Role of Urinalysis in the Diagnosis of Chronic Kidney Disease (CKD)

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Abstract

As of the end of Year 2008, 1 out of 450 people was a dialysis patient in Japan, and patients with chronic kidney disease (CKD) at stages 3 and 4 accounted for nearly 10% of the total population. An epidemiological study in Okinawa that used the introduction of dialysis treatment as the outcome revealed that the 10-year cumulative incident rate of end-stage renal disease (ESRD) was about 3% of the participants who were positive (≥ 1+) for both proteinuria and hematuria, while there was hardly any difference between those who were positive for hematuria alone and those who were negative for both proteinuria and hematuria. When the incidence of ESRD (dialysis introduction) was examined in relation to the severity of proteinuria (5 grades ranging from [−] to [≥ 3+]) as determined by dipstick, the cumulative incidence rate during the 17-year observation period was 16% for proteinuria (≥ 3+) and about 7% for proteinuria (2+). In contrast, among participants who were negative for proteinuria, the rate of dialysis introduction in 10 years is about 1 out of 1 million. The CKD Practice Guide of the Japanese Society of Nephrology recommends referral to a nephrologist when a case meets any of the following 3 criteria: 1) 0.5 g/g creatinine or higher, or proteinuria (≥ 2+), 2) an estimated glomerular filtration rate of less than 50 ml/min/1.73 m^2, or 3) positive results (≥ 1+) for both proteinuria and hematuria tests.

Key words Chronic kidney disease (CKD), Urinalysis, Proteinuria, Hematuria, Screening, Dialysis

Introduction

According to a survey of the Japanese Society for Dialysis Therapy, the number of patients on dialysis exceeded 280,000 at the end of Year 2008, which corresponds to a rate of 1 per 450 population.[1] Patients with chronic kidney disease (CKD) at stages 3 and 4 who may require dialysis in the future accounts for nearly 10% of the total population, and the percentage increases further among the elderly aged 65 years or older. The mortality rate due to cardiovascular disorders is higher than the dialysis introduction rate among CKD patients, meaning CKD can considerably influence the society and medical economy. Although it is not contagious, the World Health Organization (WHO) recognizes CKD as a non-infectious disease that requires global control measures.

In Japan, universal urinalysis screening, an ideal procedure for the early detection of CKD, has been implemented throughout the nation through mass screening such as school health checkups, health examination of adult residents, and basic health checkups specifically designed for senior residents. Considering that the incidence of dialysis introduction due to chronic nephritis (IgA nephropathy), a condition often diagnosed by the presence of asymptomatic proteinuria and hematuria, has decreased, and that the average age of new dialysis patients is rising, these urinalysis screening measures seem to be successful.[2] In Specific Health Check and Guidance System* for adults implemented since April 2008, urinalysis was initially planned to be offered as an optional test; however, an appeal led by

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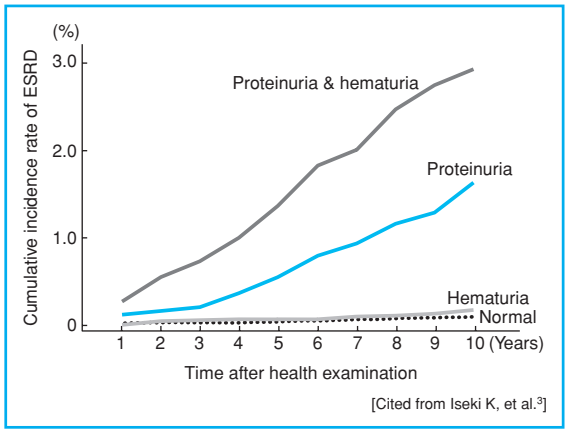

Fig. 1 The results of urinalysis for proteinuria and hematuria in relation to the cumulative incidence rate of ESRD (introduction of dialysis treatment) in years, obtained from mass health examination of residents

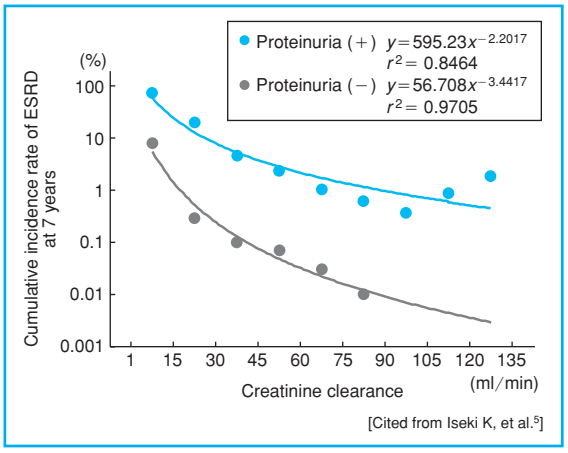

Fig. 2 The relationship between renal function levels (creatinine clearance) and the cumulative incidence rate of ESRD (introduction of dialysis treatment) at 7 years by the presence/absence of proteinuria, obtained from mass health examination of residents

Japanese Society of Nephrology (JSN) was successful, and urinalysis has been conducted as an standard test item. The inclusion of urinalysis as a standard item is to be reevaluated in 2013, and JSN is liable to verify the effectiveness of urinalysis screening by the time of the revision. There is currently no evidence to show that screening for proteinuria leads to a decrease in the number of dialysis patients. A strategy study initiated in April 2008 called Frontier of Renal Outcome Modifications in Japan (commonly known as FROM-J) is investigating the usefulness of the clinical care system for the prevention of worsening of CKD patients in order to promote collaborations between primary care physicians (non-specialists) and nephrologists.

Clinical Significance of Proteinuria

Proteinuria refers to persistent protein excretion of 150 mg or more per day in urine. Although protein may be found in urine due to physiological reasons (e.g., strenuous exertion, after fever, stress, prolonged standing, etc.), persistent urinary protein suggests the presence of disorder involving the kidney and to the urinary tract. It has long been known that the higher the level of urinary protein, the poorer the vital prognosis. Proteinuria is a factor that determines the rate of decrease in the glomerular filtration rate (GFR), and thus is the most important target of treatment.

An epidemiological study was conducted in Okinawa from the data obtained from the participants of mass health examination for adults and senior residents, using the introduction of dialysis treatment as the outcome (as end-stage renal disorder, ESRD). The study revealed that the cumulative incidence rate of ESRD in 10 years was about 3% in patients who were positive (≥ 1+) for both proteinuria and hematuria, while there was no distinct difference between those who were positive only for hematuria (condition predominant among women of advanced age) and those who were negative for both proteinuria and hematuria (**Fig. 1**).[3] When the cumulative incidence rate of ESRD during the 17-year follow-up period was examined in relation to 5 grades of proteinuria ([−], [+/−], [1+], [2+], and [≥ 3+]) as determined by dipstick, it was 16% for proteinuria (≥ 3+) and about 7% for proteinuria (2+).[4] Among those who are negative for proteinuria, only about 1 out of 1,000,000 entered dialysis program in 10 years. Low GFR levels, which are common in the elderly, seldom lead to dialysis treatment unless accompanied by proteinuria (**Fig. 2**).[5] Since the decreases in GFR level due to aging were relatively mild (<0.4 ml/min/1.73 m^2/year) among the participants of mass health examination, it seems unlikely that

aging alone was the cause for the introduction of dialysis treatment.[6]

The mean age of patients at the time of dialysis introduction has been increasing along with the increase of the elderly population and prevalence of obesity and diabetes in Japan. In the US, the dialysis introduction rate is increasing only among people aged 75 years and older, while the corresponding rates are decreasing in other age groups. In Japan, a microalbuminuria screening is covered by public health insurance only in early cases of diabetic nephropathy. However, in a survey that included the general population for investigative purposes, the prevalence of microalbuminuria was unexpectedly high, exceeding 10% in both men and women aged 65 years or older, and more than 20% of those aged 75 years old or older were positive for microalbuminuria.

Referral to Nephrologists

Annual urinalysis, and possibly a serum creatinine test, is recommended for individuals with diabetes, hypertension, and/or obese. In addition, differential diagnosis of CKD is necessary when there is anemia, bone fracture, or cardiovascular disorder of unknown cause. The CKD Practice Guide by JSN recommends referral to nephrologists if a person meets any of the following 3 criteira.[7]

(1) ≥0.5 g/g creatinine, or proteinuria (≥ 2+)
(2) ≤50 ml/min/1.73 m^2 of estimated GFR (eGFR)
(3) Positive results (≥ 1+) for both proteinuria and hematuria

In North America, there has been a report that questioned the cost-benefit aspect of the appropriateness of annual proteinuria screening by dipstick for all adults.[8] However, there is an undeniable possibility that a considerable proportion of people with proteinuria (≥ 1+) already have considerably decreased GFR. In Japan, some insist on expanding the insurance coverage for microalbuminuria screening.

Use of Urinalysis Results

Non-pharmacotherapy

Recently, the concept of obese nephropathy has been proposed. Since the correction of obesity normalizes proteinuria and enhances the prognosis, the modification of lifestyle habits is the recommended procedure. To avoid protein catabolism (reduction in muscle mass), patients with obese nephropathy should first be guided to consume sufficient calories (30–35 kcal/kg standard body weight per day). Excessive protein intake induces glomerular hypertension and temporarily promotes an increase in GFR, but in the long run leads to glomerular sclerosis. In the elderly, improvement of GFR occurs gradually because the regulation of GFR is inadequate. Fasting and dehydration (rapid and excessive restriction of salt) should be avoided in all cases, and sufficient calorie intake must be planned for those with protein-restricted diet.

Pharmacotherapy

Antihypertensive therapy: In CKD patients, blood pressure should be controlled to achieve the target value of less than 130/80 mmHg using mainly a renin-angiotensin system (RAS) inhibitor. When proteinuria of 1 g/day or more is present, the target value should be below 125/75 mmHg. In this regard, a RAS inhibitor is working more like a renoprotective drug than an antihypertensive. In conditions with increased glomerular filtration rates (single kidney, diabetes mellitus, glomerular nephritis, puromycin nephropathy, etc.), the use of RAS inhibitors decreases proteinuria.

Diabetes mellitus: Blood glucose should be controlled to achieve the target value of less than 6.5% HbA1c.

Conclusion

(1) Although GFR decreases with aging, the dialysis introduction is not likely to be necessary unless accompanied by proteinuria. However, due caution is required, considering that the dialysis introduction among elderly patients (aged 75 years or older) who have no proteinuria has been increasing recently. As for the test methods to be used in urinalysis, the guideline between the dipstick method and microalbuminuria screening is not clear.
(2) Decreased GFR levels increases the incidence rates of anemia, bone fracture, infections, and cardiovascular complications. The relationship between GFR levels and the presence/absence of proteinuria remains to be investigated in the future.
(3) Hematuria is clearly more frequent among

women, whereas proteinuria and the dialysis introduction are more frequent among men. Compared with Caucasian people, hematuria and IgA nephropathy are more common in Asians, and thus the role that urinalysis is expected to play is different in Japan. It is therefore necessary to develop our own CKD screening guideline that meet the needs of Japanese people.[9,10]

* *Specific Health Check and Guidance System* in Japan is a new annual health examination since April 2008 for any insured aged 40 to 74 years. It is specifically designed to detect life-style related diseases such as diabetes, hyperlipidemia, hyperuricemia, and metabolic syndrome.

References

1. The Japanese Society for Dialysis Therapy (ed). Illustrated Guide to Present Status of Chronic Dialysis Therapy in Japan (as of December 31, 2008). Tokyo: The Japanese Society for Dialysis Therapy; 2009. (in Japanese)
2. Yamagata K, Iseki K, Nitta K, et al. Chronic kidney disease perspectives in Japan and the importance of urinalysis screening. Clin Exp Nephrol. 2008;12:1–8.
3. Iseki K, Iseki C, Ikemiya Y, et al. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int. 1996; 49:800–805.
4. Iseki K, Ikemiya Y, Iseki C, et al. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–1474.
5. Iseki K, Kinjo K, Iseki C, et al. Relationship between predicted creatinine clearance and proteinuria and the risk of developing ESRD in Okinawa, Japan. Am J Kidney Dis. 2004;44:806–814.
6. Imai E, Horio M, Yamagata K, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433–441.
7. The Japanese Society of Nephrology (ed). CKD Practice Guide 2009. Tokyo: Tokyo Igakusha; 2009. (in Japanese)
8. Boulware LE, Jaar BG, Tarver-Carr ME, et al. Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA. 2003;290:3101–3114.
9. Iseki K. Chronic kidney disease in Japan from early predictions to current facts. Nephron Clin Pract. 2008:110;c268–c272.
10. Meguid EI, Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet. 2005;365:331–340.