Frontiers in Nephrology

Nephron Number, Hypertension, Renal Disease, and Renal Failure

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J Am Soc Nephrol 16: 2557–2564, 2005. doi: 10.1681/ASN.2005020172

Essential hypertension is one of the most common diseases in the Western world, affecting about 26.4% of the adult population, and it is increasing (1). Its causes are heterogeneous and include genetic and environmental factors (2), but several observations point to an important role of the kidney in its genesis (3). In addition to variations in tubular transport mechanisms that could, for example, affect salt handling, structural characteristics of the kidney might also contribute to hypertension.

The burden of chronic kidney disease is also increasing worldwide, due to population growth, increasing longevity, and changing risk factors. Although single-cause models of disease are still widely promoted, multideterminant or "multihit" models that can accommodate multiple risk factors in an individual or in a population are probably more applicable (4,5). In such a framework, nephron endowment is one potential determinant of disease susceptibility.

Some time ago, Brenner and colleagues (6,7) proposed that lower nephron numbers predispose both to essential hypertension and to renal disease. They also proposed that hypertension and progressive renal insufficiency might be initiated and accelerated by glomerular hypertrophy and intraglomerular hypertension that develops as nephron number is reduced (8). In this review, we summarize data from recent studies that shed more light on these hypotheses. The data supply a new twist to possible mechanisms of the "Barker hypothesis," which proposes that intrauterine growth retardation predisposes to chronic disease in later life (9).

The review describes how nephron number is estimated and its range and some determinants and morphologic correlates. It then considers possible causes of low nephron numbers. Finally, associations of hypertension and renal disease with reduced nephron numbers are considered, and some potential clinical implications are discussed.

Assessment of Nephron Number in Humans

Nephron numbers are estimated through the surrogate of glomerular number. Direct assessment of glomerular number in living humans is currently not possible, although a combination of magnetic computer tomography and histologic analysis of kidney biopsies has enabled rough estimates of the number of glomeruli per kidney (10). A relatively noninvasive technique to estimate nephron number would be immensely useful.

The only really quantitative information so far has come from studies of whole kidneys at autopsy (11–19). Glomerular number is estimated using either the acid maceration method, which assesses the entire organ and takes into account the different density of glomeruli in the various zones of the renal cortex, or unbiased techniques, *e.g.*, with the disector/fractionator combination, that do not involve assumptions about the size and shape of glomeruli (20,21). Although the laborious nature of these techniques has restricted them to a few specialized centers, such studies are beginning to expose the range and relationships of glomerular number and glomerular size in humans and their possible relationships to hypertension and renal disease.

In a study of 208 adults from Mississippi in the United States and the Northern Territory of Australia, who underwent autopsy for sudden or unexpected death, there was a 10-fold range in glomerular number, a five-fold variation in mean glomerular volume, and an astonishing 13.5-fold range of estimated total glomerular tuft volume (Table 1) (13,14,16)

Glomerular number was significantly linked to gender (approximately 17% higher in men), age (inversely), race (lower in Australian Aborigines), and birth weight (13,14,16,18,19). The loss of glomeruli with age seemed to operate over a continuum of adult life, with a mean predicted loss of approximately 4500 glomeruli per kidney per year between ages 18 and 70 yr, although in Nyengaard's Danish autopsy series the phenomenon was mostly discernible after age 60 yr (12).

Published online ahead of print. Publication date available at www.jasn.org.

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ISSN: 1046-6673/1609-2557

Table 1. US/Australian autopsy series: Characteristics of the right kidney, in subjects age ≥18 yr, $n = 208$

	No. of Glomeruli	Mean Glomerular Tuft Volume ($\mu m^3 \times 10^6$)	Total Glomerular Tuft Volume (cm^3)
Range	227,327 to 2,026,541	3.3 to 17.0	1.1 to 14.8
Mean (SD)	870,582 (31,062)	7.8 (2.7)	6.6 (2.5)

Two important determinants of mean glomerular volume defined in these autopsy studies were body surface area, directly, and glomerular number, inversely. The relationship with glomerular number has been interpreted as compensatory enlargement of remaining glomeruli in situations of nephron deficiency or loss, a process "targeted" at restoring total filtering surface toward "normal." It is one of the first responses to nephron loss in animal models. Thus, increased glomerular volume (or area in biopsies), which is described in several populations at high risk for kidney disease and kidney failure (22–27), might be a surrogate marker for nephron deficiency. Nephrons with critically enlarged glomeruli seemed doomed to premature death. Most hypotheses revolve around premature glomerulosclerosis, developing first as segmental lesions, perhaps mediated through injury of podocytes, and reflected in proteinuria (8,28–31). However, contributions from tubular and interstitial injury, possibly mediated through protein toxicity, are probably also important (31). Ongoing nephron loss potentially accelerates development of hypertension and progression of renal injury (32,33).

Birth weights, available from the state registry for many of the Mississippi participants, were strongly correlated with glomerular number (13,14,16), with an additional 232,217 nephrons predicted in each kidney for each 1-kg increase in birth weight after adjustment for other factors ($P < 0.001$). Birth weight was also significantly and inversely correlated with mean glomerular volume, an effect that was mediated through variation in nephron number (Table 2). This compensatory hypertrophy resulted in a mean total glomerular mass that did not differ by birth weight groupings. Finally, Australian Aborigines had, on average 250,000 (or approximately 30%) fewer glomeruli per kidney than their non-Aboriginal Australian counterparts, with a mean glomerular volume increased by the same proportion (18,19).

It is likely that people with lower glomerular numbers are more susceptible to hypertension and renal disease, which are initiated and propagated through the cascade of events that follows compensatory nephron hypertrophy. Determination of the causes of low nephron numbers will help us understand how exacerbated risk for these conditions is established.

Causes of Low Nephron Number

Studies in rats and sheep show that an experimentally induced loss of a critical nephron mass during fetal development or shortly after birth favors the development of hypertension and kidney damage (34,35). In humans, loss of substantial kidney mass (accidents, resections, cancers, obstructions, vascular occlusions, cortical necrosis, etc.) can have similar results, whereas transplantation of small kidney donor organs into large recipients increases the risk for hypertension and graft failure (36,37).

A potentially more broadly relevant model, however, is that of developmental nephron underdosing, or reduced nephron endowment. Influences on nephron development, in turn, can be grouped broadly as genetic or related to the early environment.

Table 2. US/Australian autopsy series: Characteristics of the right kidney, in subjects age ≥18 yr, by birth weight tertiles, adjusted mean (95% CI), $n = 87$[a]

Birth Weight (kg)	*n*	No. of Glomeruli[b]	Mean Glomerular Tuft Volume ($\mu m^3 \times 10^6$)[c]	Total Glomerular Tuft Volume (cm^3)[c]
Range 1.81 to 3.121		770,860	9.2	6.7
Mean (SD) 2.65 (0.29)	29	(658,757 to 882,963)	(8.3 to 10.1)	(5.9 to 7.5)
Range 3.18 to 3.38		965,729	7.2	6.8
Mean (SD) 3.27 (0.07)	28	(885,714 to 1,075,744)	(6.3 to 8.2)	(6.1 to 7.7)
Range 3.41 to 4.94		1,005,356	6.9	6.6
Mean (SD) 3.93 (0.35)	30	(900,094 to 1,110,599)	(6.1 to 7.8)	(5.9 to 7.4)
P[d]		0.0126	0.0022	0.920

[a]CI indicates confidence interval.
[b]Adjusted for age, gender, and race.
[c]Adjusted for age, gender, race, and body surface area.
[d]Test for the difference of three means.

Genetics

Little is yet known about genetic influences in nephron endowment in humans (32,33). Congenital oligomeganephronia, in which glomeruli are few, very large, and prone to sclerosis (38,39), is one blatant model of nephron underendowment. Although most cases are sporadic, it sometimes occurs in family clusters, suggesting a genetic background (40), and an association with PAX2 gene mutations has been described (41). More modest deficiencies of nephron endowment might be part of the same spectrum (31). Mice that are heterozygous for glial-derived neurotrophic factor (GDNF), a critical factor for renal development, are born with approximately 30% fewer nephrons and develop hypertension in adulthood in the absence of renal disease (42). Transgenic mice expressing wild-type P53 have defective nephron development, small kidneys, approximately 50% fewer nephrons, and compensatory enlargement of nephrons that remain and they ultimately develop renal failure (43).

Early Life Influences

Nephron development in humans begins in the ninth week of gestation. Proliferation of nephrons is particularly rapid in the last trimester, continuing up through the 36th week, then it ceases (32–44). The final complement of nephrons, which is reflected in kidney volume estimates by ultrasound, as well as in kidney mass and nephron number, is critically dependent on two factors: gestational age and a favorable intrauterine environment.

In the stressed intrauterine environment, development and growth of the brain and the heart are preserved at the expense of the kidney and other organs and general somatic growth (45). In both animals and humans, nephron number is strongly correlated with fetal weight and is disproportionately reduced by factors that restrict intrauterine growth (44–54). Such factors include protein and micronutrient deficiencies, hypoxia, infections, toxins, certain drugs, metabolic perturbations, and probably psychosocial as well as physical stress (47–51). Their effects are often reflected in various degrees of intrauterine growth retardation (IUGR), with infants that are small for gestational age and sometimes thin relative to their length. These infants have smaller kidneys, whose circumferential dimensions are often more compromised than their length (52,53), and fewer nephrons, with glomeruli enlarged in proportion to their reduced numbers (54). Internationally, most low birth weight in humans is associated with small maternal stature, particularly in mothers with low weight for height, which is a consequence of generations of suboptimal nutrition (55). However, overt malnutrition and specific protein deficiency are also regionally important. The global impact of maternal smoking on fetal growth and potentially nephron number is, apparently, enormous (55,56). Other factors that might not be reflected in measures of fetal growth can also impair nephrogenesis, such as selective vitamin deficiencies, certain antibiotics (including β lactams, penicillin, amoxicillin, ampicillin, and cephalosporins), maternal infections, steroid administration, and hyperglycemia (47–51). A recent report also suggests that maternal alcohol ingestion impairs kidney development (57).

Mechanisms through which adverse intrauterine environments restrict nephrogenesis are still under investigation. They could operate at any of the key steps in kidney development: branching of the ureteric duct in the metanephric mesenchyme (driven strongly by GDNF), condensation of the mesenchymal cells at the tips of the ureteric branches, and conversion of the mesenchymal condensates into epithelium (58). Retinoic acid, derived from dietary vitamin A, regulates the c-Ret receptor for GDNF so powerfully that much of the variation in nephron number in the general population might be regulated through this nutritional marker (48–51,59). This has important implications for disadvantaged populations, where subtle and overt deficiencies of vitamin A and related micronutrients can be widespread. Iron deficiency might also be important. Adequate iron is critical for the rapidly developing fetal organ system, and, in the rat, maternal iron restriction leads to reduced birth weight and elevated BP in the offspring (60).

Factors that restrict fetal growth might impair nephrogenesis through less direct mechanisms as well. In one animal model, maternal protein deprivation was associated with suppression of the renin-angiotensin system in the growth-impaired fetus, which had impaired nephrogenesis and later developed hypertension (61). Another important system is the renal cortisol/cortisone shuttle (62). The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) regulates the inactivation of mineralocorticoid-active cortisol to inactive cortisone. Newborn and adult rats with IUGR have increased renal expression of the mineralocorticoid receptor and a significant reduction of the 11β-HSD2 gene (63). Approximately 20% of children with former IUGR have an increased cortisol/cortisone ratio, suggesting decreased activity of 11β-HSD2. In humans, mutations of the 11β-HSD2 gene cause low birth weight and placental 11β-HSD activity correlates directly with fetal weight. In addition, in rats and sheep, glucocorticoid administration during pregnancy, which inhibits 11 β-HSD, reduces birth weight of offspring, which develop permanent hypertension, hyperglycemia, and increased hypothalamic-pituitary-adrenal (HPA) axis activity as adults. Higher plasma cortisol levels have been documented in humans with former IUGR, indicating HPA axis programming (63,64).

Welham *et al.* (65) showed recently that maternal diet programs the embryonic kidney, altering cell turnover and gene expression when nephrons and glomeruli have yet to form. They also showed that nephron deficit in fetuses with maternal low-protein diets was associated with increased apoptosis in the metanephros (66), indicating accelerated cell turnover and death. It is not known whether the nephron deficit represents direct deletion of nephron precursors or an indirect effect from loss of supportive interstitial precursors.

A recent study by serial ultrasounds has shown that human infants with IUGR have, not only smaller kidneys at birth, but also reduced kidney growth during the first 18 months of life, both in absolute terms and relative to current body size (67,68).

The renal implications of low birth weight associated with prematurity are potentially important, given the large cohorts

of very low birth weight premature infants who are now surviving infancy due to advances in neonatal and perinatal care. It is unlikely that even a relatively "stable" extrauterine environment can support development of the kidney and other organs as adequately as continuation of pregnancy to term under favorable circumstances. One histologic study, which confirmed that nephron number in premature infants is dramatically reduced, showed that nephrogenesis could continue after premature birth, but it was suboptimal, was further impaired by renal insults, and did not progress beyond 40 d after delivery (69). Glomerulomegaly and mesangial proliferation were evident in longer-term survivors. Postnatal and catch-up kidney growth in premature infants is even more impaired than in infants with low birth weight caused by IUGR alone (67,68). Finally, a recent study showed lower GFR and disturbed tubular function in children who were survivors of very low birth weight, usually associated with prematurity (70).

Less well explored is the influence of the postnatal environment on renal development. Infant and childhood malnutrition and repeated infections, which are common in disadvantaged populations, might impair appropriate kidney maturation and hypertrophy, with an especially severe impact on children who are survivors of IUGR (71).

BP and Nephron Number

Some animal experiments show a strong link of nephron number at birth to postnatal blood pressure (47,72,73). The findings of many studies in children and adults, which link IUGR or birthweight, inversely, to higher blood pressure in postnatal life, are at least compatible with a role for nephron endowment in blood pressure regulation in humans as well (9).

Two recent autopsy studies support the notion that hypertension in humans is associated with reduced nephron number. In Western Europe, an autopsy study of white victims of accidents compared stereologic findings in the kidneys of 10 adults who had a history of hypertension and left ventricular hypertrophy with those of age-, gender-, and height-matched control subjects (15). The number of glomeruli was diminished by approximately 46% in the hypertensive individuals. In addition, mean glomerular volume was markedly increased, on average by approximately 50% but in some cases was three times the normal size. In the autopsy study of people in Mississippi, among 80 people whose records were examined scrupulously for evidence of hypertension, glomerular number was significantly reduced in those with hypertension, with a significant increase in mean glomerular volume (Table 3), which was independent of body surface area (16). Again, this compensatory hypertrophy seemed to compensate total glomerular mass to "normal." In both studies, the general paucity of glomerulosclerosis and cortical fibrosis seemed to weigh against recent accelerated nephron loss as the chief cause of the nephron deficiency. Among Aboriginal Australians, whose nephron number, on average, was already reduced, there was a further reduction in nephron number and increase in mean glomerular volume among those with a history of hypertension (18,19).

Low Nephron Number, Renal Disease, and Renal Failure

In some animal models, congenital nephron deficiency, both genetic and experimental, is associated with development of renal disease and renal failure in postnatal life (43,74).

In humans, the rapid development of proteinuria, hypertension, and renal failure in children with oligomeganephronia (38,39) and the lower number of nephrons in Australian Aborigines (18,19), whose rates of renal failure are excessive, are compatible with a link between low nephron number and renal disease. An influence of congenital nephron underdosing on renal disease susceptibility is otherwise largely inferred through links of low birthweight or IUGR to renal disease or to reduced renal size. This body of research is less well developed than that of IUGR, hypertension, the metabolic syndrome, and cardiovascular disease. Indeed, relationships between low birthweight and renal disease could be mediated in part through their mutual links to these other conditions (75–77), independent of nephron number.

Links of birth weight to renal disease susceptibility can be explored at the levels of asymptomatic albuminuria/proteinuria, overt nephropathy, development or progression of renal impairment in specific sorts of kidney disease, and renal failure and renal death. Exposure to famine in midgestation during the Dutch "Hongerwinter" was associated with microalbuminuria in people who survived to late middle age (78). A study of people without diabetes in the United Kingdom found higher rates of microalbuminuria in people of low birth weight or with IUGR (79,80). In Pima Indians with type 2 diabetes, birth

Table 3. Characteristics of right kidney, by documented presence of hypertension (US participants only)[a]

	No. of Glomeruli[b]	Mean Glomerular Tuft Volume ($\mu m^3 \times 10^6$)[c]	Total Glomerular Tuft Volume (cm^3)[c]
No hypertension (n = 30)	1,010,622 (915,997 to 1,105,277)	6.9 (6.0 to 7.9)	7.0 (6.0 to 7.9)
Hypertension (n = 50)	743,531 (670,759 to 816,304)	9.6 (8.8 to 10.4)	6.8 (6.0 to 7.5)
P[d]	<0.0001	0.00022	0.743

[a]Blacks = 44, whites = 36, men = 51, women = 29, mean age 44 (9.0) yr.
[b]Adjusted for age, gender, and race.
[c]Adjusted for age, gender, race, and body surface area.
[d]Test for the difference of three means.

weights at the highest and lowest ends of the range were associated with increased rates of albuminuria (81). In individuals with type 1 diabetes studied thus far, the effect of birth weight on nephropathy has been equivocal (82,83). In one remote Australian Aboriginal community with generally low birth weights, birth weight in young adults was strongly and inversely correlated with the level of albuminuria and with the presence of overt nephropathy (84,85). Low birth weight children in this same population had lower kidney volumes than those of higher birth weights (22). Furthermore, adults with the lowest kidney volumes, examined in the context of current weight, had the highest rates of albuminuria and highest BP (23), tending to support a role of nephron underdosing in these pathologies. Lower birth weights have been associated with higher relapse rates in children with the nephrotic syndrome (86,87) and with progression in children with IgA nephropathy (88). Associations of birth weight with renal deaths are obscured by the competing effects of the higher numbers of cardiovascular and other nonrenal natural deaths that are predicted by renal markers (75–77,89) and by deficient documentation of the contribution of renal disease to natural deaths (90). Evaluation through ESRD treatment registries poses problems of selection, especially in developing countries with restricted access; however, a study in the southeastern United States did show that ESRD patients tended to be of lower birth weights than matched controls (91).

In some of these studies, the birth weight effect was more pronounced in women (20,83,84,86). Most, too, showed the important effect of higher levels of body fat in postnatal life in educing or exacerbating the adverse effects of lower birth weights, not only on renal disease but also on BP and metabolic profiles. Maintenance of a lean adult weight minimized or effaced the potential adverse effects of low birth weight in all settings in which it was studied.

Further studies might inspect the influence of birth weight in existing population-based surveys of renal markers. Its influence on progression could be studied in longitudinal cohort studies such as the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study, the African-American Study of Kidney Disease and Hypertension (AASK) study, and in existing Aboriginal cohorts.

Conclusions and Clinical Implications

Nephron endowment is probably one determinant of blood pressure levels and renal disease risk in later life. Multideterminant models can incorporate nephron endowment as one risk factor for hypertension or renal disease while retaining other risk factors whose roles are better recognized. The contribution of low or marginal nephron endowment to the burden of disease in different populations could range from trivial to highly significant, depending on the frequency of factors impairing nephron development, such as IUGR, and of postnatal factors that compromise vascular or renal health, such as obesity, diabetes, and infections.

Implications for populations in epidemiologic transition are especially important (92). The burden of chronic disease increases as populations grow, as adults live longer, and as body fat increases, all of which are happening more rapidly in the developing world (71). In that setting, too, reductions in infant deaths associated with social advances and health interventions are resulting in survival of sometimes large cohorts of low birthweight babies to adult life, at exacerbated risk for chronic disease. In affluent groups in westernized countries, the impact of the increased survival of very low birthweight premature babies is yet to be fully ascertained, although rates of IUGR are now quite low. In that setting, the predominant challenge is to moderate the harmful influence of the current epidemic of obesity and inactivity on even adequately formed organs (93).

Currently, with so little known about genetic or other intrinsic modulators of nephron endowment, prevention depends on optimizing intrauterine conditions, and specifically avoiding maternal smoking, micronutrient deficiency, frank malnutrition, and probably drinking. For survivors of low birthweight, surveillance and minimization of exacerbating postnatal factors are central. Avoiding the secular trend towards increasing body mass is important, although some programmed preferential deposition of central fat might not easily be prevented without pharmacologic intervention. Avoidance of infections and potentially harmful drugs is also wise. Finally, for those in whom elevated blood pressure or albuminuria has already appeared, multipronged therapy that includes renal protective drugs promises extension of life by many years (94).

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