receptors have also been examined thus far. However, even these studies could not draw a definite conclusion.

Recent development in the SNP typing technology and collation of information regarding linkage disequilibrium in the human genome have facilitated GWAS and candidate gene analyses in a large number of subjects by using tagging SNPs that can completely cover the gene or locus of interest. Because, in the case of common genetic variations, the genotype-specific differences in biological functions are expected to be very small, an appropriate association study such as that conducted by Ng *et al.*[1] with a sufficient number of subjects, probably several thousand case and control subjects, should be performed for each candidate gene before evaluation of the functional significance of genetic variations.

Inflammatory cytokine genes might be good candidates for genes that confer susceptibility to diabetic nephropathy. Moreover, well-organized approaches, such as GWASs for diabetic nephropathy, are being conducted in several independent populations; a conclusion regarding the susceptibility genes for diabetic nephropathy may be drawn in the near future.

DISCLOSURE

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Gender differences in chronic kidney disease

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Women live longer than men. Can this phenomenon be explained by chronic kidney disease (CKD)? Gender differences in the prevalence and incidence of CKD are discussed.

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Women live longer than men. Can this phenomenon be explained by chronic kidney disease (CKD)? Proteinuria is a known risk factor for cardiovascular disease (CVD) and mortality. Recently, a low estimated glomerular filtration rate (eGFR) *per se* has also become widely accepted as a risk factor for CVD and mortality.[1] The high incidence of infection and malignancies in the elderly population may be, in part, due to CKD. The mortality rate increases with a decline in glomerular filtration rate (GFR) and is highest among patients with end-stage renal disease (ESRD). Therefore, an estimation of GFR is recommended among patients with CVD. In such patients, serum creatinine should be examined to determine the eGFR. The World Health Organization now considers kidney disease a major chronic disease.

CKD is defined as either kidney damage indicated by urine, imaging, and histologic findings, or a low eGFR, less than 60 ml/min/1.73 m^2, for more than 3 months. GFR is calculated by either the Modification of Diet in Renal Disease (MDRD) Study equation or the Cockcroft–Gault formula. The concept of CKD was developed to educate physicians and the general public in the prevention of ESRD and other related medical complications. The mechanisms underlying the increased risk of CVD in CKD patients, however, are not well understood. In addition to the conventional risk factors for CVD, CKD patients often have associated non-conventional risk factors such as volume expansion, sympathetic overactivity, sleep disturbance, hypoxia, increased oxidative stress, dyslipidemia, anemia, and serum calcium and phosphate

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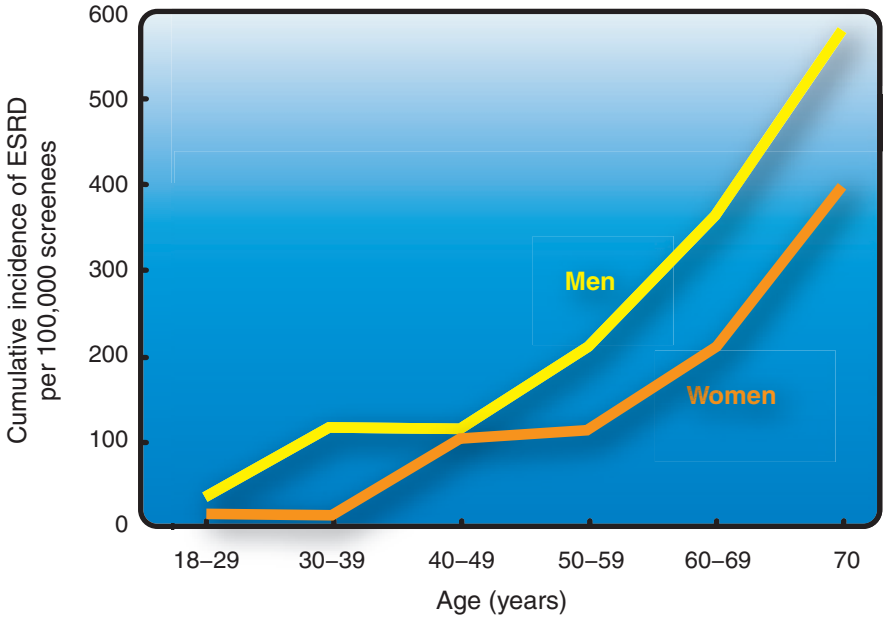

Figure 1 | The cumulative incidence of ESRD per 100,000 screenees, shown by age at screening in both men and women. Figure was created from database of ref. 2.

disturbances, which are proportional to the decline in GFR. ESRD patients, therefore, have multiple risk factors to be corrected. Trials toward the treatment of any single risk factor—for example, correction of anemia and high low-density lipoprotein cholesterol—have failed to show an improvement in CKD patient survival. CVD remains the main cause of death among ESRD patients. These observations suggest the importance of early detection of and early intervention in CKD, preferably at stages 1–3.

Gender differences have been documented in the field of nephrology. Women seem to be somewhat protected from developing ESRD.[2] The cumulative incidence of ESRD remains low during the reproductive ages and begins to rise 10 years later in women than in men among participants in community-based screenings (Figure 1).[2] A nationwide survey of ESRD by the Japanese Society for Dialysis Therapy revealed a higher incidence and prevalence in men than in women. Further, the mean age at the start of dialysis is also higher in women than in men.

The natural course of CKD progression is largely unknown. CKD is often asymptomatic, and late referral to nephrologists, defined as referral within 6–12 months of starting dialysis, is common. CKD, however, often develops in those with conventional risk factors for atherosclerosis, such as hypertension, diabetes mellitus, hyperlipidemia, and a history of CVD. We identified screening participants who later entered a dialysis program and found that dipstick-positive proteinuria and hypertension are important predictors of developing ESRD.[2] Lifestyle-related factors that are often associated with obesity and metabolic syndrome may also have a role in the development and progression of CKD. The obesity-related risk of developing proteinuria is independent of that of hypertension and diabetes mellitus. Smoking may accelerate kidney damage in patients with metabolic syndrome. Among the lifestyle-related factors, smoking and excess alcohol intake are known risk factors for CKD. Moderate alcohol intake, less than 20 g per day, however, decreases the risk of CKD. There is a protective effect of weight loss on CKD progression and proteinuria reduction prior to progression to ESRD.

Kidney function deteriorates with aging. The extent of an age-related GFR decline, however, differs between ethnic groups and sexes. Longitudinal studies in the United States[3] and Norway[4] revealed a decline in GFR of 0.75–1.03 ml/min/1.73 m^2 per year. In the general Japanese population, the average GFR decline is 0.36 ml/min/1.73 m^2 per year. GFR has declined at a similar rate in men and women in all age groups.[5] Others have reported that one-third of normal individuals showed no change in creatinine clearance in a 20-year longitudinal study.[6] Halbesma *et al.*[7] (this issue) report that there are gender differences: –0.33 (women) and –0.55 (men) ml/min/1.73 m^2 per year, based on the relatively new method of 'slope-based analysis' rather than 'threshold analysis.' They compared the age-related changes in kidney function based on reciprocal serum creatinine (1/SCr) and the MDRD Study equation. The evaluation of a decline in GFR is not accurate with the use of the MDRD Study formula, particularly in those with eGFR greater than 60 ml/min/1.73 m^2 or in those with obesity, and results in an underestimation of GFR in those with normal renal function. It is also not suitable for evaluating long-term changes in GFR, as people may lose muscle mass with aging.

Among the risk factors for GFR decline, proteinuria, including microalbuminuria, is a strong predictor of GFR decline. Low GFR per se, which is often observed in the elderly population, is not a strong predictor of developing ESRD if not otherwise associated with proteinuria. In the study by Halbesma *et al.*,[7] systolic blood pressure in women was 10 mm Hg lower than in men. Blood pressure is a major determinant of atherosclerosis and developing ESRD; therefore, the gender difference in systolic blood pressure may contribute to the slower decline in GFR in women. Other plausible explanations for the gender differences in GFR decline include hormonal status and lifestyle differences, such as dietary protein intake, salt, smoking, and alcohol intake. On the basis of their report, Halbesma *et al.*[7] rule out the possible role of diet based on the estimated amount of protein intake shown by urine urea nitrogen excretion and salt intake. The prevalence and impact of metabolic syndrome, which is related to the development of CKD, may also contribute to the gender difference in the age-related decline in GFR. Obesity induces a state of hyperfiltration, which, if continued for a certain period, can cause a decline in GFR, as in diabetic nephropathy.

Baseline GFR differs among sex, age, and ethnic groups. The prevalence of CKD is increasing, particularly in those of age 70 and over in the United States[8] and in Japan (the Hisayama study).[9] The prevalence of CKD has doubled in both men and women from 1974 to 2002 (T. Ninomiya, personal communication). The prevalence of CKD is expected to increase, particularly in the elderly population. They may survive after CVD and are then exposed to multiple CKD predictors, such as smoking, metabolic syndrome, obesity, and multiple nephrotoxic substances. As a whole, the prevalence of CKD will probably increase with the growing elderly population. Subjects with low birth weight, which is a predictor of low nephron number, develop insulin resistance and therefore have an increased risk for both CKD and ESRD.

Multidisciplinary collaboration among physicians, health-care workers, and governments is necessary to halt the progression of CKD. The incidence of ESRD is increasing worldwide despite several strategies, including universal or targeted screening and new drugs.[10] More attention must be focused on the early detection of CKD, particularly in the elderly population and in those with obesity, metabolic syndrome, hypertension, or diabetes mellitus. Further studies on the gender differences in GFR decline may supply another tool toward the prevention of CKD.

DISCLOSURE

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