Risk factors for chronic kidney disease: an update

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Chronic kidney disease has become a serious public health issue. There are currently over 1.4 million patients receiving renal replacement therapy worldwide. One way to reduce the economic burden of chronic kidney disease would be early intervention. In order to achieve this, we should be able to identify individuals with increased risk of renal disease. An individual's genetic and phenotypic make-up puts him/her at risk for kidney disease. Factors such as race, gender, age, and family history are highly important. For instance, being of African-American decent, older age, low birth weight and family history of kidney disease are considered to be strong risk factors for chronic kidney disease. Moreover, smoking, obesity, hypertension, and diabetes mellitus can also lead to kidney disease. An uncontrolled diabetic and/or hypertensive patient can easily and quickly progress to an end-stage kidney disease patient. Exposure to heavy metals, excessive alcohol consumption, smoking, and the use of analgesic medications also constitute risks. Experiencing acute kidney injury, a history of cardiovascular disease, hyperlipidemia, metabolic syndrome, hepatitis C virus, HIV infection, and malignancy are further risk factors. Determination of serum creatinine levels and urinalysis in patients with chronic kidney disease risk will usually be sufficient for initial screening.

Kidney International Supplements (2013) **3,** 368–371;
doi:10.1038/kisup.2013.79

KEYWORDS: age; chronic kidney disease; diabetes mellitus; gender; hypertension

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Chronic kidney disease (CKD) is a health problem, which could lead to end-stage renal disease (ESRD) and increased cardiovascular morbidity and mortality. According to the registries of different countries including the United States, CKD affects 10–16% of adults around the world.[1] Within the Turkish population the prevalence of CKD is 15.7%.[2] Identification of factors predisposing an individual to CKD is essential in terms of personal and community health, as some risk factors can be modified and can prevent or slow down progression to ESRD. This paper aims to review the risk factors, such as age, gender, race and ethnicity, family history, drug use, smoking, and socioeconomic status; and concurrent diseases, such as hypertension and diabetes which are traditionally or nontraditionally associated with CKD.[3]

GENETIC COMPONENT

As CKD has a heritable component, Köttgen *et al.*[4] have conducted genome-wide association studies to identify susceptibility loci for glomerular filtration rate (GFR), estimated by serum creatinine (eGFRcrea), cystatin C (eGFRcys), and CKD (eGFRcrea <60 ml/min per 1.73 m^2) in European ancestry participants of four population-based cohorts (2388 CKD cases). They tested for replication in 21,466 participants (1932 CKD cases). Uromodulin (which encodes Tamm–Horsfall protein in the urine) mutations were associated with differences in renal function.[4]

Another identified mutation is related to APOL1.[5] An autosomal recessive pattern of inheritance is demonstrated and associated with a substantially higher risk of ESRD (10-fold higher risk of ESRD due to focal glomerulosclerosis and 7-fold higher risk of ESRD due to hypertension). APOL1 mutations are found exclusively among individuals of African descent and make them more prone to CKD.[5]

The involvement of renin–angiotensin system genes seems to be particularly relevant to CKD. In a study by Su *et al.*,[6] 135 CKD patients and 270 healthy controls among Han Chinese in Taiwan were genotyped for angiotensinogen (AGT-M235T, T174M, A-20C), angiotensin-I-converting enzyme (ACE-A2350G), and angiotensin II type 1 receptor (AGTR1-A1166C, C573T, C-521T) polymorphisms by polymerase chain reaction-restriction fragment length polymorphism analysis. Significant associations were observed in ACE-A2350G and AGTR1-C573T polymorphism in CKD patients ($P=0.01$ and $P=0.03$, respectively).[6]

FAMILY HISTORY

Family members of CKD patients have a high prevalence of CKD and its risk factors. Song *et al.*[7] have screened incident dialysis patients between 1 January 1995 and 31 December 2003 in the United States. The participants were asked to complete a voluntary questionnaire on family history of ESRD. After the exclusion of patients with ESRD due to hereditary disorders and urologic causes, nearly 23% of incident dialysis patients had close relatives with ESRD.[7] Hence, it is advised to screen the high-risk family members of those with CKD, in an attempt to prevent any kidney disease.

GENDER

Many registries including the *Japanese Society for Dialysis Therapy* have demonstrated that ESRD is more frequent among men.[8,9] In one study, a total of 107,192 subjects over 18 years of age (51,122 men and 56,070 women) from Okinawa, Japan participated in a 10-year follow-up where odds ratio for ESRD was 1.41 among male participants.[8] In contrast, the CREDIT study demonstrated that CKD is higher in women than in men (18.4 vs. 12.8%) in Turkey.[2]

ETHNICITY

Several studies performed in the United States have confirmed an increased risk for the development of ESRD in African Americans compared with Caucasians.[10] Moreover, the risk of hypertensive ESRD is approximately fivefold higher in African Americans.[11] In a recent study, it was found that the lifetime risk of ESRD was 7.8% for 20 year old black women, 7.3% for black men, 1.8% for white women, and 2.5% for white men.[3]

AGE

Renal function decreases with age in both men and women.[8] Among the elderly population, more than one-half of the subjects screened had CKD stages 3–5 (GFR <60 ml/min per 1.73 m^2) according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines.[8] Thus, the elderly population is more prone to develop CKD after various renal insults.[12] In the CREDIT study the odds ratios of CKD ranged from 1.45 to 2.18 for every 10-year increase in age among subjects older than 30 years of age in Turkey.[2]

LOW BIRTH WEIGHT

In the 1980s, Brenner and colleagues hypothesized that intrauterine growth restriction might cause a low nephron number, which could predispose to hypertension and renal disease (also known as the Barker hypothesis).[13] In support of this hypothesis, it has been shown that there is an increase in nephron numbers by 257,426 glomeruli per kg increase in birth weight.[14] Low nephron number leads to intraglomerular hypertension and hyperfiltration in the available nephrons and lower over-all GFR and higher urine albumin-to-creatinine ratio.[15] In a recent cohort study with a maximum follow-up of 38 years, low birth weight and intrauterine growth restriction were significantly associated with increased risk for ESRD among Norwegians.[15]

OBESITY

One of the strongest yet modifiable risk factors for ESRD in the twenty-first century is obesity.[16] Glomerular hypertrophy and hyperfiltration may accelerate kidney injury by increasing capillary wall tension of the glomeruli and decreasing podocyte density.[16]

A large-scale epidemiologic study from Sweden demonstrated the role of obesity in CKD.[17] In this study, native Swedes between the ages of 18 and 74 with CKD whose serum creatinine exceeded 3.4 mg/dl (men) or 2.8 mg/dl (women) during the study period were analyzed.[17] Overweight (body mass index (BMI) $\geqslant 25$ kg/m^2) at age 20 was associated with a significant threefold excess risk for CKD, in comparison with BMI <25 kg/m^2. Obesity (BMI $\geqslant 30$ kg/m^2) among men and morbid obesity (BMI $\geqslant 35$ kg/m^2) among women anytime during lifetime was linked to three- to fourfold increases in CKD risk.[17]

Obesity may contribute to the pathogenesis of kidney damage through inflammation, oxidative stress, endothelial dysfunction, prothrombotic state, hypervolemia, and adipokine derangements.[18]

Besides high BMI, carrying excess weight around the abdomen is linked to an increased risk of CKD. Kwakernaak *et al.*[19] found that in multivariate analyses, higher waist-to-hip ratio was associated with lower GFR, lower effective renal plasma flow, and higher filtration fraction, even after adjustment for sex, age, mean arterial pressure, and BMI.

SOCIOECONOMIC STATUS

Socioeconomic status may be determined by income, occupation, education, wealth, and housing situation.[20] Krop *et al.*[21] reported that income $<$\$16,000 compared with income $>$\$35,000 was associated with 2.4-fold increase in CKD. A case–control study demonstrated that those with CKD were more likely to come from families of unskilled workers.[21] Moreover, NHANES results show that unemployed non-Hispanic blacks and Mexican Americans in the United States had twice more CKD prevalence than their employed counterparts.[21] In the ARIC study those with less than high school education had 1.7 times CKD risk in comparison with those with college education.[20,21]

SMOKING

Smoking can increase the CKD risk through proinflammatory state, oxidative stress, prothrombotic shift, endothelial dysfunction, glomerulosclerosis and tubular atrophy.[18] In a study where 7476 nondiabetic participants were enrolled, smoking >20 cigarettes per day increased the risk of CKD.[22] In another study, each additional five smoked cigarettes per day was associated with an increase in serum creatinine >0.3 mg/dl by 31%.[23]

NEPHROTOXINS

Alcohol and recreational drugs have been linked to CKD progression as well as excessive use of analgesic drugs and exposure to heavy metals.[12] When persons who had taken fewer than 1000 pills containing acetaminophen in their lifetime were used for reference, the odds ratio for ESRD was found to be 2.0 for those who had taken 1000–4999 pills and 2.4 for those who had taken 5000 or more pills.[24]

ACUTE KIDNEY INJURY

Researchers have recognized the importance of acute kidney injury (AKI) episodes in the development of CKD.[25] According to 2009 USRDS data, adults with a history of AKI during hospitalization had a 10-fold greater risk of developing ESRD in the next 12 months than those without AKI episode.[25] Even after a single episode of experimental AKI, histologic repair can be impaired and focal tubulo-interstitial fibrosis may develop.[25]

DIABETES MELLITUS

Diabetes mellitus (DM) is the leading cause of CKD and ESRD in both developed and developing countries.[3] According to the registry of Turkish Society of Nephrology, diabetic patients constitute 37.3% of the hemodialysis population in Turkey.[26] According to the USRDS data, half of the new ESRD patients in the United States have diabetic nephropathy.[27]

Mechanisms that lead to kidney disease in diabetes include hyperfiltration injury, advanced glycosylation end products, and reactive oxygen species.[27] At the molecular level, numerous cytokines, growth factors and hormones such as transforming growth factor-beta and angiotensin II cause pathologic changes associated with diabetic nephropathy.[27]

Eight percent of new patients with type 2 DM already have proteinuria at diagnosis.[27] Among those who are initially free of proteinuria, the 20-year risk of diabetic nephropathy is 41%.[3] After the onset of proteinuria, the subsequent 10-year risk of progressive CKD is 11%.[3] Thus, about half of those with type 2 DM will develop nephropathy and 10% of these individuals will experience progressive loss of renal function.[27]

HYPERTENSION

Hypertension has long been a defined risk factor for both CKD and ESRD, and accounts for 27% of all ESRD patients in the United States and 28% of hemodialysis patients in Turkey.[26,27]

Systemic hypertension is transmitted to intraglomerular capillary pressure leading to glomerulosclerosis and loss of kidney function; thus variable risk of impaired renal function has been reported among hypertensive subjects.[27] At study entry, 5.9% of the Hypertension Detection and Follow-up Program trial participants had a serum creatinine of 1.5 mg/dl or greater. Among the 8683 participants, 2.3% of those with serial serum creatinine measurements above 1.5 mg/dl experienced clinically significant loss of renal function over 5 years.[28]

Essential hypertension is generally diagnosed between 25 and 45 years of age but overt kidney dysfunction does not develop unless the patient sustains at least 10 years of uncontrolled hypertension.[27] According to the MRFIT study, adjusted relative risk of reaching ESRD was 1.9 for high-normal blood pressure, 3.1 for stage I, 6.0 for stage II, 11.2 for stage III, and 22.1 for stage IV hypertension.[29] A history of cardiovascular disease, hyperlipidemia, metabolic syndrome, hepatitis C virus, human immunodeficiency virus infection, and malignancy are further risk factors for CKD.

NEWLY DEFINED RISK FACTORS

Obstructive sleep apnea is a disease associated with complete and partial breathing disturbances during sleep for at least five events per hour.[18] In one study, 30.1% of obstructive sleep apnea patients had CKD.[18] Besides sharing the same risk factors, obstructive sleep apnea has an independent effect on CKD risk and progression.[18]

Heart rate has also been suggested as a risk factor for CKD. A total of 6759 Japanese subjects (20–84 years of age) were split into quartiles according to the baseline heart rate and were followed up for a mean of 47 ± 16 months.[30] Seven hundred thirty-four subjects developed CKD over the 5-year follow-up period. Subjects with higher heart rates had greater magnitude of decreasing estimated GFR and higher odds ratio of developing proteinuria. Each heart rate category increment led to approximately 1.1 times increased risk of developing CKD and 1.2 times increased risk of developing proteinuria in middle-aged or older subjects.[30]

Periodontal diseases, which are initiated by gram-negative tooth-associated microbial biofilms have also been defined as a risk factor CKD.[31] The inflammatory response in those patients has been associated with CKD.[31]

Data from 21,475 healthy volunteers of the Vienna Health Screening Project who were followed prospectively for a median of 7 years were analyzed to examine the association between uric acid level and CKD.[32] A slightly elevated uric acid level (7.0–8.9 mg/dl) was associated with doubled risk for CKD and an elevated uric acid ($\geqslant$9.0 mg/dl) was associated with a tripled risk.[32]

CONCLUSION

CKD is a major health issue in many societies. Understanding the risk factors and implementing screening of at risk populations will increase early detection, initiate treatment of modifiable risk factors for ESRD, along with appropriate treatment for CKD. In addition, the economic burden caused by the cost of renal replacement therapy might be mitigated by early detection of CKD risk factors.

DISCLOSURE

RK has received lecture fees from Fresenius Kabi AG. Publication costs for this article were supported by the

Turkish Society of Hypertension and Renal Diseases, a nonprofit national organization in Turkey.

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