Mechanisms and Fetal Origins of Kidney Disease

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The kidney disease epidemic remains a major public health burden with exponentially increasing trends such as will overtake the health care budget in the coming decades if not averted (1–3). Kidney failure and ESRD also demonstrate racial and geographic disparities with excess risks for segments of the population (1–3). As kidney function declines with the aging process, the challenge is to slow the disease progression process. Thus, it is critical to identify the factors associated with the disease risks and disease progression. Clearly, hypertension and diabetes are major factors involved in the progression of kidney disease. However, the increasing trends in disease incidence and early onset of kidney failure indicate other parameters are also involved in the disease progression.

Professor David Barker introduced the “Fetal Origins of Adult Disease Hypothesis” over a decade ago, identifying associations of fetal and early life events with adult chronic diseases (4,5). Numerous epidemiologic studies have confirmed the associations suggesting fetal programming and mechanisms associated with disease progression. Identification of these mechanisms is essential in the development of interventions to reduce the disease risks (6). With the increasing burden of disease and the development of the renal system in utero, the focus on the kidney in assessment for a fetal etiology is logical (7). Indeed, ESRD was inversely associated with birth weight for white and black men and women (8). The association was significant for all causes of ESRD (i.e., hypertension, diabetes, other, and unknown), with greatest risks in subjects with lower birth weights (9). The increased risks remained evident after adjustments for family history of ESRD (10).

Various mechanisms have been proposed to explain the fetal origins of kidney disease. Both hypertension and diabetes have been shown to be associated with birth weight, (11,12) increasing the risks of kidney disease. Uncontrolled high BP and diabetes increase the progression of renal failure and ESRD. Renal development in utero resulting in the number of nephrons has been proposed as a mechanism for the increased adult disease risk (13,14). This reduced fetal growth of the kidney is associated with defects in the development of the kidney increasing the vulnerability to various pathologic processes (15,16). Brenner and Mackenzie (15) have suggested that retarded fetal growth results in a reduced number of nephrons, which is further associated with increased hydrostatic pressure in the glomerular capillaries and glomerular hyperfiltration (15). Increased pressure and hyperfiltration increase the development of glomerular sclerosis. Fetal development and early life events are also associated with the renin-angiotensin system, and the subsequent development of elevated BP and disease process (17). The development of blood vessels and arterial walls has also been associated with fetal development, with stiffer vessel associated with low birth weight (18). Most likely, there are multiple mechanisms associated with the fetal origins of kidney disease. Among individuals with hypertension, different antihypertensive treatment classes were associated with birth weight, supporting the concept of different mechanisms involved with disease risks (19).

In this issue of the Journal of the American Society of Nephrology, Keijzer-Veen and colleagues (20) have identified a significant positive association of birth weight and GFR. The investigators also detected a negative association of birth weight and serum creatinine (20), suggesting that individuals born premature and/or small at birth are at greater risk to develop progressive renal failure. This work makes a significant contribution to understanding the mechanisms associated with the progression of ESRD and birth weight by identifying risk prior to the end-organ disease. Nonetheless, the study has some limitations that must be noted. There is a potential selection bias, and it is difficult to predict the future effects of birth weight on renal function as the subjects age. However, the authors have identified a factor that fits a scheme identified by numerous other studies. It is essential to accurately identify such mechanisms to develop interventions for reducing the disease risks early in life (21). The study of the fetal origins has several challenges, including the complicated study design, unclear genetic-environment relationships, and the fact that some disease processes in the population do not have a fetal origin. However, with the magnitude of the ESRD epidemic and increasing disease burden of kidney disease with an unclear etiology, the continued study of fetal origins is reasonable and logical, and the findings of investigators such as Keijzer-Veen et al. should be considered in the development of future investigations and studies.

References

2. Brancati FL, Whittle JC, Whelton PK, Seidler AJ, Flag MJ:


See related article, “Microalbuminuria and Lower Glomerular Filtration Rate at Young Adult Age in Subjects Born Very Premature and after Intrauterine Growth Retardation,” on pages 2762–2768.