Nephron Mass and Cardiovascular and Renal Disease Risks

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Summary: The nephron endowment begins with the complex process of nephrogenesis, which is controlled through genetic and environmental influences from preconception up until approximately 36 weeks of gestation. The total number of nephrons in human beings averages about 1 million per kidney but varies up to 10-fold, from approximately 200,000 to more than 2 million. Low nephron mass is associated with the development of hypertension and, in some ethnic populations, the concurrence of cardiovascular and renal disease risks in later life. Kidney size and nephron number also are related directly to birth weight with persons born preterm or with evidence of intrauterine growth restriction more likely to develop certain diseases in later life.

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Nephron mass refers to the total number of functioning nephrons a person has at any given time and is considered integral to the study of progression of kidney disease.[1,2] However, nephron endowment or the total number of nephrons formed begins with the process of nephrogenesis and is subject to decline through natural aging, as well as through various adverse events that may be imposed on a person throughout life.[3-6] Cardiovascular and renal disease risks are entwined not only through hormonal mechanisms but by virtue of the linked ontogeny of angiogenesis and nephrogenesis.[6] As a consequence, the concept that specific patterns of cardiorenal diseases are influenced developmentally, particularly in certain ethnic populations, has emerged. The seminal epidemiologic studies of Barker et al[7] in the late 1980s brought to light the association of low birth weight with hypertension, type 2 diabetes, and cardiovascular disease in later life. In turn, low birth weight has become a surrogate marker for low nephron endowment in both animal models[8] and human infants whose kidneys were studied at autopsy.[9-11] Almost simultaneous with the initial work of Barker et al,[7] Brenner et al[1,12] published work supporting the concept that low nephron mass could lead to a cascade of events including glomerular hyperfiltration with glomerulomegaly, proteinuria, and, ultimately, the development of focal glomerulosclerosis.

Although low nephron mass, as defined earlier, may be a component of natural aging, disease, trauma, or surgical removal, there appears to be an acceleration of the process among certain populations such as the Pima Indians,[13] Australian aborigines,[14] Mexican Americans,[15] and African Americans of the southeast United States.[16] In a small case-controlled autopsy study in young hypertensive adults who died accidentally, total nephron mass was 50% less as compared with their age-matched nonhypertensive controls.[17] In a recent Norwegian cross-sectional study of more than 2 million children born between 1967 and 2004, those with low birth weights (<10th percentile) had a relative risk of 1.7 (95% confidence interval, 1.4-2.2; $P < .001$) of developing end-stage kidney disease when compared with those of normal birth weight.[18] This association remained after adjustment for birth-related confounders including intrauterine growth restriction. Simi-

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larly, in an Australian case-control study, patients with advanced chronic kidney disease (CKD) were more likely to have been low-birthweight babies, regardless of the etiology of their primary kidney disease.[19] Recent studies in adults[20] and children[21] relate lower birth weight with increased salt sensitivity. For example, smaller kidney size and higher 24-hour blood pressures in children were related to their response to a sodium load; those with smaller renal size and higher blood pressures had the greatest response.[21] These observations support the hypothesis that, irrespective of its etiology, low birth weight (the lower end of the normal Gaussian distribution for birth weight, a product of intrauterine growth restriction or preterm birth), may predispose to aberrant physiological responses that potentially would lead to the development of hypertension. That such responses may be detected during childhood suggests that preventive interventions not previously considered might be initiated before disease becomes established.[22]

NEPHROGENESIS AND NEPHRON ENDOWMENT

Renal development in human beings is complete once the fetus reaches approximately 34 to 36 weeks of gestation, and the number of nephrons does not increase subsequently.[6] Thereafter, there is only loss of nephron mass,[4] which may be accelerated by disease, trauma, or surgical ablation. When a renal allograft is performed, the nephron mass of the allograft appears to be a strong determinant of both the renal function and longevity of the allograft.[23,24] Relative nephron mass for body size also appears to be important, as shown by the observations that obesity[25] and excessive body size, as in some nonobese African American athletes,[26] have been associated with the development of hypertension and focal glomerulosclerosis in early life. Consistent with such observations, a Spanish cohort of adults with low renal mass owing to unilateral renal agenesis or uninephrectomy were prone to progressive CKD if they were or became obese.[27] In contrast, multiple reports have indicated that living kidney donors rarely manifest untoward effects even when followed up for decades.[28-31]

The kidney forms by a complex process called *branching morphogenesis*, which is similar in various organ systems including the lungs, pancreas, and mammary glands.[6,32,33] The process involves a genetically programmed sequence of events in which the branching ureteric bud invades the primordial metanephric mesenchyme (MM) and induces iterative branching, which occurs about 15 times during human renal development. Arborization from the main trunk laterally into sequential terminal bifid branches occurs through this process. The final incursion into the MM ultimately determines the number of glomeruli.[6,32,33] The initial glomeruli form at the site of the final bifid branching and become nephrons located in the first layers of the renal cortex near the medullary rays. The other nephrons develop through the poorly understood process of arcade formation and late-phase branching that occurs between 22 and 36 weeks of gestation. This creates a radial glomerular pattern, which lends itself to the technique used to estimate nephron numbers, a method similar to counting the rings in the trunk of a tree to estimate age.[6,32-34] Approximately one generation of new nephrons forms every 2 weeks during the last trimester, ultimately reaching 10 to 12 generations by term birth (Fig. 1).[6,32,33] As each ureteric tip connects to the MM, negative feedback prevents further branching. The process of glomerulogenesis proceeds with the MM forming an initial comma-shaped structure, followed by an S-shaped body.[6,32,33,35] The S-shaped body from the MM ultimately becomes the proximal and distal renal tubules and the epithelial (podocyte) component of the glomerulus.

The process of glomerular vascularization is incompletely understood. At the time of the initial branching of the ureteric bud, the fetal kidney is considered to be avascular,[35] after which the vasculature of the developing kidney then takes place concomitantly with the development of the renal epithelium.[35] The glomeruli initially are avascular.[6,35] The growth and development of the renal arterial tree is a complex network in which the single renal artery ramifies from the hilum to the cortex, serially forming lobar, arcuate, interlobar, and, finally, into the afferent arterioles. Each glomerulus develops afferent and efferent arterioles and peritu-