Risk Factors for Progressive Chronic Kidney Disease

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Abstract. The occurrence of chronic kidney disease and subsequent rate of loss of renal function are highly variable among individuals with the same underlying cause of renal injury or degree of functional impairment. Individual variability of risk is typical of complex diseases and reflects the multifactorial nature of the biologic mechanisms that are involved in the underlying disease process. The utility of the risk factor concept in developing CKD prevention and control strategies includes identifying individuals at high risk for the occurrence and progression of CKD, defining at-risk populations, elucidating potential targets for intervention, and generating explanatory hypotheses for the variable risk of CKD noted in different populations. Future application of the risk factor concept in the prevention and control of CKD will entail developing multivariate prediction equations; using spatial and temporal, as well as personal, characteristics, to define at-risk populations; identifying biomarkers for complex risk factors like race; and translating this information into testable interventions. This should include active extension of our current understanding of health care, social, and economic risk factors at both the individual and the community level.

The incidence and progression of renal injury vary substantially among individuals who are at-risk for kidney disease. For example, 8% of new patients with type 2 diabetes mellitus already have proteinuria at diagnosis (1). Among patients with type 2 diabetes mellitus who are initially free of proteinuria, the 20-yr risk of diabetic nephropathy is 41% (1). After proteinuria occurs, the subsequent 10-yr risk of progressive chronic kidney disease is 11% (2). Thus, about half of those with type 2 diabetes will develop nephropathy and 10% of these individuals will experience progressive loss of renal function. Variable risk of impaired renal function has also been reported among hypertensive subjects. 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 and 2.3% of the 8683 participants with serial serum creatinine measurements over 5 yr experienced clinically significant loss of renal function (3).

Similarly, the rate of loss of renal function among individuals with CKD also displays considerable person-to-person variability. For example, the Modification of Diet in Renal Disease (MDRD) study reported that the mean (SD) rate of decline in GFR during follow-up was 3.8 (± 4.2) ml/min per yr for patients with moderate and 4.0 (± 3.1) ml/min per yr for those with severe renal insufficiency at baseline (4). Substantial proportions of each group, 19% and 11%, respectively, showed no progression during follow-up, further indicating variability in progression.

Risk Factors and Variable Risk of CKD

Risk Factors and Variable Risk. Variability of risk for the occurrence and progression of CKD suggests that biologically relevant characteristics exist that influence the occurrence or course of the renal disease. The variable progression of CKD among individuals with autosomal dominant polycystic kidney disease (ADPKD) illustrates this concept. The mutation of the polycystin gene that occurs within family members is a necessary risk factor for ADPKD. However, family members who inherit the same mutation demonstrate highly variable rates of progression to ESRD (5). The within-family heterogeneity of time of onset of ESRD indicates that the rate of progression of CKD among individuals with the same ADPKD gene is associated with one or more independent exposures other than the mutation itself. Combinations of causal factors that result in rapid progression to ESRD define sufficient causes for early loss of renal function among ADPKD patients (6). Although some or all of the other component causes for rapid progression of ADPKD may also be genetic, this formulation of necessary and sufficient causes tempers inclinations to monogenic determinism and emphasizes the multifactorial nature of most, if not all, diseases.

The risk factor concept emphasizes that an exposure may be causal or may simply be associated with some other, perhaps unidentified, causal factor. Evidence supporting a potential causal role for a risk factor includes strong, graded associations with the disease that are consistent across different populations and study designs. A biologic link between the risk factor and the disease, relevant animal models, and strong dose-response relationships can also provide support of a causal role for a risk factor.
Prediction of Risk

Prediction of increased risk of occurrence or progression of CKD enables clinicians to identify individuals who may benefit from closer supervision of care or more intensive disease modifying interventions. Risk stratification using single patient characteristics is a straightforward application of this concept. Extending this concept to multiple risk factors requires statistical models that combine the contribution of multiple factors into a single summary score. For chronic kidney disease, interest has focused on risk factors for its occurrence and rate of progression. Information about these risk factors can be used in risk prediction (7,8).

Risk for Occurrence

Associations between patient characteristics and the occurrence of kidney disease identify risk factors for disease occurrence. For a factor that increases risk, the probability of disease when the factor is present exceeds that in absence of the characteristic

\[ p(\text{disease} \mid \text{characteristic present}) > p(\text{disease} \mid \text{characteristic absent}) \]

Multivariate logistic regression models can account for the joint effects of multiple factors on the occurrence of CVD (19,20). The multivariate logistic model provides an estimation of risk for subsequent disease:

\[
p(\text{disease} \mid \text{risk factors}) = \frac{\exp(\alpha + \sum \beta_i (\text{risk factor}_i))}{1 + \exp(\alpha + \sum \beta_i (\text{risk factor}_i))}
\]

where \( p \) is the probability of CKD during a stipulated period of observation, \( \alpha \) and \( \beta_i \) are logistic regression parameters derived from data for the population of interest, risk factor \( i \) is the individual’s value for the \( i \)th characteristic and the summation is over risk factors \( i = 1, 2, 3, \ldots, n \).

Although a widely accepted prediction model for the occurrence of CKD has not yet been developed for CKD, a recent cohort study illustrates a type of study design from which a prediction model could be derived (9). The study examined the 10-yr risk of developing ESRD among 107,192 participants aged 18 yr and older at baseline. ESRD occurred in 193 patients (0.18%). Patient characteristics considered as candidate risk factors for progressive CKD included gender, age at screening, proteinuria, hematuria, and systolic and diastolic BP. An independent association (adjusted odds ratio, 95% confidence interval) was found between risk of ESRD and proteinuria (14.9, 10.9 to 20.2), hematuria (2.30, 1.62 to 3.28), male gender (1.41, 1.04 to 1.92), and diastolic BP (1.39, 1.17 to 1.64).

Risk for Rate of Progression

Information about the rate of change in renal function over time can serve as a measure of disease progression. Progression rates, which measure change in renal function per unit of time, should be clearly distinguished from incidence rates for CKD, which are measured in incident cases per person-year. Progression of CKD can be measured using serum creatinine (10), reciprocal of the serum creatinine (11), Cockcroft-Gault estimated GFR (or similar estimating equation) (12), creatinine clearance (13), or log-normalized albumin excretion rate (14). At present there is no consensus as to which of these measures is best for risk prediction.

Risk factors for progression can be defined in a manner similar to that for occurrence:

\[
\text{Rate of change} \mid \text{risk factor present} > \text{Rate of change} \mid \text{risk factor absent}
\]

Multivariate linear models can extend the simple comparison of rates in two groups to account for multiple risk factors. Finally, individual rates of progression can be predicted by the multivariate model:

\[
\text{Predicted rate} = \alpha + \sum \beta_i (\text{risk factor}_i)
\]

where the predicted rate is the expected decline in renal function, \( \alpha \) and \( \beta_i \) are linear regression parameters derived from the data for the population of interest, and risk factors \( i \) the individual’s values for the characteristics included in the model. Because renal function is measured serially for each patient, it is necessary to account for the correlated nature of the outcome data using a linear growth curve or similar models (15).

A widely accepted prediction model for the rate of progression of CKD has not yet been developed. A report from the MDRD trial illustrates how an equation to predict progression of CKD might be derived (4). The MDRD investigators examined 41 potential risk factors for loss of renal function as measured by \( ^{125} \text{I}-\text{iothalamate GFR} \). Factors independently associated with the progression of CKD included black race, increased mean arterial BP, baseline urine protein excretion, a diagnosis of polycystic kidney disease, and lower baseline levels of serum transferrin and HDL cholesterol. These six factors accounted for 34.5% of the variation in the rate of progression in mild and 33.9% in moderate renal insufficiency.

Potential Targets for Intervention

The search for risk factors for CKD seeks to identify modifiable processes or mediators responsible for the occurrence and progression of renal failure. Table 1 lists some known risk factors.
factors for renal failure. Some of these factors, like the use of angiotensin converting enzyme inhibitors, BP control and glycemic control, have been tested in randomized clinical trials (RCT) that have established them as disease-modifying interventions and suitable targets for intervention. Others, like analgesic abuse and smoking, are supported by strong observational evidence. Although RCT evidence is lacking that cessation of smoking or of chronic analgesic use is renoprotective, it is reasonable to suggest that interventions targeted at these risk factors, particularly in high-risk populations, can be supported. Other factors, like anemia, are currently the subjects of large, well designed RCT; recommendations for specific intervention await supportive evidence from the completion of these trials.

In contrast, many of the risk factors listed in Table 1 like race, family membership, and socioeconomic status are complex measures and the biologic mechanisms that link them to the occurrence and progression of CKD are not defined. One challenge posed by these poorly characterized risk factors is to find associated biomarkers that directly link them to disease processes. Biomarkers are measured at the tissue, cellular, subcellular, molecular, or genetic level (43). They can potentially reduce misclassification and measurement variation. Furthermore, biomarkers may be more indicative of relevant disease processes that can suggest therapeutic interventions, which can be tested in RCT. Examples of biomarkers associated with increased risk of CKD are listed in Table 1.

### At-Risk Populations
Risk factors can be used to define at-risk population that can be targeted for education and early intervention programs. Groups defined by race are often mentioned as at-risk populations. Blacks, for example, have a considerably higher risk of ESRD partially due to hypertension and diabetes. This increased risk peaks during early adulthood and cannot be fully accounted for by racial differences in the underlying prevalence of hypertension (44). A recent study by Kibard and Clase estimated the cumulative risk of ESRD among different gender-race groups (45). They found that the lifetime of ESRD for a 20-yr-old black woman was 7.8%; for black males, 7.3%; for white women, 1.8%; and for white males, 2.5%. The number of years of life lost due to ESRD was comparable to the loss due to breast cancer among black women and prostate cancer among black men.

Space and time can also define at-risk populations. For example, maps of race- and cause-specific ESRD incidence published by the United States Renal Data System reveal a substantial nonrandom distribution of high risk populations for diabetes and hypertension (46). Those geographic areas where higher ESRD rates are found might be considered for targeted interventions. These geographic variations in risk also suggest that there may be environmental and social determinants of CKD risk, which are not accounted for within the traditional risk factor model.

A recent study by Lopes and Port of the age-specific patterns of black to white risk of nondiabetic ESRD illustrates the use of time as a risk factor to identify high-risk groups (47). They found that the relative risk of blacks compared to whites for CKD demonstrated considerable variability with age, peaking in middle adulthood and then declining, suggesting that blacks in middle life experience greater absolute and relative risk of CKD than at other times during their life span.

### Explanatory Hypotheses
Risk factors generate explanatory hypotheses that can lead to potential interventions. One set of explanatory hypotheses seeks to reduce complex exposures to potential causal factors. Well defined CKD risk factors that display a strong, graded association with the occurrence of CKD, which is consistent across studies in different populations and is related to biologic mechanisms responsible for renal injury and progressive loss of function, identify potential targets for disease modifying interventions. However, as noted above, many CKD risk factors are complex and not well defined. In such cases, it is necessary to consider how they might be linked to potential interventions.

A second explanatory issue revolves around the amount of the risk within a population that can be accounted for by a set of risk factors, a measure called population attributable risk (48). Questions of this nature seek to quantify the proportion of risk that can be prevented by eliminating a set of known causal risk factors. Understanding the amount of disease within a

### Table 1. Factors associated with the occurrence or progression of CKD

<table>
<thead>
<tr>
<th>CKD Risk Factors</th>
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<tbody>
<tr>
<td>older age (14,16)</td>
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</tr>
<tr>
<td>race and ethnicity (17–19)</td>
<td></td>
</tr>
<tr>
<td>gender (20)</td>
<td></td>
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<tr>
<td>lower birth weight (21)</td>
<td></td>
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<tr>
<td>low socioeconomic status</td>
<td></td>
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<tr>
<td>smoking (23)</td>
<td></td>
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<tr>
<td>alcohol consumption (24)</td>
<td></td>
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<tr>
<td>familial aggregation (25)</td>
<td></td>
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<tr>
<td>lead and other heavy metals (26)</td>
<td></td>
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<tr>
<td>analgesic abuse (27)</td>
<td></td>
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<tr>
<td>illicit drug use (28)</td>
<td></td>
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<tr>
<td>dietary phytoestrogens (29)</td>
<td></td>
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<tr>
<td>Biomarkers</td>
<td></td>
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<tr>
<td>hemoglobin (30)</td>
<td></td>
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<tr>
<td>oxidative stress/Carbonyl stress (31)</td>
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<tr>
<td>Insulin Resistance Syndrome (32)</td>
<td></td>
</tr>
<tr>
<td>hyperlipidemia (33)</td>
<td></td>
</tr>
<tr>
<td>proteinuria (34)</td>
<td></td>
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<tr>
<td>Genetic Markers</td>
<td></td>
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<tr>
<td>Access to Adequate Health Care</td>
<td></td>
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<tr>
<td>high blood pressure (35, 36)</td>
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<tr>
<td>poorly controlled diabetes (37–39)</td>
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<tr>
<td>ACE inhibitor use (40)</td>
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<tr>
<td>access to health care (22)</td>
<td></td>
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<tr>
<td>Social System</td>
<td></td>
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<tr>
<td>poverty (41, 42)</td>
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</table>
population attributable to one or more risk factors can facilitate a more appropriate allocation of resources for prevention programs.

**Race as a Complex Risk Factor**

An approach to dealing with a complex exposure is to identify, separately measure, and study the components of the exposure. Even complex risk factors like race can be related directly or indirectly to genetic and molecular events responsible for the pathogenesis and progression of kidney disease. For example, the increased risk of ESRD associated with race has generated multiple explanatory hypotheses. Examples include studies of misclassification of hypertensive renal disease (49,50), racial differences in birth weight (51), familial aggregation of risk (25), variations in mitochondrial genes (52), poverty (22), and differential access to health care (22). Many of these risk factors are in themselves complex and subject to reduction component factors. The goal of reduction toward simpler component factors is to identify molecular biomarkers or environmental factors that account for the observed risk and that can be linked to biologically relevant disease mechanisms (43).

**Context as a Complex Risk Factor**

Characteristics measured at the group level that are associated with increased risk are called contextual factors. The geographic variation in risk of ESRD described above is an example of a contextual risk factor. As one of many hypotheses, it has been suggested that economically and environmentally disadvantaged neighborhoods may account for geographic variations in risk (53,54). For example, Whittle et al. examined the association between ESRD incidence rates due to hypertension and neighborhood level measures of socioeconomic status derived from a random household survey (55). They found an ecological association—that is, one occurring at the group level—wherein communities with lower educational and income levels tended to have higher ESRD incidence rates. The inference of an association based on ecological observations is subject to ecologic bias if the exposure (low SES) and the CKD occur in different segments of the population (56).

In a case-control study, the same group reported increased risk of ESRD associated with individual measures of socioeconomic status (household annual income and years of education) and with measures of health care access (health insurance status, dental health, usual source of health care, and use of preventive health care) (22). However, this study used individual level information and failed to capture the ecological information about risk that was observed in the population-based study. One way of dealing with this limitation is to include measures of SES and access to health care at both the individual and group level in a multilevel model. The statistical models should account for the complex correlated data structure that arises when individuals within communities are studied (57). A recent article by Diez Roux et al. examining neighborhood environments, individual socioeconomic status, and risk of coronary heart disease illustrates this approach to contextual, multilevel models of risk (58).

**Population-Attributable Risk**

A recent report by Tarver-Carr et al. illustrates how multivariate risk models can be used to estimate the fraction of excess risk for CKD among African-Americans that can be attributed to risk factors other than race (59). They used data from the second National Health and Nutrition Examination survey (NHANES II) follow-up study to examine risk factors associated with higher risk of ESRD among African Americans compared with whites. They adjusted black to white relative risk estimates for: (1) age and gender alone; (2) sociodemographic factors; (3) lifestyle factors; and (4) clinical factors. They found that the proportion of the black versus white excess risk attributable to sociodemographic (poverty status, educational level, and marital status) factors was 12%; for lifestyle factors, 24%; and for clinical factors, 32%. All studied risk factors accounted for 44% of the excess risk for CKD experienced by African Americans. These results suggest that the factors included in the sociodemographic, lifestyle and clinical risk sets represent important intervention targets, and that substantial variation in black to white risk of ESRD remains to be explained.

**Conclusion**

Increasing our understanding of risk factors for the occurrence and progression of CKD poses substantial challenges. Predictive models for risk and rates of progression based on this information should be derived and validated and their clinical applications studied. Biomarkers should be sought to clarify the associations between complex risk factors and risk of CKD. Once a risk factor has been fully characterized, therapeutic interventions based on this understanding should be devised and tested with randomized clinical trials. We should actively extend our understanding of health care and social and economic factors at the individual level and at the contextual level.

**References**

5. Gabow PA, Johnson AM, Kaehny WD, Kimberling WJ, Lezotte DC, Duley IT, Jones RH: Factors affecting the progression of


