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REVIEW ARTICLE

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Factors influencing the development of end-stage renal disease

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Abstract
Epidemiological evidence is needed to design effective strategies for preventing chronic kidney disease (CKD) and end-stage renal disease (ESRD). Several types of health check are routinely performed in Japan, including the screening of asymptomatic individuals, but the potential benefits of these procedures remain unknown. We evaluated the predictors of ESRD, using community-based mass screening and a dialysis registry. This approach revealed the significance of proteinuria, hypertension, obesity, anemia, and high fasting plasma glucose levels (which indicate diabetes mellitus; DM), for the risk of developing ESRD. Lifestyle-related factors, such as smoking, alcohol consumption, and low levels of exercise, are also associated with these conditions and, in particular, with a high risk of ESRD. Over-nutrition and low levels of exercise can ultimately lead to DM, hypertension, hyperlipidemia, and obesity, and are important risk factors worldwide for cardiovascular diseases, CKD, and ESRD. The early detection and treatment of predictors of ESRD, along with appropriate treatment for CKD, may decrease the incidence of ESRD. In addition, the economic burden caused by the costs of dialysis presents a compelling argument for implementing a cost-effective preventive strategy against ESRD.

Key words End-stage renal disease · ESRD · Hematuria · Hypertension · Proteinuria · Screening

Introduction

The number of cases of end-stage renal disease (ESRD) requiring chronic dialysis therapy is increasing worldwide.[1–3] Within Japan, the Okinawa prefecture has the highest incidence of ESRD.[4] Factors associated with this phenomenon may be suitable targets for intervention strategies to reduce the incidence of ESRD. Several types of health check and laboratory examination are routinely carried out on members of the Japanese population, from school children to the elderly.[5] These health checks represent opportunities for collecting data on blood pressure, urinalysis, and other laboratory variables. However, there is no clear evidence of the benefit of such tests for the prevention of ESRD, and there have been few outcome studies of screening in the adult population.[6,7] Recent progress in pharmacological therapy for patients with chronic kidney disease (CKD) has suggested that early detection and appropriate treatment may reduce the incidence of ESRD. Epidemiological evidence is therefore needed to design an effective preventive strategy against ESRD, particularly among individuals identified as being at high-risk of developing this disorder.

We investigated the renal outcomes of the screened population in Okinawa, Japan.[8–13] Standard analysis files were available for the 1983 and 1993 screenings. Renal outcome was confirmed using the ESRD patient registry, which has been available since the introduction of dialysis therapy in this region in 1971.[14,15] Using two computerized registries, we evaluated the impact of commonly measured variables – including age, sex, body-mass index (BMI), blood pressure, urine tests, and laboratory data – on the risk of developing ESRD. We also examined the effects of lifestyle-related variables on the incidence of CKD in a subgroup of the screened subjects, and determined the outcome in renal biopsy (RBX) recipients. Our results will aid the detection of high-risk candidates for ESRD. This information may also enhance the compliance of subjects who are in need of interventions, such as lifestyle modification or drug therapy.

Patients, materials, and methods

Screening program

The Okinawa General Health Maintenance Association (OGHMA), which is under the direction of Dr. Y. Ikemiya

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and (currently) Dr. K Kinjo, conducts a large community-based health examination annually. The OGHMA is a non-profit organization founded in 1972.[8] Once each year, doctors and nurses and other staff members visit residences and workplaces throughout the prefecture to carry out health examinations. All subjects participate voluntarily in the screening. The OGHMA personnel provide mass screening, inform the participants of the results, and, when necessary, recommend further evaluation or treatment. This process includes an interview concerning health status, a physical examination, and urine and blood tests. A nurse or doctor measures blood pressure, using a standard mercury sphygmomanometer, with the subject in the sitting position. Dipstick testing for proteinuria, hematuria, and glucosuria (Ames dipstick; Tokyo, Japan) is performed in spontaneously voided fresh urine. The results of the urine test are interpreted by the physicians or their assistants, and are recorded as (−), (±), (1+), (2+), (3+), or (4+). BMI is calculated as weight (kg) divided by the square of height (m).

Computer-based data were available from April 1, 1983, through March 31, 1984 (n = 106 182), for the 1983 screening, and from April 1, 1993, through March 31, 1994 (n = 143 948), for the 1993 screening. Serum creatinine (SCr) was measured using a modified Jaffe's reaction in an autoanalyzer at the OGHMA laboratory. The assay method was changed to an enzyme method in April 2002, which resulted in SCr levels showing a 0.25 mg/dl decrease compared with levels measured using the previous method; this adjustment was confirmed in normal subjects at the OGHMA laboratory. The estimated creatinine clearance (CCr), which is a surrogate marker of the glomerular filtration rate (GFR), was calculated using the Cockcroft-Gault method. Diabetes mellitus (DM) was diagnosed when the fasting plasma glucose (FPG) levels were 126 mg/dl or more. Subjects who were already on chronic dialysis were excluded from the screening registry.

A subgroup of the screening participants was examined at the central OGHMA clinic. These subjects answered questions about various lifestyle habits, including smoking, alcohol consumption, and exercise, as well as their medical history, current medications, and whether or not they had been diagnosed with DM. The responses to the questionnaires were verified and all subjects were interviewed by a physician. The 1997 OGHMA registry, for which data were compiled from April 1, 1997, through March 31, 1998, included questionnaire data in addition to the results of the physical and laboratory examinations. The ethics committee of the OGHMA approved the study protocol.

ESED patients

The details of every ESRD patient treated in Okinawa since 1971 are held in an independent community-based registry, known as the Okinawa Dialysis Study (OKIDS) registry. All chronic dialysis patients residing in the prefecture who survived for at least 1 month on scheduled dialysis were included in the registry.[14,15] By the end of 2000, there were 46 dialysis units in Okinawa: 9 in the public sector, 17 in private hospitals, and 20 in clinics. Patients who died within 1 month of the start of dialysis were not included in the registry, because of the possibility that their renal function had been improving and that other medical conditions accounted for their deaths. The physicians acknowledged in this report recorded all relevant clinical data on new dialysis patients and details of medical events in existing dialysis patients; the data collection was thorough. Diagnoses of primary renal diseases were mainly clinical. Records were updated at least twice a year for medical events such as death, renal transplantation, and patient transfer out of Okinawa. Other information was obtained through nurses, medical clerks, and patients where necessary. All patients were followed up until the occurrence of a major medical event or until January 2001, whichever occurred first, and all outcomes were verified. The Okinawa prefecture consists of subtropical islands that are separated from mainland Japan, so there was relatively little migration of patients.

RBX registry

The RBX computer registry was established with the collaboration of the physicians listed in the "Acknowledgments." This registry includes every RBX patient recorded in Okinawa from the first case in 1967 up until 1994. We examined the indications for RBX, as well as the clinical demographics of the patients. These factors were compared for patients who received RBX between 1967 and 1984 versus those who received RBX between 1985 and 1994. The two registries (ESRD and RBX) were used to identify RBX patients who later developed ESRD. This was confirmed through a review of medical records. The cumulative incidence of ESRD after RBX was also calculated.

Factors related to the development of ESRD

Most cases of CKD are insidious at onset and the course of their progression is difficult to ascertain. We therefore studied the renal outcome form the start of dialysis therapy in screened subjects.[16,17] At the time of writing, we have published a number of significant predictors of ESRD, as listed in Table 1, and several others are still under investigation.

Age

Renal function decreases with age in both men and women (Fig. 1). Among the elderly population (≥60 years), more than one-half of the subjects screened were at stage 3 to 5 (GFR <60 ml/min per 1.73 m^2) according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines. However, the extent of these changes has recently been reappraised.[18–20] Previous cross-sectional studies frequently involved elderly patients suffering from comorbid conditions, such as hypertension and heart disease, and many included institutionalized sub-

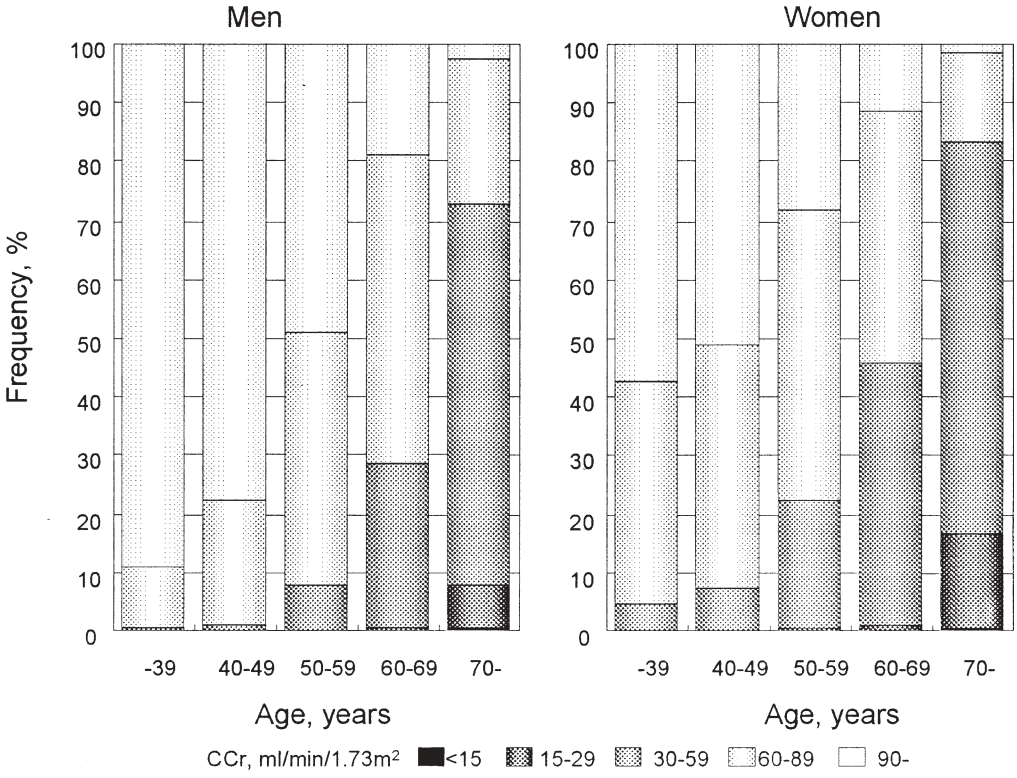

Fig. 1. Distribution of estimated creatinine clearance (*CCr*) by age at the 1993 screening. CCr was estimated using the Cockcroft-Gaulf formula

Table 1. Summary of the known risk factors for the development of ESRD in screened subjects in Okinawa, Japan

Significant factors
Male sex, proteinuria, hematuria, and hypertension
Elevated serum creatinine and high fasting plasma glucose
Previous history of stroke or AMI
Obesity (men only), low CCr and anemia
Hyperuricemia (women only)
Nonsignificant factors
Age and dyslipidemia
Factors to be further examined (possible)
Family history of hypertension and CKD
Smoking

ESRD, end-stage renal disease; AMI, acute myocardial infarction; BMI, body-mass index; CCr, creatinine clearance; CKD, chronic kidney disease

jects. A common feature of renal function in the elderly is a reduction in renal reserves.[21] We have shown that aging per se is not a major risk factor for developing ESRD.[8] However, using the incidence of dialysis patients as a surrogate marker of ESRD may have underestimated its true incidence. In addition, in some cases, subjects with low CCr or elderly subjects may have died before they developed ESRD.

Sex

According to the annual reports of the Japanese Society for Dialysis Therapy (JSDT), the ESRD incidence ratio of men to women has steadily increased during the past 20 years. This could be attributed to a higher incidence of ESRD in men or to an under-acceptance of dialysis therapy in women. We found a higher risk of ESRD among men, even after adjusting for age, abnormal urinalysis findings, and blood pressure.[8] Sex differences in disease progression have also been shown in studies on renal biopsies, lupus nephritis, and autosomal dominant polycystic kidney disease.[22,23] Diabetic nephropathy is known to be more prevalent and to progress more rapidly in men than in women.[24] However, when SCr data were added to the analysis, the changes in the adjusted relative risk of ESRD were similar in men and women.[10] Other confounding variables, such as smoking, obesity, and lifestyle factors, may have played a role in the observed sex difference in the incidence of ESRD. However, the precise mechanisms underlying the difference in renal disease progression between men and women remain to be discovered.

BMI

The relationships between excess body weight and both "all-cause" and cardiovascular mortality are well established.[25–28] However, few studies have examined the influence of being overweight or obese on the risk of developing ESRD. The relationship between BMI and proteinuria is of particular interest. In a large cross-sectional population study, Ramirez et al.[29] found a J-shaped relationship between BMI and the prevalence of proteinuria. Donor-recipient body-size mismatch is an important predictor of disease progression and graft loss in renal transplantation. Being overweight or obese may therefore be a significant

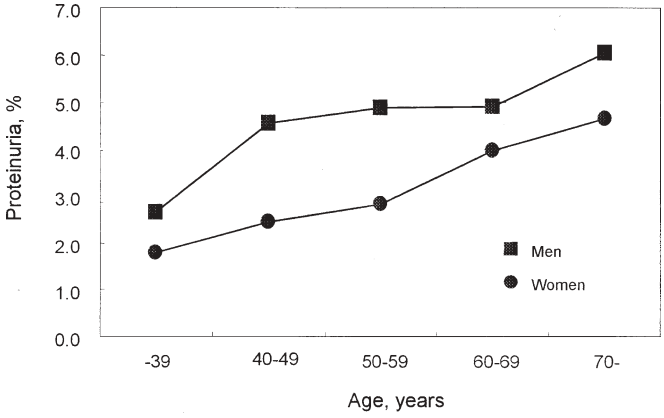

Fig. 2. Prevalence of proteinuria by age at the 1993 screening. Proteinuria is defined as a dipstick value of 1+ or greater

risk factor for ESRD. Our preliminary report suggested that BMI was not a major risk factor for the development of ESRD.[11] However, the 10-year follow-up period may have been insufficient to establish the relationship between these factors. We therefore extended the follow-up period to 17 years, which revealed a significant relationship between BMI and the risk of ESRD.[30]

Proteinuria

The prevalence of proteinuria increased with age at screening in both sexes. However, the incidence was higher in men than in women in every age subgroup examined (Fig. 2). Proteinuria is a well-known marker of renal disease, and the beneficial effects of treatment are often associated with a reduction of proteinuria.[31,32] This condition is also a crucial factor in the pathogenesis of chronic renal injury.[33] Dipstick urinalysis is not generally recommended for screening for renal disease; there is little evidence of a relationship between proteinuria detected using this method and either long-term renal survival or cost-saving benefits.[34] In addition, the natural course of progressive renal disease is largely unknown. Many patients consult a nephrologist at a relatively late stage of the disease, and undergo chronic dialysis therapy with only a short follow-up period.[35,36] We found epidemiological evidence to support the use of dipstick urinalysis for proteinuria as a predictor of ESRD.[8,13] However, the costs and benefits of treatment for those with proteinuria of (±) or (1+) require further evaluation.

Hematuria

Hematuria is common in women. Although we had no information about their age at menopause, we found that the incidence of hematuria increased with age and was greater than 10% in women aged 70 years or more.[8] Hematuria was a significant predictor of ESRD, although there was no clear relationship between the degree of hematuria and the ESRD risk. Those who had both proteinuria and hematuria had the highest risk of developing ESRD. However, isolated hematuria may not have clinical significance in terms of the risk of developing ESRD. Further follow-ups may not be necessary for women with asymptomatic hematuria.

Blood pressure

Among men who were screened during the Multiple Risk Factor Intervention Trial, both high-normal and high blood pressure were judged to be strong independent risk factors for ESRD.[37] We showed, from a 10-year follow-up of the screened cohort, that high diastolic blood pressure was a significant predictor of ESRD.[9] In recent studies stratified by sex,[38] high blood pressure has been found to be a significant predictor of ESRD.[39] In addition, subjects with hypertension often have multiple risk factors that are associated with ESRD.[40]

Laboratory variables

SCr

Using the 1983 screening data, we examined renal outcome according to SCr levels. The cutoff values for the development of ESRD were 1.4 mg/dl or more for men and 1.2 mg/dl or more for women.[10] However, SCr data were available for only 13.7% of the total screened cohort. The GFR classification depends upon SCr measurements, and a recent overestimation of CKD was reported to be due to changes in the SCr assay.[18–20] We re-examined the relationship between the calculated CCr and proteinuria on the development of ESRD.[41] However, as we did not have serial SCr data, we were unable to comment on the progression of renal disease.

Serum uric acid

Hyperuricemia may be directly pathogenic, rather than simply acting as a marker for other associated risk factors. It has recently been reported that hyperuricemia per se can cause hypertension and has a role in the progression to ESRD.[42–45] We showed the significance of hyperuricemia in the early detection of renal failure in a cohort of screened subjects.[46,47] Although evidence to support the idea that chronic hyperuricemia contributes to renal damage and the development of ESRD is still lacking, we observed a higher cumulative incidence of ESRD in hyperuricemic (serum uric acid, ≥6.0 mg/dl) women.[100]

Dyslipidemia

This condition is often observed in patients with chronic renal failure. Experimental studies suggest that dyslipidemia plays a significant role in the pathogenesis of renal damage. Therefore, it could be a causative factor in the progression of renal failure in humans. Recently, hypercholesterolemia was shown to be a risk factor for renal dysfunction in apparently healthy men.[48] Atherogenic lipoprotein

profiles have also been reported to be associated with renal dysfunction in type 1 DM. We found that triglyceride levels could predict the development of proteinuria.[49] However, as lipid profiles may change with proteinuria, which is the strongest predictor of ESRD, the role of dyslipidemia as a risk factor for ESRD remains controversial.[12]

Anemia

Chronic anemia has a significant impact on cardiac function, but its effect on renal outcome is not known. We found that subjects with low hematocrit levels, less than 40% in men and less than 35% in women, had a significantly increased risk of ESRD.[50] The underlying causes of anemia should be evaluated in association with other conventional risk factors, such as hypertension, proteinuria, and hematuria. Chronic hypoxia associated with tubulointerstitial damage may be a final common pathway leading to ESRD.[51] To maintain an adequate quality of life, both European[52] and United States[53] guidelines recommend that hemoglobin levels should be more than 11 g/dl. Furthermore, potential benefits from correcting anemia in slowing the progression of renal failure have been reported in small studies.[54,55]

FPG

Subjects with high FPG levels, 126 mg/dl or more, are considered to have DM, which is known to cause diabetic nephropathy and accelerated atherosclerosis. In Japan, DM has been a leading cause of ESRD since 1998, and DM is fast becoming a worldwide epidemic. Early detection and proper treatment may reduce the incidence of dialysis in DM patients. However, in addition to type 1 DM, patients with type 2 DM often consult nephrologists at a relatively late stage of the disease. We evaluated the prevalence of high FPG and the risk of developing ESRD in screened subjects.[56] The prevalence of high FPG was 5.2% in the 1993 OGHMA screening cohort.[57] FPG and proteinuria measurements were equally important in detecting individuals at high risk for developing ESRD. Hyperinsulinemia and glucose intolerance are also relevant indicators of renal function in the general population.[58]

Lifestyle factors

Smoking

Cigarette smoking is hazardous to renal function as well as to other organ systems.[59,60] It also plays a significant role in the development of proteinuria in the general population.[61] There are several mechanisms of smoking-related renal injury, including increases in blood pressure, heart rate, and sympathetic nerve activity, and direct toxic effects on endothelial cells.

Alcohol intake

Alcohol consumption has several effects on the cardiovascular system.[62] Moderate amounts of alcohol may have a protective effect on renal function.[63] However, few studies have examined the relationship between alcohol intake and the incidence of ESRD.

Exercise habits

Activity levels may have a significant impact on the cardiovascular system. In an animal study, swimming was shown to alleviate hyperlipidemia and prevent progressive renal dysfunction in adriamycin-induced nephritic rats.[64] Exercise is also known to improve insulin sensitivity in skeletal muscle, and to prevent or delay the onset of type 2 DM and hypertension.[65]

Additional factors

Dialysis patients include individuals who have survived medical events such as malignancies, collagen disease, stroke, acute myocardial infarction, atherosclerosis, infections,[66] and drug abuse. Nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and contrast media should be used with caution, particularly among the aged population. We found that survivors of stroke and acute myocardial infarction had a higher incidence of ESRD than those who had not experienced such events.[67] This was as expected, as these conditions often have risk factors similar to those for ESRD. For example, a high heart rate is a cardiovascular risk factor that is often associated with other risk factors for ESRD.[68] Tachycardia is also a surrogate marker of sympathetic overactivity.

Family history of CKD

A family history of CKD and dialysis is a risk factor for proteinuria and, therefore, for the development of ESRD.[69,70] Hypertension, DM, obesity, and hyperlipidemia are frequently present in relatives of ESRD patients, who may share similar lifestyle and dietary habits. However, there is insufficient epidemiological evidence of the effect of these factors on the development of ESRD. It is possible that genes producing susceptibility to the initiation or progression of renal failure might explain the observed familial clustering of cases.[71]

Strategies for the prevention of ESRD

Asymptomatic and low-risk subjects

CKD has recently been recognized as a cardiovascular risk factor.[72] Screening for CKD is therefore important, not only for preventing ESRD but also for preventing cardiovascular disease. CKD is diagnosed by estimating GFR or CCr and proteinuria. In Japan, 24-h CCr levels have been estimated[73] and the Cockcroft-Gault formula has been used to calculate CCr.[74] However, there is no formula to estimate inulin clearance, which is a precise marker of GFR, among the

Japanese population. The dipstick urine test for proteinuria has low sensitivity but is convenient to use. In fact, in Japan, there are laws mandating that all employees and school children, from elementary to high school, undergo routine health examinations including such tests. It is also common for university students to undergo similar health checks. However, it is not yet clear whether all asymptomatic adults should be screened for proteinuria.[34,43]

High-risk subjects

Late referral to a nephrologist is common in Japan[35] and other countries.[36,75] This is partly because many CKDs are insidious at onset and are asymptomatic. However, some individuals who show evidence of CKD during screening do not seek subsequent medical attention or treatment. The progression rates of renal diseases to ESRD vary according to the type of disease and the frequency of follow up.[76] However, remission is generally possible with comprehensive treatment.[77] Subjects who have the risk factors listed in Table 2 are considered to be at high risk of developing ESRD. We found that those who had a high SCr entered a dialysis program, on average, 5 years after screening.[10]

The role of RBX

Between 1967 and 1994, a total of 2832 (1395 male and 1437 female) subjects received RBX in Okinawa.[78] The mean (SD) age at RBX was 30.0 (10.0) years (range, 1.0 to 88.0 years). The most common clinical indications for RBX were: proteinuria/hematuria (46.7%), nephrotic syndrome (21.2%), acute glomerulonephritis (10.1%), and systemic lupus erythematosus (7.5%). Patients who received RBX between 1985 and 1994 (n = 1480) were significantly less likely to have had acute glomerulonephritis than patients who were treated between 1967 and 1984 (n = 1352). The rates of proteinuria/hematuria, renal failure, and DM were slightly higher in the latter period. Between 1971 and 2000, 5246 patients began dialysis therapy, 468 of whom (260 men and 208 women) underwent RBX. The cumulative incidence of ESRD among these patients was 17% in 17 years. One-half of these patients developed ESRD in the 5.8 years after RBX. Among the dialysis patients, the RBX rate was 12.6% in those with chronic glomerulonephritis, 1.7% in those with DM, 2.6% in those with nephrosclerosis, and 52.1% in those with systemic lupus erythematosus.

RBX is a common diagnostic procedure in nephrology and can provide essential histological evidence of renal disease. RBX also allows the selection of appropriate treatment and may therefore be useful for the prevention of disease progression. However, it is debatable whether RBX is always useful in predicting the future progression of renal diseases, and it is not performed in subjects with small kidneys or significant renal dysfunction. Proteinuria and hematuria are often detected during mass screening. The glomerular changes in such subjects are generally minor and progression is often associated with tubulointerstitial change. These findings are commonly associated with hypertension, aging, drugs, and other confounding variables. Therefore, the degree of glomerular damage may not correlate with the renal prognosis. Regardless of the histological findings, subjects with a high risk of developing ESRD should be evaluated by a nephrologist. However, Paone and Mayer[79] showed that RBX led to major therapeutic decisions in only 19% of such subjects. Furthermore, RBX is costly and potentially hazardous. Its potential benefits must therefore be assessed carefully.[80] Few epidemiological studies have examined long-term outcome after RBX, especially in terms of the risk of progression to ESRD.[81] It is possible that the epidemiological outcome in primary glomerulonephritis depends on both the patient's age and the period during which the disease was detected.[82]

Table 2. Factors for a high risk of ESRD

Proteinuria (≥2+ by dipstick test)
High SCr (≥2.0 mg/dl)
Severe hypertension (JNC-VI)
Family history of ESRD

SCr, serum creatinine; JNC, Joint National Committee

Perspectives for future research

Strategies for the prevention of ESRD (Table 3)

As discussed above, most renal diseases are insidious at onset, and asymptomatic. In addition, the progress of patients who eventually enter dialysis programs has not been well delineated. Most subjects who showed proteinuria, hypertension, and high SCr were either left untreated or were not referred to a nephrologist. ESRD may have been prevented by a combination of multiple drugs and lifestyle modifications in these patients. However, most patients consulted nephrologists only at a relatively late stage.[83] The early detection and treatment of predictors of ESRD may be an effective and low-cost strategy, particularly for those individuals who are at high risk of developing ESRD. Yet it

Table 3. Strategies for preventing ESRD

Detection
All individuals aged >40 years
Once a year
Check: proteinuria, blood pressure, and serum creatinine
Follow up
Individuals with slight abnormalities
Every 2 to 3 months
Intervention
Proteinuria (dipstick 1+ or ±), hypertension, obesity, high fasting plasma glucose (≥126 mg/dl), and hyperuricemia (serum uric acid; men, ≥7.0 mg/dl; women, ≥6.0 mg/dl)
Refer to nephrologist (prevention clinic)
High risk of ESRD
Follow every month
Comments
Create AV fistula in advance
Workups for possible renal transplantation

is not clear when is the optimal time to offer therapy to asymptomatic subjects.[43] Cost–benefit analyses of the frequency of screening and the extent of tests have been evaluated.[84] Recently, Boulware et al.[85] reported that the early detection of proteinuria, aimed at slowing the progression of CKD and decreasing mortality, was not cost-effective unless selectively directed toward high-risk groups. However, contrary to such reports, screening programs for employees, members of the general population aged 40 years or more, school pupils, and university students are routinely carried out in Japan. The mean age at the start of dialysis is steadily increasing in Japan.[1] Also, an increase in the number of patients with multiple comorbid conditions at the start of dialysis has been reported. Such trends may be explained by the increase in the elderly population or by improvements in medical and social conditions.

Geographical differences in the incidence of ESRD

The number of new dialysis patients does not necessarily reflect the true incidence of ESRD. The number of patients is largely dependent on the availability of facilities, such as dialysis beds. This may, in turn, depend on the number of physicians, socioeconomic conditions, and the incidence of ESRD itself. Therefore, the reported incidence of dialysis patients is likely to be an underestimate. It is also possible that the acceptance rate – the incidence of new dialysis patients/true incidence of ESRD – may vary over time, or may vary among different districts or countries. The mortality rate due to cardiovascular disease varies according to geographical location, and the stroke death rate has decreased markedly in Japan.[86] Both nephron number and kidney size may differ among ethnic groups and regions. Nephron number does not increase after birth, and is dependent on maternal age.[87] Individuals with low birth weight tend to have a smaller number of nephrons, and may be at greater risk of developing hypertension and renal dysfunction later in life.[88,89]

Other environmental factors, including microbes, toxins, and nephrotoxic drugs, may also contribute to the differences in the incidence of ESRD. Interestingly, the use of antihypertensives, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), has been shown to correlate with the incidence of ESRD in Japan.[90]

Indigenous populations and developing countries

In 2002, the incidence of new DM dialysis patients was 265 per million population in Japan, and the prevalence was more than 1800 per million population.[1] This increase in DM dialysis patients may reflect a larger number of DM sufferers in the general population. Such trends are more serious in indigenous populations and developing countries. It is estimated that the number of maintenance dialysis patients will be more than 2 million worldwide by 2010. The predicted cost during the forthcoming decade is approximately $1.1 trillion.[91] A recent editorial commentary by Schieppati, Perico, and Remuzzi, which was published in *Kidney International*[92] and *Nephrology Dialysis and Transplantation*,[93] was devoted to what is now one of the most important issues in the field of nephrology: the prevention of ESRD. The authors suggested that screening programs could be implemented using simple, cheap, and reliable tests, such as body weight, blood pressure, blood glucose, and dipstick urinalysis for protein. A systematic treatment program combining blood pressure reduction and improved glucose and lipid control with health education could lead to improvements in clinical profiles and lower mortality. In Japan, the early detection of CKD is not an issue; the important problem is how to ensure that patients receive adequate medical attention, particularly from nephrologists. A steady increase in the incidence of ESRD in Japan, despite the extensive screening programs, highlights the need for a comprehensive approach toward the prevention of ESRD.

Study limitations

Our study had several limitations. First, as in other large-cohort studies, the follow-up was passive. Fortunately, the rate of migration from Okinawa to other parts of Japan is relatively low. Although all new ESRD patients were accounted for the data, those subjects who died during the study period were not excluded from the logistic analysis. An increased risk of death has been reported for individuals with proteinuria,[94,95] hypertension, and low GFR.[96] According to government reports, the annual death rate due to renal failure, including both acute and chronic cases, was around 10 per 100000 population in Okinawa. We excluded patients who died within 1 month of the start of dialysis; therefore, we may have underestimated the risk of the development of ESRD based on dipstick proteinuria, blood pressure, and other laboratory variables.

Second, the screened subjects were relatively healthy individuals who showed concern about their general health, and they should therefore be considered as a self-selected population. The proportion of the total number of ESRD patients who were diagnosed during the study period was 19 per 10000 subjects in the cohort, compared with 22 per 10000 population in the whole Okinawa area. Individuals who had already been diagnosed with CKD may have been less likely to participate in the screening.

Third, the measurements of proteinuria and other laboratory variables were carried out only once. This may have resulted in an underestimation of the strength of the association between the variables studied and the incidence of ESRD.

Fourth, we were not certain about the causes of low CCr and proteinuria, which could be associated with DM nephropathy and other types of renal disease. We also lacked information on the treatments for DM, hypertension, and hyperlipidemia.

Fifth, data on lifestyle-related variables – such as smoking, alcohol intake, exercise, socioeconomic factors, and

family history of cardiovascular disease – were only available for subgroups of the cohort. Low income/education is an additional potential risk factor for susceptibility to, and the progression of, CKD.[97]

Sixth, significant changes in risk factors and treatments have occurred over the past 30 years; for example, increases in DM and obesity, and the introduction of new antihypertensive drugs such as ACEIs and ARBs. Both of these groups of drugs have been shown to retard the progression of renal failure in DM and non-DM patients.[31,32] Moreover, a combination of an ACEI and an ARB is beneficial in suppressing the progression of renal failure.[98] ACEIs and ARBs have been available since 1983 and 1998, respectively. However, the incidence of ESRD is continuing to increase, accompanied by an increase in the prevalence of DM among the general population. The number needed to treat (that is, the number of patients who must be treated in order to prevent one additional bad outcome) was 16 in a recent study.[32] Therefore, only about 6% of the individuals treated did not progress to ESRD. In addition, we recently observed a patient whose renal function did not progress further after ARB treatment for severe renal failure.[99]

Seventh, and finally, although we adjusted our analyses for age, sex, and other confounding variables, additional factors that may be associated with ESRD were not evaluated in our study. The relative homogeneity of the Okinawa population enhanced the internal validity of our results. However, the results remain to be confirmed in other parts of Japan and among other ethnic groups.

Summary

Given the steady increase in the number of ESRD patients and the economic burden of dialysis therapy, serious efforts need to be made to prevent the development of ESRD. Epidemiological evidence showing the predictive significance of various factors for the development of CKD and ESRD is important in designing a preventive strategy for detecting high-risk individuals and producing follow-up guidelines. Fortunately, routine health checks provide several opportunities for CKD to be detected among the Japanese population. However, cost-effective analysis is necessary to justify the efforts towards preventing ESRD. It is becoming increasingly evident that lifestyle-related factors, such as over-nutrition and low levels of exercise, are contributing to the increases in CKD and ESRD, particularly among the elderly population. The clinical significance of low CCr levels ($<$60 ml/min) remains to be examined. Clearly, better public information about ESRD and CKD is essential in order to ensure the compliance of individuals with intervention strategies.

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