Predicting initiation and progression of chronic kidney disease: Developing renal risk scores

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Epidemiological studies have raised awareness of the problem of undiagnosed chronic kidney disease (CKD) and suggest that early identification and treatment will reduce the global burden of patients requiring dialysis. This has highlighted the twin problems of how to identify subjects for screening and target intervention to those with CKD most likely to progress to end-stage renal disease. Prospective studies have identified risk factors for CKD in the general population as well as risk factors for progression in patients with established CKD. Risk factors may thus be divided into initiating factors and perpetuating factors, with some overlap between the groups. In this paper, we review current data regarding CKD risk factors and illustrate how each may impact upon the mechanisms underlying CKD progression to accelerate loss of renal function. We propose that these risk factors should be used as a basis for developing a renal risk score, analogous to the Framingham risk score for ischemic heart disease, which will allow accurate determination of renal risk in the general population and among CKD patients.

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THE NEED TO DEFINE RISK IN CHRONIC KIDNEY DISEASE

The past decade has seen a growing awareness of the problem of undiagnosed chronic kidney disease (CKD) and the implications for provision of renal replacement therapy (RRT). Substantial success has been achieved in promoting improved screening for and treatment of CKD to improve outcomes and reduce demand for RRT. These important aims have highlighted the twin problems of how to identify subjects for screening and target intervention to those with CKD most likely to result in end-stage renal disease (ESRD). Cost-effectiveness studies indicate that screening whole populations is not a viable[1] and a means of identifying high-risk individuals for targeted screening is therefore required.

The US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) has proposed a classification system for CKD that stratifies patients according to the level of kidney function to facilitate the development of appropriate management plans.[2] The K/DOQI classification is now widely accepted and has proved valuable in particular in identifying the prevalence of different stages of CKD in epidemiological studies.[3] It has been noted, however, that the K/DOQI classification provides little information on the future risk of decline in renal function.[4] Previous studies have identified a wide range of rates of decline in glomerular filtration rate (GFR) among patients with CKD and up to 15% may even show an increase over time.[5] Thus, within CKD stage 3, for example, there are some patients who will require renal replacement therapy within a variable period, whereas others never progress to ESRD. Clearly, these two scenarios require very different management plans necessitating accurate assessment of the risk of CKD progression.

RISK FACTORS AND MECHANISMS OF CKD PROGRESSION

It has been appreciated for several decades that once GFR has decreased to below a critical level, CKD tends to progress relentlessly toward ESRD. This observation suggests that loss of a critical number of nephrons provokes a vicious cycle of further nephron loss. Detailed studies have elucidated a number of inter-related mechanisms that together contribute to CKD progression including glomerular hemodynamic

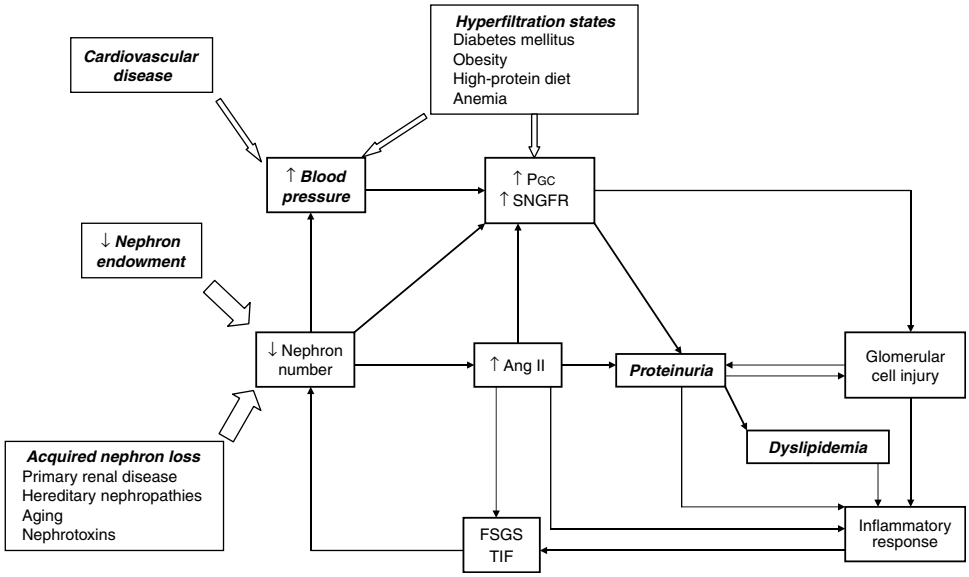

Figure 1 | Schema showing the interaction of risk factors for CKD progression with pathophysiological mechanisms that contribute to a vicious cycle of progressive nephron loss. Ang II – angiotensin II; FSGS – focal and segmental glomerulosclerosis; P_{GC} – glomerular capillary hydraulic pressure; SNGFR – single nephron glomerular filtration rate; TIF – tubulointerstitial fibrosis.

responses to nephron loss (raised glomerular capillary hydraulic pressure and single nephron GFR), proteinuria, and proinflammatory responses. A generally good prognosis after unilateral nephrectomy[6] attests to the fact that a single pathogenic factor may be insufficient to initiate progressive CKD, but the 'multi-hit' hypothesis proposes that multiple factors interact to overcome renal reserve and provoke progressive nephron loss.[7] Epidemiological studies have identified several variables that are predictive of CKD outcomes and may therefore be regarded as risk factors for CKD progression.[8] Figure 1 shows how risk factors may interact with pathophysiological mechanisms to accelerate CKD progression. It is clear that risk factors may be divided into *initiating factors* (Table 1) that play a role in starting the cycle of nephron loss and *perpetuating factors* (Table 2) that drive the process onwards.

Table 1 | Risk factors for CKD: initiating factors

Initiating factors
Older age
Family history of CKD
Hereditary nephropathies
Family history of CKD
Ethnicity
Gender
Diabetes mellitus
Metabolic syndrome
Hyperfiltration states
↓ Nephron number
Blood pressure >125/75 mmHg
Obesity
High protein intake
Anemia
High normal urinary albumin excretion
Dyslipidemia
Nephrotoxins
NSAIDS
Antibiotics/anti-virals
Radiological contrast
Light chains
Primary renal disease
Urological disorders
Obstruction
Recurrent urinary infections
Cardiovascular disease

Abbreviations: CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug.

A RENAL RISK SCORE

We propose that risk factors for CKD progression should be incorporated into a multi-variable scoring system that would predict an individual's future risk of ESRD. This would allow targeted population screening for CKD, identification of patients at high risk for CKD progression for more intensive intervention, and risk stratification in clinical trails. Such a system would be similar to the Framingham Risk Score[9] that has been instrumental in defining cardiovascular risk to guide therapy in patients at risk for ischemic heart disease. Detailed discussion of the statistical methods available for developing such a score is beyond the scope of this paper, but at least two studies have demonstrated the potential benefit of such an approach. Investigators from the Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study have reported that a risk score based on urine albumin to creatinine ratio, serum creatinine, serum albumin, and hemoglobin improved the risk prediction for progression of nephropathy to ESRD from 50% for albuminuria alone to greater than 80% for the risk score.[10] Dimitrov *et al.*[11] have shown that an alternative method of utilizing decision tree Bayesian modeling can be used to

Table 2 | Risk factors for CKD: perpetuating factors

Perpetuating factors
African-American race
↓ Nephron number
Proteinuria
SBP >130 mmHg
High dietary protein intake
Obesity
Anemia
Dyslipidemia
Smoking
Nephrotoxins
Cardiovascular disease

Abbreviations: CKD, chronic kidney disease; SBP, systolic blood pressure.

determine individual patient risk of ESRD based on basic epidemiological data and simple clinical information such as blood pressure and proteinuria.

The past 5–10 years have seen the publication of a large number of prospective studies identifying risk factors for the development of CKD in the general population as well as risk factors for progression to ESRD in patients with established CKD. In this paper, we review these data and identify the factors that should now be investigated in further studies to develop a renal risk score.

DEMOGRAPHIC VARIABLES

Age

Longitudinal studies of subjects without kidney disease have observed a decline in GFR with increasing age in some subjects implying that nephron loss may be part of normal aging.[12] Several population-based studies have found a higher incidence of proteinuria and CKD,[13,14] as well as ESRD with increasing age.[15] Similarly, the incidence of a decline in renal function over 5 years was greater among older patients with hypertension.[16] Paradoxically advanced age appears to be a negative predictor of ESRD among patients with CKD. The risk of progression to ESRD was decreased among older patients with CKD stage 3 (hazard ratio (HR) 0.75; 95% confidence interval (CI) 0.63–0.89 for each 10-year increase in age).[17] Nevertheless, older age was associated with a greater rate of decline in GFR.[17] This apparent contradiction is most likely explained by the competing risks of death and ESRD in older patients. On the other hand, one study has found that age $\geqslant$65 years was associated with slower decline in renal function than age <45 years among patients with CKD stages 4 and 5.[18] Thus, older age appears to act as an initiating factor but not necessarily a perpetuating factor.

Gender

In experimental studies, male rodents were more susceptible to age-related glomerulosclerosis than females, an effect that was independent of glomerular hemodynamics or hypertrophy and was attributable to a specific androgen effect.[19] Data regarding the role of gender in determining renal risk in humans are somewhat contradictory. Many studies suggest that male gender is associated with worse renal outcomes. Studies have reported a higher incidence of proteinuria and CKD among men in the general population,[13] an increased risk of ESRD, or death associated with CKD among men in the general population,[13,15,20] a higher risk of decline in renal function among male hypertensive patients,[16] a lower risk of ESRD among female patients with CKD stage 3,[17] and a shorter time to renal replacement therapy among male patients with CKD stages 4 and 5.[18] Data from the United States Renal Data System show a substantially higher incidence of ESRD among males (413/million population in 2003) versus females (280/million population).[21] Furthermore, a meta-analysis of 68 studies that included 11 345 patients with CKD found a higher rate of decline in renal function in men.[22] On the other hand, a meta-analysis of individual patient data from 11 randomized trails evaluating the efficacy of angiotensin-converting enzyme inhibitor (ACEI) treatment in CKD did not show an increased risk of doubling of serum creatinine or ESRD, or ESRD alone among men.[23] Indeed, after adjustment for baseline variables including blood pressure and urinary protein excretion, women evidenced a significantly higher risk of these end points than men.[23] One limitation of this and several of the other studies quoted is that menopausal status of the women was not documented.

Ethnicity

It is clear that African-Americans evidence a higher incidence of CKD and are overrepresented in the dialysis population of the US: population-based studies have found a higher incidence of ESRD among African-Americans that is attributable only, in part, to socio-economic and other known risk factors;[15,24–26] the risk of early renal function decline (increase in serum creatinine of $\geqslant$0.4 mg/dl) was approximately three-fold higher (odds ratio (OR) 3.15; 95% confidence interval (CI) 1.86–5.33) among black versus white diabetic adults, but 82% of this excess risk was attributable to socio-economic and other known risk factors;[27] the risk of decline in renal function over 5 years among hypertensive patients is greater in African-Americans;[16] black race was independently associated with greater rate of GFR decline in the Modification of Diet in Renal Disease (MDRD) study.[5] Interestingly, the prevalence of estimated GFR (eGFR) 50–59 ml/min/1.73 m^2 was lower in African-American versus Caucasian subjects (adjusted OR 0.42; 95% CI 0.40–0.46) among patients >45 years enrolled into the Geographical and Racial Differences in Stroke Cohort Study (REGARDS), whereas the prevalence of eGFR 10–19 ml/min/1.73 m^2 was higher among African-Americans (adjusted OR 1.73; 95% CI 1.02–2.94), suggesting that in this population African-American race acted as a risk factor for progression but not initiation of CKD.[28] CKD and ESRD have also been found to be more common among other ethnic groups, including Asians,[29,30] Hispanics[31] Native Americans,[32] Mexican Americans,[33] and Australian Aboriginals.[34] The mechanisms underlying these associations remain to be elucidated, but

possible explanations include increased prevalence of diabetes mellitus, lower nephron endowment, increased susceptibility to salt-sensitive hypertension, and other genetic factors, as well as environmental, lifestyle, and socio-economic differences.

HEREDITARY FACTORS

Hereditary renal diseases resulting from a single gene defect including autosomal-dominant polycystic kidney disease, Alport's disease, and Fabry's disease account for a relatively small yet clinically significant proportion of all patients with CKD. Moreover, there is substantial evidence that genetic factors account for familial clustering of other forms of CKD with multi-factorial etiology. Among 25 883 incident ESRD patients, 22.8% reported a family history of ESRD[35] and screening of the relatives of ESRD patients revealed evidence of CKD in 49.3%.[36] In another case–control study including 689 patients with ESRD and 361 controls, having one first-degree relative with CKD increased the risk of ESRD by 1.3 (95% CI 0.7–2.6) and having two such relatives increased it by 10.4 (95% CI 2.7–40.2) after controlling for multiple known risk factors including diabetes and hypertension.[37] Similarly a case–control study of 103 white American patients with ESRD reported a 3.5-fold increase (95% CI 1.5–8.4) in risk of ESRD with the presence of either a first-, second-, or third-degree relative with ESRD.[38] Other studies suggest that genetic factors also increase susceptibility to early manifestations of CKD. In one study of 169 families with one type II diabetic proband, the diabetic siblings of probands with micro-albuminuria had a significantly increased risk of also having microalbuminuria after adjustment for confounding risk factors (OR 3.94; 95% CI 1.93–9.01) than the diabetic siblings of probands without microalbuminuria.[39] Furthermore, the non-diabetic siblings of diabetic probands with micro-albuminuria evidenced significantly higher urinary albumin excretion rates (within the normal range) than the non-diabetic siblings of normo-albuminuric diabetic probands.

DIABETES MELLITUS

Diabetic nephropathy is rapidly becoming the single most common cause of ESRD worldwide and diabetes was associated with a substantially increased risk of ESRD or death associated with CKD (relative hazard 7.5; CI 4.8–11.7) in one population-based study of 23 534 subjects[20] as well as an increased risk of moderate chronic renal impairment (estimated creatinine clearance <50 ml/min) in another study of 1428 subjects with estimated creatinine clearance >70 ml/min at baseline.[40] In patients with diabetes, poor glycemic control is a risk factor for the development of nephropathy and randomized trials among patients with type I[41] and type II[42] diabetes have confirmed that tight glycemic control reduces the risk of developing diabetic nephropathy. The pathogenesis of diabetic nephropathy is complex and involves multiple mechanisms, including glomerular hemodynamic factors (see below),[43,44] advanced glycation end-product formation, generation of reactive oxygen species as well as upregulation of profibrotic growth factors such as transforming growth factor-β and connective tissue growth factor.[45]

HYPERFILTRATION STATES

Experimental studies have shown that glomerular hemodynamic responses to nephron loss[46] and chronic hyperglycemia[43] (raised glomerular capillary hydraulic pressure and increased single nephron GFR) are critical factors in establishing the vicious cycle of nephron loss characteristic of CKD. In addition, any factor that further increases glomerular hypertension and hyperfiltration may be expected to compound the effects of nephron loss and accelerate progression (Figure 1).

Decreased nephron number

Nephron endowment. A substantial body of evidence exists to support the hypothesis that low nephron endowment predisposes individuals to CKD by provoking an increase in single nephron GFR, and therefore, a reduction in renal reserve.[47] In human autopsy studies, low birth weight is directly associated with reduced nephron number[48,49] and birth weight may therefore serve as a marker of nephron endowment. Low birth weight is also a risk factor for later life hypertension and diabetes mellitus, both of which further increase the risk of CKD.[50] Several studies have found a link between low birth weight and CKD. Investigation of 422 subjects born very preterm (gestational age <32 weeks), at age 19 years, revealed a significant positive correlation between birth weight (expressed as standard deviation from normal for gestational age) and estimated GFR as well as a negative correlation between birth weight and the logarithm of urine albumin to creatinine ratio.[51] Renal function was normal in all subjects. Furthermore, low birth weight was associated with an increased risk of albuminuria in Pima Indians with type II diabetes[52] as well as Australian Aboriginals,[53] and ESRD was significantly associated with low birth weight in a case–control study of patients in the Southeastern US.[54] Interestingly, a recent autopsy study reported significant associations between mean arterial pressure and glomerular number ($r=-0.46$; $P=0.005$), mean arterial pressure and birth weight ($r=-0.42$; $P=0.04$) as well as glomerular number and birth weight ($r=0.57$; $P=0.002$) among Caucasian but not African-American patients in the Southeastern US.[55]

Acquired nephron deficit. Experimental models of acquired nephron loss have shown that severe nephron loss (5/6 nephrectomy) alone can initiate a cycle of progressive injury in the remaining glomeruli mediated largely through glomerular hypertension and hyperfiltration.[46] Similarly, among 14 humans subjected to partial resection of a single kidney, two developed ESRD and nine developed proteinuria, the extent of which was inversely correlated with the amount of renal tissue remaining.[56] Lesser degrees of acquired nephron loss may not be sufficient alone to cause CKD,[6] but may predispose individuals to other forms of CKD as

evidenced by the observation that uninephrectomy exacerbates renal injury in experimental[57] and human diabetic nephropathy.[58] In most forms of human CKD, focal nephron loss initially occurs as a result of primary renal disease, multisystem disorders that involve the kidney, or exposure to nephrotoxins, but we and others have proposed that hemodynamic adaptations in remaining glomeruli contribute to further nephron loss. Several epidemiological studies attest that patients with reduced GFR are at increased risk for a further decline in renal function. At least one study has found an increased risk of developing CKD associated with an eGFR <90 ml/min/1.73 m^2 in participants without evidence of CKD at baseline (OR 3.01; CI 1.98–4.58 versus eGFR $\geqslant 120$ ml/min/1.73 m^2).[14] Among patients known to have CKD, several longitudinal studies have reported an increased risk of ESRD with decreased eGFR: 3047 patients with CKD stage 3 evidenced an HR of 2.5 (95% CI 1.89–3.31) for each 10 ml/min/1.73 m^2 decrease in eGFR;[17] among 131 patients with CKD (mean eGFR 31 ± 15 ml/min/1.73 m^2), each 1 ml/min/1.73 m^2 increase in eGFR was associated with an HR of 0.914 (95% CI 0.864–0.968) for ESRD;[59] among 920 CKD stage 4 and 5 patients, an eGFR of 13.7–16.6 ml/min/1.73 m^2 was associated with a relative risk (RR) for ESRD of 1.5 (95% CI 1.21–1.91) versus eGFR >18.5 ml/min/1.73 m^2.[18] Furthermore, higher serum creatinine was an independent risk factor for the development of albuminuria or renal impairment among patients with type II diabetes without CKD at baseline[30] and elevated serum creatinine as an independent predictor of progression to ESRD among patients with type II diabetes mellitus and nephropathy in the RENAAL study (HR = 3.59; 95% CI 2.90–4.45).[10] On the other hand, detailed analysis of data from the MDRD study confirmed a wide range of rates of GFR decline among CKD patients, but found no association between the level of GFR at baseline and subsequent rate of decline.[5]

Blood pressure

Hypertension has long been recognized as a consequence of renal impairment and an important factor in the progression of CKD. Within the model of CKD progression described in Figure 1, it is easy to appreciate that elevated systemic blood pressure transmitted to the glomerulus would contribute to glomerular hypertension and thus accelerate glomerular damage. Hypertension was predictive of ESRD risk in several large population-based studies[13,14,20,60] and raised systolic blood pressure was an independent risk factor for development of albuminuria or renal impairment among patients with type II diabetes.[30] Furthermore, several studies have found a close association between the magnitude of increased risk and the level of blood pressure such that even modest elevations in blood pressure, below the threshold for a diagnosis of hypertension, are associated with increased risk of ESRD.[13,20,61] Among patients with CKD in the MDRD study, higher baseline mean arterial pressure independently predicted a greater rate of GFR decline.[5] These observations have prompted a call for blood pressure to be viewed as a continuous rather than a dichotomous risk factor for CKD with less emphasis on traditional definitions of 'hypertension' and 'normotension'.[62] At least three large prospective randomized trials have sought to investigate the potential renoprotective benefit of 'intensive' versus 'standard' blood pressure lowering. In the MDRD study, the primary analysis found no significant difference between the rate of change in GFR during a mean of 2.2 years follow-up between patients randomized to achieve a mean arterial pressure of <92 mmHg (equivalent to $<125/75$ mmHg) or <98 mmHg if $\geqslant 61$ years, versus <107 mmHg (equivalent to 140/90 mmHg) or <113 mmHg if $\geqslant 61$ years, but secondary analysis did show significant benefit associated with the low blood pressure target among patients with higher levels of baseline proteinuria.[63] Lower achieved blood pressure was also closely associated with a slower rate of GFR decline, an effect that was also more marked among patients with greater baseline proteinuria.[64] Moreover, long-term follow-up (mean 6.6 years) of patients from the MDRD study reported a significant reduction in the risk of ESRD (adjusted HR 0.68; 95% CI 0.57–0.82) or a combined end point of ESRD or death (adjusted HR 0.77; 95% CI 0.65–0.91) among patients randomized to 'low' blood pressure targets even though treatment and blood pressure data were not available beyond the 2.2 years of the original trial.[65] In the African-American Study of Kidney Disease and Hypertension (AASK), no significant difference in the rate of GFR decline was observed between patients randomized to a mean arterial pressure goals of $\leqslant 92$ versus 102–107 mmHg. It should be noted, however, that patients in AASK generally had low levels of baseline proteinuria (mean urine protein 0.38–0.63 g/day).[66] Thus, the MDRD and AASK study results suggest a significant interaction between blood pressure and proteinuria as risk factors for CKD progression. In a third study, additional blood pressure reduction with a calcium channel blocker in patients with non-diabetic CKD on ACEI treatment failed to produce additional renoprotection, but the degree of additional blood pressure reduction was modest (4.1/2.8 mmHg) and may have been insufficient to improve outcomes in patients already receiving optimal ACEI therapy.[67] A recent longitudinal study of 217 Veterans with CKD has confirmed that systolic blood pressure measurements, and in particular home blood pressure recordings, are independent predictors of the risk of ESRD or death or a combined end point of both.[68] Interestingly, blood pressure was not an independent predictor of ESRD among diabetic patients in the RENAAL study.[10] This is likely due to the fact that blood pressure was well controlled in all patients and illustrates how risk factors may vary in importance depending on the population studied.

Obesity and metabolic syndrome

In experimental studies, obesity is associated with hypertension, proteinuria, and progressive renal disease. Micropuncture studies have confirmed that obesity is another cause of glomerular hyperfiltration and glomerular hypertension that

can be expected to exacerbate the progression of CKD.[69,70] Recent attention has focused on the observation that adipocytes produce a variety of hormones and proinflammatory molecules that may also contribute to progressive renal damage.[71] In humans, severe obesity is associated with increased renal plasma flow, glomerular hyperfiltration, and albuminuria, abnormalities that are reversed by weight loss.[72] Obesity as defined by increased body mass index (BMI) has been associated with increased risk of developing CKD in several large population-based studies.[14,73] Furthermore, one study has found a progressive increase in relative risk of developing ESRD associated with increasing BMI (RR 3.57; CI 3.05–4.18 for BMI 30.0–34.9 versus BMI 18.5–24.9 kg/m^2) among 320 252 subjects confirmed to have no evidence of CKD at initial screening.[74] There is evidence that obesity may directly cause a specific form of glomerulopathy characterized by proteinuria and histological features of focal and segmental glomerulosclerosis,[75] but it is likely that it also acts as a risk factor in the development of several other forms of renal disease. Recently, interest has focused on the role of the metabolic syndrome (insulin resistance), defined by the presence of abdominal obesity, dyslipidemia, hypertension, and fasting hyperglycemia, in the development of CKD. An analysis of the Third National Health and Nutrition Examination Survey data found a significantly increased risk of CKD and microalbuminuria in subjects with the metabolic syndrome as well as a progressive increase in risk associated with the number of components of the metabolic syndrome present.[76] Furthermore, a large longitudinal study of 10 096 patients without diabetes or CKD at baseline identified metabolic syndrome as an independent risk factor for the development of CKD over 9 years (adjusted OR 1.43; 95% CI 1.18–1.73). Again there was a progressive increase in risk associated with the number of traits of the metabolic syndrome present (OR 1.13; 95% CI 0.89–1.45 for one trait versus OR 2.45; 95% CI 1.32–4.54 for five traits).[77] In another study, patient hip–waist ratio, a marker insulin resistance, was independently associated with impaired renal function even in lean individuals (BMI $<25\,kg/m^2$) among a population-based cohort of 7676 subjects.[78] The effect of obesity on the progression of established CKD is less well documented. In one study, increased BMI was an independent risk factor for CKD progression among 162 patients with IgA nephropathy.[79] On the other hand, BMI was unrelated to the risk of ESRD among an cohort CKD stage 4 and 5 patients.[18]

High dietary protein intake

Protein feeding has been shown to provoke an increase in GFR in rodents[80] and humans.[81] Consistent with the hypothesis that the glomerular hemodynamic changes associated with hyperfiltration accelerate glomerular injury, experimental studies have reported that high protein diet accelerates renal disease progression, whereas dietary protein restriction attenuates it.[82,83] Furthermore, dietary protein restriction results in normalization of glomerular capillary hydraulic pressure as well as single nephron GFR and marked attenuation of glomerular damage in the 5/6 nephrectomy model.[46] Observational studies in humans have found an increased risk of microalbuminuria associated with higher dietary protein intake among subjects with diabetes and hypertension (OR 3.3; 95% CI 1.4–7.8), but not among healthy subjects or those with isolated diabetes or hypertension,[84] again illustrating the interaction between risk factors for CKD. In one prospective study, high protein intake, particularly non-dairy animal protein, was associated with a greater rate of decline in estimated GFR among women with estimated GFR 80–55 ml/min/1.73 m^2 but not in those with estimated GFR >80 ml/min/1.73 m^2.[85] The MDRD study was a randomized trail designed to investigate the renoprotective potential of dietary protein restriction in patients with CKD. Whereas the primary analysis revealed no significant difference in the mean rate of GFR decline,[63] secondary analysis revealed that an initial reduction in GFR resulting from the functional effects of decreased protein intake obscured a later reduction in the rate of GFR decline in the low protein diet group.[63] Analysis of outcomes according to achieved dietary protein intake showed that a reduction in protein intake of 0.2 g/kg/day correlated with a 1.15 ml/min/year reduction in the rate of GFR decline, equivalent to a 29% reduction in mean rate of GFR decline.[86] Three meta-analyses of smaller studies have all reported a significant renoprotective benefit associated with dietary protein restriction.[87–89]

Glycogen storage diseases

Glycogen storage diseases provide another example where glomerular hyperfiltration is associated with the development of albuminuria and a subsequent decline in renal function.[90]

BIOMARKERS

Urinary protein excretion

Abnormal excretion of urinary protein is a marker of glomerulopathy and an index of disease severity, but recent experimental evidence suggests that proteinuria may also contribute to progressive renal damage in CKD.[91] A large body of evidence attests to a strong association between proteinuria and the risk of CKD progression. Mass screening of a general population of 107 192 participants by means of dipstick urinalysis identified proteinuria as the most powerful predictor of ESRD risk over 10 years (OR 14.9; 95% CI 10.9–20.2).[13] Furthermore, increased urinary albumin levels within the normal range were independently associated with subsequent development of albuminuria or renal impairment in patients with type II diabetes but no albuminuria at baseline.[30] Among patients with CKD owing to a wide variety of etiologies, baseline proteinuria has consistently predicted renal outcomes.[59,92,93] In three large prospective studies that included patients with non-diabetic CKD (MDRD study, Ramipril Efficacy In Nephropathy (REIN) study and AASK), higher baseline proteinuria was strongly associated with a more rapid decline in GFR.[5,64,94,95] Similarly, among patients with diabetic nephropathy, baseline urinary albumin to creatinine ratio was a strong independent predictor of ESRD

in the RENAAL study and Irbesartan in Diabetic Nephropathy Trial (IDNT).[10,96] Furthermore, the extent of 'residual proteinuria' that persists despite optimal treatment with an ACEI or angiotensin receptor blocker also predicts renal prognosis: Secondary analysis of REIN study data found that percentage reduction in proteinuria over the first 3 months as well as the absolute level of proteinuria at 3 months were strong independent predictors of the subsequent rate of decline in GFR;[97] in the IDNT, greater reduction in proteinuria at 12 months was associated with a greater reduction in the risk of ESRD (HR 0.44; 95% CI 0.40–0.49 for each halving of baseline proteinuria);[96] in AASK, change in proteinuria from baseline to 6 months predicted subsequent progression.[95] A meta-analysis of data from 1860 patients with non-diabetic CKD showed that during antihypertensive treatment, the current level of proteinuria was a powerful predictor of the combined end point of doubling of baseline serum creatinine or onset of ESRD (RR 5.56; 95% CI 3.87–7.98 for each 1.0 g/day increase in proteinuria).[98] These data support the notion that proteinuria, like blood pressure, should be regarded as a continuous risk factor for CKD progression.[62] Proteinuria thus appears to be a marker of renal risk in the general population, patients with CKD prior to treatment and CKD patients on treatment. Furthermore, analysis of data from the RENAAL study found that baseline albuminuria was the most important independent predictor of ESRD risk in all ethnic groups, including White, Black, Asian, and Hispanic. Reduction in albuminuria at 6 months also predicted renoprotection in all ethnic groups.[31]

Serum albumin

Serum albumin levels are widely regarded as a marker of nutritional status, but may also be reduced due to proteinuria or inflammation. Analysis of data from the MDRD study found a univariate correlation between higher baseline serum albumin and slower subsequent rate of GFR decline, but in the multivariate analysis, this was displaced by a similar correlation with baseline serum transferrin levels, another marker of protein nutrition.[5] Three studies have found associations between serum albumin and renal outcomes among patients with type II diabetes and CKD. Among 182 patients with a mean serum creatinine of 1.5 mg/dl at baseline, hypoalbuminemia was an independent risk factor for ESRD.[99] In a long-term follow-up of 343 patients, low baseline serum albumin was an independent predictor of CKD progression,[100] and in the RENAAL study, low serum albumin was an independent predictor of ESRD.[10] In both of these studies, the predictive value of hypoalbuminemia was independent of and additional to that of proteinuria, indicating that it is not merely acting as a marker of albuminuria.

Anemia

Chronic anemia owing to inherited hemoglobinopathy is associated with increased renal plasma flow as well as glomerular hyperfiltration and subsequent development of proteinuria, hypertension, and ESRD.[101,102] Anemia is a common complication of CKD, but several studies have shown that it is also an independent predictor of renal risk. In the RENAAL study, baseline hemoglobin was a significant independent predictor of ESRD among diabetic patients such that each 1 g/dl decrease in hemoglobin was associated with an 11% increase in the risk of ESRD.[103] Baseline hemoglobin was also one of four variables included in the renal risk score developed from the RENAAL data.[10] Similarly, higher hemoglobin was independently associated with lower risk of progression to ESRD (halving of GFR or need for dialysis) or death among 131 patients with all forms of CKD (HR = 0.778; 95% CI 0.639–0.948 for each 1 g/dl increase).[59] Furthermore, time-averaged hemoglobin of <12 g/dl was associated with a significantly increased risk of ESRD among 853 male Veterans with CKD stages 3–5 (HR 0.74; 95% CI 0.65–0.84 for each 1 g/dl increase in hemoglobin).[104] Consistent with the hypothesis that anemia contributes directly to CKD progression, two small randomized studies have reported renoprotective benefit associated with erythropoietin therapy. Among patients with serum creatinine 2–4 mg/dl and hematocrit $<30\%$, erythropoietin treatment was associated with significantly improved renal survival,[105] and in non-diabetic patients with serum creatinine 2–6 mg/dl, early treatment (started when hemoglobin <11.6 g/dl) with erythropoietin alpha was associated with a 60% reduction in the risk of doubling serum creatinine, ESRD, or death versus delayed treatment (started when hemoglobin <9.0 g/dl).[106]

Dyslipidemia

Lipid abnormalities are commonly associated with CKD, but only recently has evidence emerged that dyslipidemias are a risk factor for the development and progression of CKD. In population-based studies, several lipid profile variables have been associated with CKD risk: elevated low-density lipoprotein/HDL-cholesterol ratio was associated with a faster rate of decline in renal function in men without renal disease at baseline;[107] subjects with higher triglyceride levels and lower HDL-cholesterol levels were at increased risk for a rise in serum creatinine among participants with normal or mildly elevated serum creatinine at baseline;[108] increased HDL-cholesterol levels were associated with decreased risk of developing CKD in apparently healthy subjects;[14] individuals with elevated total cholesterol, low-HDL-cholesterol, or elevated total to HDL-cholesterol were at increased risk of a rise in serum creatinine to $\geqslant 1.5$ mg/dl among healthy men in the Physicians' Health Study.[109] Evidence is also accumulating that lipid abnormalities are a risk factor for CKD progression. In the MDRD study, lower HDL-cholesterol levels independently predicted a more rapid decline in GFR,[5] and in a smaller study of patients with CKD total cholesterol, LDL-cholesterol and apolipoprotein B levels were all associated with more rapid decline in GFR.[110] Among 223 patients with IgA nephropathy, hypertriglyceridemia was independently predictive of CKD progression.[111] The results of large prospective randomized trials on the effect of statin

treatment in CKD are still awaited. Subgroup analysis of a prospective randomized trial of pravastatin treatment in patients with previous myocardial infarction found that pravastatin slowed the rate of decline in patients with estimated GFR <40 ml/min/1.73 m^2, an effect that was more pronounced in those with proteinuria.[112] On the other hand, a similar analysis of patients with estimated GFR 30–59.9 ml/min/1.73 m^2 in a randomized trial of gemfibrozil in men with coronary disease showed no renoprotective benefit. One meta-analysis of 13 small controlled trials found that lipid-lowering therapy was associated with a significantly slower rate of GFR decline (0.156 ml/min/month; 95% CI 0.026–0.285 ml/min/month, $P=0.008$) among patients with CKD.[113]

Serum uric acid

Hyperuricemia is a common consequence of chronic renal failure, but may also contribute to CKD progression. In one population-based study, baseline hyperuricemia was an independent risk factor for subsequent increase in serum creatinine.[114] A larger study from the same population subsequently identified hyperuricemia as an independent risk factor for ESRD among women, but not men.[115] In patients with IgA nephropathy, hyperuricemia has emerged as a risk factor for CKD progression in two studies.[111,116] To date, only one small randomized study has investigated the effect of lowering serum uric acid levels on CKD progression. Among 54 patients with CKD, patients randomized to treatment with allopurinol evidenced stable serum creatinine values over 12 months, whereas patients in the control group showed an increase, but this benefit did not correlate with uric acid levels.[117] Possible mechanisms whereby hyperuricemia may contribute to CKD progression are glomerular hypertension,[118,119] endothelial dysfunction,[120] and pro-inflammatory effects.[121]

Plasma asymmetrical dimethylarginine

Elevated plasma asymmetrical dimethylarginine levels are a marker of endothelial dysfunction in the general population and are a risk factor for death in patients with ESRD. One relatively small study has identified increased asymmetrical dimethylarginine levels as an independent risk factor for ESRD or death among 131 CKD patients (HR = 1.203; 95% CI 1.07–1.35 for each 0.1 μM/l increase).[59] Further studies are required to confirm asymmetrical dimethylarginine as a risk factor for ESRD in larger populations.

NEPHROTOXINS

Smoking

Cigarette smoking has been identified in several large population-based studies as an independent risk factor for different manifestations of CKD, including proteinuria,[122] increased serum creatinine,[123] decreased estimated GFR (OR 1.42; 95% CI 1.06–1.91),[14] and development of ESRD or death associated with CKD (relative hazard 2.6; 95% CI 1.8–3.7).[20] In the latter study, 31% of the attributable risk of CKD was associated with smoking. Smoking has also been shown to increase the risk of progression of CKD due to diabetes,[124,125] hypertensive nephropathy,[126] glomerulonephritis,[127] lupus nephritis,[128] IgA nephropathy,[129] and Adult Polycystic Kidney Disease.[129] Possible mechanisms whereby cigarette smoking may contribute to renal damage include sympathetic nervous system activation, glomerular capillary hypertension, endothelial cell injury, and direct tubulotoxicity.[130]

Alcohol and recreational drugs

The role of alcohol consumption as a potential risk factor for CKD remains unclear. One case–control study found a significant association between ESRD and consumption of >2 alcoholic drinks per day,[131] whereas another similar study found no association (with the exception of 'moonshine').[132] Population-based studies have also found that alcohol consumption is not related to CKD risk.[133,134] The role of recreational drugs as a risk factor for CKD has not been widely studied but one case–control study reported a positive between heroin, cocaine, or other psychedelic drug use and ESRD.[135]

Analgesics

Analgesic nephropathy is well described as a cause of CKD and several epidemiological studies have reported links between analgesic consumption and CKD.[136–139] It has been pointed out, however, that these studies suffered from important limitations as well as potential biases and further studies are required to resolve this issue.[140]

Lead

Overt lead toxicity results in the well-recognized entity of lead nephropathy, characterized by chronic interstitial nephritis and an association with gout. In addition, epidemiological studies have reported that mild elevations in blood lead levels are associated with moderate reductions in GFR and/or hypertension in the general population.[141] Furthermore, one prospective study has identified elevations in blood lead levels and body lead burden within the normal range as important risk factors for progression among patients with CKD.[142]

PRIMARY RENAL DISEASE

Whereas considerable variation in the rate of GFR decline has been observed between individuals with a common cause of CKD, there is also evidence that some forms of CKD appear to result in more rapid progression than others. In the MDRD study, a diagnosis of Adult Polycystic Kidney Disease was an independent predictor of a greater rate of GFR decline,[5] and in a cohort of patients with CKD stages 4 and 5, diabetic nephropathy was associated with shorter time to ESRD than other diagnoses.[18]

CARDIOVASCULAR DISEASE

Much attention has focused recently on the important observation that CKD is associated with markedly increased

cardiovascular risk[143] and it is therefore not surprising that cardiovascular disease is also associated with an increased risk of CKD. Among hospitalized Medicare beneficiaries, the prevalence of CKD stage 3 or worse was 60.4% for those with heart failure and 51.7% for those with myocardial infarction. The presence of CKD in addition to heart disease was associated with a significantly increased risk of death and progression to ERSD.[144] These observations may, in part, be explained by the fact that cardiovascular disease and CKD share many risk factors, including obesity, metabolic syndrome, hypertension, diabetes mellitus, dyslipidemia, and smoking. In addition, cardiovascular disease may have direct effects on the kidneys that may promote initiation and progression of CKD, including decreased renal perfusion in heart failure and atherosclerosis of the renal arteries. For example, renal atherosclerosis was detected in 39% ($\geqslant$70% stenosis in 7.3%) of patients undergoing elective coronary angiography.[145] The interaction between cardiovascular and renal disease is further illustrated by the observation that among 313 patients with CKD, a diagnosis of cardiovascular disease was associated with an increased risk of progression to ESRD (RR 1.58).[146]

FURTHER CONSIDERATIONS

It is clear from the above that a large number of prospective studies have identified a wide range of risk factors for the development (Table 1) and progression of CKD (Table 2) in different populations. Whereas many studies have identified similar risk factors, there is also considerable variation between studies and some even appear contradictory. This variation is probably explained by differences in the variables included and the populations studied. In order to develop a clinically useful renal risk score, further prospective studies are required that investigate all of the variables of interest in clinically relevant cohorts with observation periods that are long enough to allow a sufficient number of hard end points. It is hoped that such studies will identify a relatively small number of risk factors (the RENAAL study analysis identified only four[10] and MDRD study, six[5]) that together accurately predict future risk of ESRD.

It is likely that the risk factors for the onset of CKD in the general population will differ somewhat from those for progression of established CKD and two separate risk scores will probably be required. If a risk score is to be used for targeting population screening, it should include only demographic data and other variables that can be obtained without specific testing. Obtaining the data required to develop accurate renal risk scores will require considerable effort and resources, but given the global burden of CKD leading to ESRD, this should be regarded as an urgent priority.

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