Stress and the Kidney

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The prevalence of CKD has increased considerably over the past 2 decades. The rising rates of CKD have been attributed to known comorbidities such as diabetes, hypertension, and obesity; however, recent research has begun to explore the degree to which social, economic, and psychological factors have implications for the prevalence and progression of CKD, especially among high-risk populations such as African Americans. It has been suggested that stress can have implications for CKD, but this area of research has been largely unexplored. One contributing factor associated with the paucity of research on CKD is that many of the social, psychological, and environmental stressors cannot be recreated or simulated in a laboratory setting. Social science has established that stress can have implications for health, and we believe that stress is an important determinant of the development and progression of CKD. We draw heavily from the social scientific and social epidemiologic literature to present an intersectional conceptual frame specifying how stress can have implications for kidney disease, its progression, and its complications through multiple stressors and pathways.

Key Words: Kidney disease, Psychological stress, Social determinants of health, Minority health, Socioeconomic factors

CKD is fast becoming a global health problem. The prevalence of CKD remains high, whereas the incidence of ESRD or kidney failure continues to increase.[1] If current trends continue, the global implications will be immense because the social and financial costs of care for ESRD patients are considerable. Current estimates for the United States indicate that the cost of ESRD exceeded $42 billion in 2009, more than doubling the cost in 2000.[2] These trends indicate that kidney disease represents a serious threat to the world's physical and financial health.

Results from a recent study reports that nearly 6 of every 10 Americans will experience moderate kidney disease in their lifetime[3]; however, the burden of kidney disease is not distributed equally across the population.[4-7] The prevalence of ESRD for African Americans, for example, quadruples the corresponding prevalence for whites.[2,8,9] The disparities in ESRD, CKD, and their complications (ie, anemia, bone disease, cardiovascular disease and death) have been linked to differing rates of kidney function decline.[10] It has been suggested that the accelerated rates of disease progression among populations such as African Americans and the poor can be attributed to the high prevalence rates of metabolic conditions known to impair kidney function (ie, diabetes, hypertension). But, the presence of these comorbidities does not entirely explain accelerated kidney disease progression among those most at risk.[7]

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Financial Disclosure: The authors declare that they have no relevant financial interests.

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1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2014.06.008

A growing segment of nephrologists has begun to examine sociologic and psychological factors potentially contributing to the incidence and progression of CKD and its complications.[9,11-19] Stress is a factor that has been studied extensively by social and behavioral scientists; however, it has remained largely unexplored in the nephrology community. As such, we draw from the social science and social epidemiologic literature to illustrate how stress can have implications for CKD initiation, progression, and complications. Figure 1 depicts a heuristic model of the multiple pathways through which stress can have implications for CKD, its progression to ESRD, and premature mortality.

Stress: A Brief Overview

Stress refers to an environmental, social, or internal demand that results in a psychological, physiological, or behavioral response.[20-22] These factors or stressors can lead to a state of physiological or emotional arousal that can affect physical and psychological health. Nearly 60 years ago, Selye[23] observed that long-term exposure to noxious stressors were associated with tissue damage and disease in laboratory animals. Work examining stress in humans was bolstered considerably by a study by Holmes and Rahe,[20] suggesting that an accumulation of major life events was related to illness. Literally, thousands of studies emerged from this early work, and nearly all have been founded on the premise that the accumulation of stressors tax or exceed the adaptive capacity of individual to a point where psychological or physiological responses to the stress condition can place them at risk for illness, injury, or disease.

This line of research has presented evidence, suggesting that stress can have implications for the development and progression of chronic diseases such as CKD. Stress has been shown to be associated with CKD risk factors such as hypertension, diabetes, or obesity.[13,24-27] Scientists agree that stress can have implications for CKD and health outcomes; however, research examining the relationship between stress and kidney disease has been limited. One factor contributing to the scarcity of research in this area is that stress is a multidimensional concept that can be operationalized in multiple ways.[13]

Stress in the empirical literature has 3 forms: major life events, chronic strains, and daily hassles.[21] Stressors categorized as major life events are occurrences that require considerable behavioral modification over a relatively short period of time (eg, death of a loved one, divorce, loss of a job). Chronic strains are persistent stressors that call for behavioral adjustment over a prolonged period of time (eg, poverty, disability). Daily hassles are stressors over the course of a day. These stressors (eg, traffic problems, interactions with rude people) are often regarded as minor; however, they can elicit physiological, psychological, and/or behavioral responses. Studies focusing on the impact of major life events or chronic strain represent the bulk of the literature examining the relationship between stress and health; however, a growing line of research has begun to examine the impact of daily hassles on health behaviors and outcomes. Much of the literature on stress and coping builds on interactional or transactional models of stress that highlight the social and cultural context of stress and coping, with each suggesting that perceptions of stressors are the primary determinants of behavior and health status.[28-30]

Stress, Pathophysiology, and Kidney Disease

Results from this extensive body of research have shown that stress can have an adverse effect on illness and disease, directly through physiological effects and indirectly through behaviors and practices that have implications for health.[31,32] No study to date has developed a comprehensive stress model specifying the biologic pathways between stressors and the devel-opment and progression of CKD because most social, psychological, and environmental stressors cannot be recreated or simulated in a laboratory setting.[33] Nonetheless, results from recent studies examining the relationship between acute stress and CKD risks factors suggest some biologic pathways through which stress may be associated with CKD and its complications.

CLINICAL SUMMARY

- Stress can have implications for kidney disease through multiple pathways.
- Intersectionality is an approach that can be useful for identifying how stress has implications for race-, gender-, and age-related disparities in kidney disease development and progression.

Many studies examining the relationship between stress and pathophysiology have focused on outcomes such as blood pressure, heart rate, and vascular reactivity.[34-41] Results from this line of research indicate that both blood pressure and heart rate increase and vascular reactivity decreases with most models of acute stress. These relationships between stress and pathophysiology are thought to be associated with alterations in the sympathetic/autonomic nervous system activity, the hypothalamic-pituitary-adrenal axis, inflammatory cytokines, and endothelin-A.[42,43] These alterations suggest that pathologic link between stress, hypertension, and CKD is possible as kidney sympathetic nerves innervate all segments of the kidney, and neural mechanisms regulate sodium and water retention.[44]

It also has been suggested that stress may be linked to CKD via diabetes and insulin resistance. Environmental stressors have been found to be associated with the development of insulin resistance, metabolic syndrome, obesity, and ultimately type 2 diabetes.[45,46] The biologic link is thought to involve alterations in the neuroendocrine system including the hypothalamic-pituitary-adrenal axis (increased glucocorticoid and other stress hormones) in addition to sympathetic nervous system factors and inflammatory cytokines.[39,47]

Stress also is thought to have implications in utero. The "Barker hypothesis" posits that disruption of the fetal environment or undernutrition translates into pathology.[48] Cell division and subsequent fetal growth are influenced by products of the hypothalamic-pituitary-adrenal axis and neuroendocrine hormones. Undernutrition brought about by stress can slow cell division in a manner that adversely affects the number of cells in particular organs and, ultimately, fetal growth. These and other alterations in the fetal environment are thought to contribute to low birth weight, a factor that has been associated with metabolic syndrome, type 2 diabetes, and CKD in adult life.[49]

Recent studies have also examined the extent to which genes are associated with CKD and ESRD in African Americans and other at risk groups. Genetic variants on the *MYH9-APOL1* region on chromosome 22 have been found to account for the excessive risk of kidney disease among African Americans.[50-60] Recent research has shown that African Americans with the *APOL1* G1 and G2 risk alleles are more likely to develop CKD and progress faster to ESRD than their counterparts with 0 or 1 risk allele.[51] These genetic variants are rare in white populations, suggesting that racial disparities in kidney disease may include a genetic component. Additional research is required to determine how other CKD risk factors and gene-environment interactions have implications for individuals with an apparent genetic risk for the development of kidney disease.

In summary, stress appears to enhance sympathetic nervous system activity, increase glucocorticoid secretion, and potentially increase levels of inflammatory cytokines. These factors contribute to higher prevalence of hypertension, diabetes, and vascular disease—all major risk factors for CKD. The physiological effects may be experienced in utero, exerting early influences that may further heighten the adult risk for CKD. In patients with CKD, the levels of another hormone, renalase, that metabolizes products of the sympathetic nervous system are lower.[61,62] Therefore, it is plausible that chronic stressors result in unchecked increased sympathetic nervous system activity once CKD develops which sets in motion a vicious cycle.

Social Determinants, Stress, and Kidney Disease

Scientists agree that kidney disease risk can vary by population, and this variance is reflected in the Chronic Kidney