximately 1000 mg per gram and accounted for 18 percent of all cases of kidney failure in the United States in 1999 (Table 4).\(^1\) A lower ratio is associated with vascular diseases (including hypertensive nephrosclerosis), tubulointerstitial diseases, and cystic kidney diseases, which accounted for 20 percent, 7 percent, and 5 percent of all cases of kidney failure, respectively.\(^1\) These diseases can usually be distinguished from one another on the basis of the patient’s history and the results of urinalysis and ultrasound examination of the kidneys.\(^3\) However, a definitive diagnosis can be difficult and sometimes requires a biopsy of the kidney. In addition, patients may have more than one disease.

### Strict Blood-Pressure Control

Most patients with chronic kidney disease have hypertension. The sixth report of the Joint National...
Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a target blood pressure of less than 140/90 mm Hg in patients who have a low risk of cardiovascular disease and of less than 130/85 mm Hg in patients who have diabetes, clinically evident cardiovascular disease, or target-organ damage, including chronic kidney disease. Clinical trials have investigated whether an even lower blood pressure (a target mean arterial pressure of less than 92 mm Hg, which is equivalent to a blood pressure of less than 125/75 mm Hg) is more effective than a usual blood pressure in slowing the progression of nondiabetic kidney disease. The Modification of Diet in Renal Disease (MDRD) Study showed that this approach had a greater beneficial effect in patients with higher rates of excretion of urinary protein. The threshold below which there was no substantial benefit was 500 to 1000 mg of protein per day (equivalent to a ratio of protein to creatinine of approximately 300 to 500 mg per gram). Consistent with these findings, the recently completed African American Study of Kidney Disease and Hypertension showed no significant beneficial effect of strict blood-pressure control in patients with hypertensive nephrosclerosis. All hypertensive agents can be used to lower blood pressure in patients with nondiabetic chronic kidney disease, although dihydropyridine calcium-channel blockers (such as amlodipine) have been associated with a higher risk of progression of diabetic kidney disease and nondiabetic kidney disease and should not be used alone. Patients in the MDRD Study achieved the lower blood-pressure target without ad-

**TABLE 2. Definitions of Proteinuria and Albuminuria.**

<table>
<thead>
<tr>
<th>VARIABLE AND METHOD OF URINE COLLECTION</th>
<th>NORMAL VALUE</th>
<th>MICROALBUMINURIA</th>
<th>MACROALBUMINURIA OR “CLINICAL” PROTEINURIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>&lt;300 mg/day</td>
<td>NA</td>
<td>&gt;300 mg/day</td>
</tr>
<tr>
<td>24-Hour collection (varies with method)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spot urine collection, dipstick</td>
<td>&lt;30 mg/dl</td>
<td>NA</td>
<td>&gt;30 mg/dl</td>
</tr>
<tr>
<td>Ratio of protein to creatinine on spot urine collection (varies with method)</td>
<td>&lt;200 mg/g</td>
<td>NA</td>
<td>&gt;200 mg/g</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour collection, albumin-specific dipstick</td>
<td>&lt;30 mg/day</td>
<td>30–300 mg/day</td>
<td>&gt;300 mg/day</td>
</tr>
<tr>
<td>Spot urine collection, albumin-specific dipstick</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of albumin to creatinine on spot urine collection†</td>
<td>&lt;17 mg/g (men)</td>
<td>17–250 mg/g (men)</td>
<td>250 mg/g (men)</td>
</tr>
<tr>
<td></td>
<td>&lt;25 mg/g (women)</td>
<td>25–355 mg/g (women)</td>
<td>355 mg/g (women)</td>
</tr>
</tbody>
</table>

*Reproduced from the National Kidney Foundation with the permission of the publisher. The term “proteinuria” includes increased urinary excretion of total protein, albumin, and other specific proteins (for example, low-molecular-weight globulins), alone or in combination. Albuminuria is defined by increased urinary excretion of albumin. Microalbuminuria is defined by the excretion of small but abnormal amounts of albumin. Older laboratory methods, such as the urine dipstick or acid precipitation, detect most urinary proteins. The detection of microalbuminuria requires more sensitive laboratory methods that are now widely available. NA denotes not applicable.

†Sex-specific cutoff values are from a single study. Use of the same cutoff value for men and women leads to a higher prevalence of disease among women than men. The American Diabetes Association defines cutoff values for the ratio of albumin to creatinine on spot urine collection as 30 mg per gram for microalbuminuria and 300 mg per gram for macroalbuminuria, without regard to sex.

**TABLE 3. Equations Developed to Predict the Glomerular Filtration Rate in Adults on the Basis of the Serum Creatinine Level.**

<table>
<thead>
<tr>
<th>TITLE</th>
<th>EQUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft–Gault equation</td>
<td>Creatinine clearance (in ml/min) = (\left(\frac{140 - \text{age in years}}{72} \times \text{weight in kilograms} \times 0.85\right)) in female subjects</td>
</tr>
<tr>
<td>Abbreviated MDRD Study equation</td>
<td>Glomerular filtration rate (in ml/min/1.73 m²) = (\left(\frac{186 \times (\text{serum creatinine in mg/dl})^{1.154} \times (\text{age in years})^{-0.203}}{72 \times \text{serum creatinine in mg/dl}}\right)) in female subjects; (\times 0.742) in female subjects; (\times 1.210) in black subjects</td>
</tr>
</tbody>
</table>

*Data on the Cockcroft–Gault equation are from Cockcroft and Gault and are based on 236 subjects. Data on the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation are from Levey et al. and are based on 1628 subjects, with 558 in the validation set. Equations may provide inaccurate results in persons with exceptional dietary intakes (those following a vegetarian diet or taking creatinine supplements) or decreased muscle mass (as a result of amputation, malnutrition, or muscle wasting). Estimates of the glomerular filtration rate may be inaccurate in persons with low serum creatinine levels (approximately 1 mg per deciliter [88.4 µmol per liter] or lower) if the serum creatinine assay used by the laboratory is not calibrated to reflect the serum creatinine assay used by the laboratory that developed the prediction equation.

verse effects but required an average of two antihypertensive agents to do so.\textsuperscript{19}

**Angiotensin-Converting–Enzyme Inhibitors**

A number of clinical trials have compared the efficacy of angiotensin-converting–enzyme (ACE) inhibitors with that of other classes of antihypertensive agents in slowing the progression of renal disease. Two large studies — the ACE Inhibition in Progressive Renal Insufficiency Study\textsuperscript{20} and the Ramipril Efficacy in Nephropathy Study\textsuperscript{21,22} — demonstrated that ACE inhibitors lowered blood pressure, decreased urinary protein excretion, and slowed the progression of kidney disease more than did other types of antihypertensive agents. The ACE Inhibition in Progressive Renal Disease Study Group conducted a pooled analysis of data from 11 randomized trials, including these 2 large studies, which confirmed these results and showed that the beneficial effect of ACE inhibitors appeared to be mediated by factors beyond their effects on blood pressure and urinary protein excretion.\textsuperscript{23} The beneficial effect of ACE inhibitors was greater in patients with higher rates of urinary protein excretion but appeared to extend to patients without proteinuria. The African American Study of Kidney Disease and Hypertension also showed that an ACE inhibitor was more efficacious than a dihydropyridine calcium-channel blocker and a beta-blocker.\textsuperscript{24}

ACE inhibitors cause a mild decrease in the glomerular filtration rate (usually less than 10 ml per minute per 1.73 m\textsuperscript{2}) and a mild increase in the serum potassium level (usually less than 0.5 mmol per liter) in patients with chronic kidney disease. The development of hypotension, acute kidney failure, or severe hyperkalemia (defined by a serum potassium level of more than 5.5 mmol per liter) after treatment with an ACE inhibitor is initiated should prompt discontinuation of the drug and a search for remediable conditions, such as volume contraction, bilateral renal-artery stenosis, and other causes of hyperkalemia (for example, metabolic acidosis or concomitant administration of beta-blockers, potassium-sparring diuretics, nonsteroidal antiinflammatory drugs, or cyclosporine and tacrolimus). ACE inhibitors may be resumed after the other condition is corrected or the other medications that contributed to side effects are discontinued.

**AREAS OF UNCERTAINTY**

**Therapy with Antihypertensive Agents**

The dose of ACE inhibitors and the level of blood pressure that slow progression of kidney disease most effectively at various levels of urinary protein excretion have not been defined. The effects on disease progression of classes of drugs other than ACE inhibitors, either alone or in combination, require further study. Short-term studies show that angiotensin-receptor blockers have effects on blood pressure and proteinuria similar to those of ACE inhibitors,\textsuperscript{25} but long-term studies of their effects on the progression of nondiabetic kidney disease have not been reported. Studies in patients with type 2 diabetes show that these agents slow the progression of kidney disease.\textsuperscript{2} Diuretic therapy is useful, even in the absence of a clinically evident expansion of extracellular volume. Some studies show a synergistic effect of angiotensin-receptor blockers, diuretics, and nondihydropyridine calcium-channel blockers (diltiazem or verapamil) in reducing proteinuria.\textsuperscript{26-29}

**Dietary Protein Restriction**

The recommended daily allowance of protein for men and nonpregnant, nonlactating women established by the World Health Organization and the Food and Agricultural Organization is 0.8 g per kilogram of body weight per day, although the average dietary intake in the United States and Europe usually exceeds 1.0 to 1.2 g per kilogram per day.\textsuperscript{30} Studies of the efficacy of low-protein diets (approximately 0.6 g of protein per kilogram per day) in slowing progression have had various results. The primary results of the MDRD Study were inconclusive,\textsuperscript{16} but a recent review of all of the published results concluded that the evidence was more consistent with a beneficial effect.\textsuperscript{31} Two meta-analyses of randomized trials of patients with nondiabetic kidney disease, including the MDRD Study, showed that a low-protein diet delayed the onset of kidney failure or death.\textsuperscript{32,33} There is insufficient evidence to recommend or advise against routinely restricting protein intake to less than 0.8 g per kilogram per day, and the decision should be made on an individual basis.

**Table 4. Classification of Chronic Nondiabetic Kidney Disease in Patients with End-Stage Renal Disease.**

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Threshold Ratio of Protein to Creatinine*</th>
<th>Approximate Prevalence Among Patients with ESRD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular diseases (e.g., autoimmune diseases, systemic infections, drug-induced toxicity, neoplasia)</td>
<td>&gt;1000</td>
<td>18</td>
</tr>
<tr>
<td>Vascular diseases (e.g., large-vessel disease, hypertensive nephrosclerosis, microangiopathy)</td>
<td>&lt;1000</td>
<td>20</td>
</tr>
<tr>
<td>Tubulointerstitial diseases (e.g., urinary tract infection, obstruction, or stones and drug-induced toxic effects)</td>
<td>&lt;1000</td>
<td>7</td>
</tr>
<tr>
<td>Cystic diseases (e.g., polycystic kidney disease)</td>
<td>&lt;1000</td>
<td>5</td>
</tr>
</tbody>
</table>

*Values are based on the Annual Data Report of the U.S. Renal Data System.†Cutoff values are meant to serve as a general guide to diagnosis.

\[mg/g \text{ %} \]

\[mg/g \text{ %} \]

\[mg/g \text{ %} \]

\[mg/g \text{ %} \]
Malnutrition is a serious complication of chronic kidney disease. Patients with a glomerular filtration rate of less than 60 ml per minute per 1.73 m² should undergo assessment of dietary protein and energy intake and nutritional status. Medicare now covers referral to a dietitian for medical nutrition therapy for patients with a glomerular filtration rate of less than 50 ml per minute per 1.73 m². Frequent monitoring and counseling are recommended for patients who are prescribed a low-protein diet.

Lipid-Lowering Agents

Chronic kidney disease is associated with elevated triglyceride levels, reduced levels of high-density lipoprotein cholesterol, and variable elevation in the levels of low-density lipoprotein (LDL) cholesterol. The recommended target LDL cholesterol level for the prevention and treatment of cardiovascular disease is below 160 mg per deciliter (4.1 mmol per liter) in low-risk patients, less than 130 mg per deciliter (3.4 mmol per liter) in high-risk patients, and less than 100 mg per deciliter (2.6 mmol per liter) in patients at very high risk. Patients with chronic kidney disease are considered to be in the highest risk category.

Various types of dyslipidemia have been associated with decreased kidney function in the general population and with faster rates of progression in patients who have chronic kidney disease. There have been several small studies of lipid-lowering agents, primarily hydroxymethylglutaryl–coenzyme A reductase inhibitors (statins), in patients with diabetic kidney disease or glomerular diseases. A meta-analysis of 12 such studies showed that lipid-lowering agents slowed the rate of decline in the glomerular filtration rate. However, the studies’ small samples and their relatively short duration of follow-up preclude the drawing of definitive conclusions regarding the benefit of lipid-lowering therapy in terms of the progression of kidney disease.

Statins appear to be as safe and effective in lowering LDL cholesterol levels in patients with chronic kidney disease as they are in the general population. Derivatives of fibric acid can also be used, but they are associated with an increased risk of adverse effects on muscle and kidney; these effects can be ameliorated by reducing the dose. Derivatives of fibric acid should not be used in combination with statins, since they may increase blood levels of statins and thereby increase the associated risks.

Cessation of Tobacco Use

Observational studies suggest that cigarette smoking is associated with a faster rate of progression of kidney disease and a higher risk of cardiovascular disease in patients with kidney failure.

GUIDELINES

Several organizations have issued guidelines and recommendations related to the evaluation and management of nondiabetic kidney disease. Table 5 summarizes these recommendations. Updates can be expected as ongoing clinical trials are completed.

CONCLUSIONS AND RECOMMENDATIONS

Measurement of urinary protein excretion is a critical step in evaluating a patient who is at increased risk for chronic kidney disease. The finding of a ratio of protein to creatinine of more than 1000 mg per gram, as in the patient described in the clinical vignette, suggests the presence of a glomerular disease. Causes of glomerular disease, such as autoimmune disease, systemic infection, drug allergy, and neoplasia, should be sought and treated if found. The moderately decreased glomerular filtration rate and small kidneys in this patient suggest that the kidney damage is not reversible. A clinical plan of action for stage 3 chronic kidney disease, based on the information given in Table 1, should be prepared, reviewed with the patient, and coordinated with the patient’s other care providers.

An ACE inhibitor should be prescribed to slow the progression of kidney disease, lower the patient’s blood pressure, and decrease urinary excretion of protein. If an ACE inhibitor is contraindicated because of cough or angioedema, then an angiotensin-receptor blocker would be a logical alternative. Patients should be apprised that the effects of such medications on kidney disease are in part separate from their effects on blood pressure and that other medications are likely to be necessary to treat persistent high blood pressure.

Blood pressure, serum creatinine, and serum potassium should be measured within one to two weeks after the initiation of therapy with the ACE inhibitor. A mild reduction in the glomerular filtration rate and an increase in the serum potassium level should be expected, but all reasonable efforts should be made to continue the ACE inhibitor. The dose of the ACE inhibitor should be increased as tolerated to achieve the target blood pressure. If the blood pressure remains above the target level, a loop diuretic should be added to lower the blood pressure and ameliorate the increase in the serum potassium level. Other antihypertensive medications could also be considered; the selection should be based on the effects of the drug on coexisting conditions (for example, dyslipidemia in the patient in the vignette). The doses of ACE inhibitors, angiotensin-receptor blockers, and concomitant antihypertensive medications have been published previously.

The patient should be referred to a dietitian. The
# Table 5. Recommendations to Slow the Progression of Nondiabetic Kidney Disease.*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Intervention</th>
<th>Comment</th>
<th>Side Effects and Contraindications</th>
<th>Source of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin–angiotensin system activity</td>
<td>ACE inhibitor or angiotensin receptor blocker</td>
<td>Dose is that used to treat hypertension; more effective in patients with proteinuria; angiotensin-receptor blockers assumed to have equivalent efficacy in patients with contraindications to ACE inhibitors and to have a lower rate of side effects</td>
<td>Side effects include: hypotension, acute kidney failure, hyperkalemia, cough, and angioedema; contraindicated in the first 3 months of pregnancy and in patients with chronic angioedema</td>
<td>Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Institute of Diabetes, Digestive and Kidney Diseases Workshop; National Kidney Foundation Clinical Practice Guidelines for Chronic Kidney Disease; National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>Target blood pressure, &lt;130/85 mm Hg, or &lt;125/75 mm Hg in patients with proteinuria</td>
<td>All agents effective; multiple agents required; diuretics usually helpful</td>
<td></td>
<td>National Institute of Diabetes, Digestive and Kidney Diseases Workshop; National Kidney Foundation Clinical Practice Guidelines for Chronic Kidney Disease; National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease</td>
</tr>
<tr>
<td>Excess dietary protein</td>
<td>Target protein intake, 0.8 g/kg/day</td>
<td>65% in the form of high-biologic-value protein</td>
<td>Protein–energy malnutrition may result if energy intake not maintained</td>
<td>National Institute of Diabetes, Digestive and Kidney Diseases Workshop; National Kidney Foundation Clinical Practice Guidelines for Chronic Kidney Disease; National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Target LDL cholesterol level, &lt;100 mg/dl (2.6 mmol/liter)</td>
<td>For the prevention and treatment of cardiovascular disease; NCEP Step 1 diet; usual doses of statins; derivatives of fibrac acid (reduction in dose required)</td>
<td>Rhabdomyolysis, decline in GFR with use of derivatives of fibrac acid; liver injury with use of statins</td>
<td>National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease; National Kidney Foundation Clinical Practice Guidelines for Nutrition in Chronic Renal Failure; Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking cessation</td>
<td>For the prevention and treatment of cardiovascular disease; counseling; nicotine-replacement therapy; bupropion (reduction in dose required)</td>
<td>Weight gain</td>
<td>National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease; U.S. Preventive Services Task Force</td>
</tr>
</tbody>
</table>

*ACE denotes angiotensin-converting enzyme, LDL low-density lipoprotein, NCEP National Cholesterol Education Program, and GFR glomerular filtration rate.
risks and benefits of a low-protein diet (0.6 g per kilogram per day) should be discussed. Dyslipidemia should be treated with diet and a statin, and smoking cessation should be recommended. These interventions may slow the progression of kidney disease as well as reduce the risk of cardiovascular disease.

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REFERENCES


