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Adult Hypertension and Kidney Disease The Role of Fetal Programming

Kambiz Zandi-Nejad, Valerie A. Luyckx, Barry M. Brenner

Abstract—Hypertension (HTN) and chronic kidney disease are highly prevalent diseases that tend to occur more frequently among disadvantaged populations, in whom prenatal care also tends to be poor. More and more evidence is emerging highlighting the important role of fetal programming in the development of adult disease, suggesting a possible common pathophysiologic denominator in the development of these disorders. Epidemiologic evidence accumulated over the past 2 decades has demonstrated an association between low birth weight and subsequent adult HTN, diabetes, and cardiovascular disease. More recently, a similar association has been found with chronic kidney disease. Animal studies and indirect evidence from human studies support the hypothesis that low birth weight, as a marker of adverse intrauterine circumstances, is associated with a congenital deficit in nephron number. The precise mechanism of the reduction in nephron number has not been established, but several hypotheses have been put forward, including changes in DNA methylation, increased apoptosis in the developing kidney, alterations in renal renin–angiotensin system activity, and increased fetal glucocorticoid exposure. A reduction in nephron number is associated with compensatory glomerular hypertrophy and an increased susceptibility to renal disease progression. HTN in low birth weight individuals also appears to be mediated in part through a reduction in nephron number. Increased awareness of the implications of low birth weight and inadequate prenatal care should lead to public health policies that may have long-term benefits in curbing the epidemics of HTN, diabetes, and kidney disease in generations to come. (*Hypertension*. 2006;47[part 2]:502-508.)

Key Words: hypertension ■ nephron number ■ kidney

Hypertension (HTN) is a prevalent disorder estimated to affect >25% of the world's adult population.¹ The incidence and prevalence of chronic kidney disease (CKD) is also on the rise with >20 million people being affected in the United States alone. Two of the major causes of CKD worldwide are HTN and diabetes mellitus (DM), particularly type 2 DM. Despite many years of concerted efforts, the etiology and molecular mechanisms underlying the development of these 2 common disorders, which, in most cases, result from a complex interplay between polygenic predisposition and environmental factors, remains unclear. The frequent concurrence of HTN, type 2 DM, insulin resistance, dyslipidemia, and CKD, all of which are also important cardiovascular risk factors, may reflect a common underlying mechanism.² One such mechanism that is becoming more and more recognized is the far reaching impact of the fetal environment.

The process through which adverse effects of an environmental insult early in life, particularly in utero, can predispose to adult disease is known as fetal programming or developmental plasticity. Fetal programming refers to the

observation that an adverse environmental stimulus experienced during a critical period of development in utero can induce long-term structural and functional effects on the developing organism. Developmental plasticity is the process whereby a variety of different phenotypes may result on a background of a single genotype in response to different environmental stimuli experienced during intrauterine life.³ These phenomena are intimately linked and have even further reaching implications if one considers that their effect(s) can be transferred and perpetuated across generations, mainly through nongenetic or epigenetic mechanisms.⁴

The association between intrauterine events and subsequent cardiovascular diseases has been recognized for some time.⁵ It was Barker et al,⁶ however, who proposed this idea as a hypothesis after finding a geographic association between mortality from cardiovascular causes in a period from 1968 to 1978 and neonatal mortality from 1921 to 1925. Since then, a large body of evidence from different populations and different parts of the globe has not only confirmed these initial findings but has expanded them to cover conditions such as impaired glucose tolerance, type 2 diabetes,

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obesity, HTN, and CKD.⁷ Of these, the relation between stress in utero, of which low birth weight (LBW) may be a marker, and subsequent HTN has been the most studied. Although several epidemiological studies have confirmed this association, the mechanistic pathways underlying this association have remained unclear.

The kidney is the organ central to the development of HTN. The relationship among renal sodium handling, intravascular fluid volume homeostasis, and HTN, initially described by Guyton et al,⁸ is well accepted. In fact, all of the known genetic mutations associated with HTN involve proteins expressed in the kidney.⁹ That factors intrinsic to the kidney itself affect blood pressure (BP) has also been demonstrated in renal transplantation (both in humans and animals), where BP in the recipient after transplantation is related to BP or HTN risk factors of the donor; that is, HTN “follows” the kidney.^{10,11}

Based on these observations and the fact that HTN is most prevalent in poorer communities, Brenner et al¹² proposed that LBW may be associated with a congenital deficit in nephron number, which would predispose to reduced renal sodium excretion and, therefore, increased susceptibility to essential HTN, especially in the setting of dietary sodium excess. This hypothesis was also based on the knowledge that in the setting of nephron loss, remaining glomeruli undergo compensatory hypertrophy (glomerulomegaly) and hyperfiltration (increased single nephron glomerular filtration rate) to sustain adequate renal function. This adaptation, however, is at the expense of intraglomerular HTN, which hastens injury to functioning glomeruli and perpetuates the vicious cycle of ongoing nephron loss.¹³ Experimentally, loss of functioning renal mass becomes clinically manifest with the development of systemic HTN and proteinuria, both of which accelerate ongoing renal injury (Figure 1).^{13,14} Interestingly, similar decline in renal function, with spontaneous development of HTN and proteinuria, has been described in animals born with reduced nephron numbers^{12,15} and in humans with congenital deficiencies in renal mass, such as unilateral renal agenesis.^{16,17} These observations support the contention that extrinsic renal injury is not a prerequisite for the initiation and perpetuation of renal injury and that under certain circumstances, more subtle, prenatally derived, intrinsic deficiencies

in functioning renal mass may be sufficient to contribute to renal functional decline and hasten the decline normally occurring with advancing age.¹⁸

Nephron Number and Glomerular Size

Although classical teaching asserts that, on average, there are ≈ 1 million nephrons in each normal kidney, the real number is a matter of controversy and depends on the counting methodology used. Studies mentioned as reference for the magical 1-million number were done years ago with the majority using acid maceration or histological section analysis,^{19,20} both of which are prone to bias and experimental error.²¹ More recently, this issue has been revisited using an unbiased fractionator–sampling/dissector–counting methodology.^{21,22} In the first of these studies in 37 adults from Denmark, the average glomerular (nephron) number was reported to be 617 000 (331 000 to 1 424 000). Two thirds of the subjects, however, were >50 years of age.²¹ The second study of 78 adults from the United States and Australia showed somewhat similar results with a mean of 810 646 glomeruli per kidney but with a very wide range from 228 441 to 1 825 380, an ≈ 9 -fold variation.²² Other studies, in addition to finding similar results, have also shown a direct relation between birth weight and the number of nephrons with ≈ 250 000 more glomeruli per kidney per kilogram increase in birth weight.^{18,23}

Despite the large variation in nephron numbers seen in these studies, 2 consistent observations have emerged: nephron numbers were lower in LBW subjects, and glomerular volume varied inversely with glomerular number. These findings suggest that larger glomeruli may be a sign of compensatory hyperfiltration and hypertrophy in subjects with fewer nephrons.^{22,24} In fact, Hoy et al²³ reported that total glomerular volume (a surrogate for total filtration surface area) was not different among groups with different nephron numbers and birth weights. This observation suggests that total filtration surface area may initially be maintained, but at the expense of glomerular hypertrophy, which is maladaptive and a predictor of poorer outcomes.²⁵ In populations at high risk for kidney failure, such as blacks, Pima Indians, and Aboriginal Australians, large glomeruli are a common finding at early stages of renal disease but become smaller and sclerosed as CKD progresses.^{26,27}

Low Birth Weight, HTN, and CKD

The World Health Organization defines LBW as birth weight of <2500 g. LBW can be attributed to intrauterine growth restriction (IUGR; birth weight less than the tenth percentile for gestational age) or premature birth. LBW associated with IUGR reflects intrauterine stress at a late stage in gestation as opposed to LBW of prematurity, which may be an appropriate weight for the specific duration of gestation, but low when compared with a full-term birth. LBW associated with IUGR has the strongest association with adult disease.²⁸ LBW is more common among blacks and Native Americans than whites, where its prevalence aggregates with greater prevalence of disorders, such as cardiovascular disease, type 2 DM, HTN, and CKD.^{29,30}

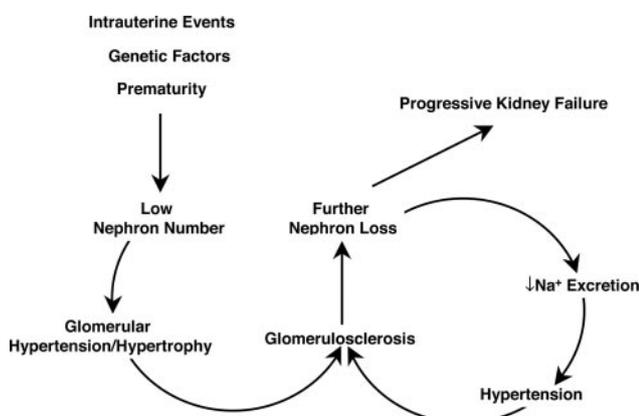


Figure 1. Proposed mechanism of fetal programming of hypertension and renal disease.

Many animal models have demonstrated the association of LBW (induced by gestational exposure to low-protein diet, dexamethasone, gentamicin, vitamin A deficiency, or uterine ischemia) with HTN in later life.^{31–34} The link between LBW and adult HTN in these models appears to be largely, although not exclusively, attributable to an associated congenital nephron deficit occurring with IUGR.^{32,33} Other possible programmed causes of susceptibility to HTN include modulation of the activity of the RAS, the sympathetic nervous system, and the cardiovascular system.⁷

Many epidemiologic studies have also revealed an inverse association between LBW and BP in humans, detected as early as infancy,^{28,35–37} although the importance of such an association has been questioned by some authors.³⁸ In young adults, many studies have reported higher BPs in those who had been of LBW, even after correction for parental BP, current weight, smoking, oral contraceptive use, and gender.^{39–41} Barker and Osmond⁴² first reported the association between overt HTN and LBW in a cohort of 46- to 64-year-old adults, in whom they found that mean systolic pressure fell by 11 mm Hg as birth weight increased from ≤ 5 to ≥ 7.5 lbs. Subsequently, many other studies have found similar associations in people of varied ethnic and geographic origins, additionally emphasizing the importance of birth weight in the risk of adult disease.^{43–46}

Studies in twins have attempted to dissect the relative impact of environmental influences and genetic predisposition on development of higher BPs. In a study of 492 pairs of female twins, an inverse association between adult BP and birth weight (within-pair difference) was found in both monozygotic and dizygotic twins.⁴⁷ In twins aged 18 to 34 years, 24-hour ambulatory BPs were found to be higher in the lower birth weight twin, but was only significant among females.⁴⁸ The confounding factors associated with the use of twins as a model, however, precludes a firm conclusion. The available data suggest that, independent of genotype, intra-uterine environmental factors appear to exert an impact on later BP.⁴⁹

Although data on the effects of birth weight on renal disease have not been as abundant, studies from several countries have demonstrated an increased prevalence of microalbuminuria and proteinuria and lower GFRs among adults with LBWs.^{50–54} With regard to renal disease, LBW has been associated with more rapid progression of renal disease in DM, IgA nephropathy, and membranous and minimal change diseases, as well as in chronic pyelonephritis.^{55–58} Similarly, in a Southern US population, the odds ratio for end-stage renal disease was 1.4 among those with birth weights < 2.5 kg compared with those of normal birth weight.³⁰

Nephron Numbers, HTN, and CKD

In support of the low nephron number hypothesis, nephron-deficient rats develop spontaneous HTN, which is salt-sensitive, exhibit greater levels of albuminuria, lower GFR and sodium excretion, and higher tissue sodium content, as compared with normal controls.^{32,59,60} Furthermore, a recent study examining kidneys of adult Caucasians who died in accidents revealed that those with a history of essential HTN

had significantly fewer glomeruli per kidney and greater glomerular volume than matched normotensive controls.⁶¹ Birth weights were not reported in this study, but in other studies (see References^{24,62}) at autopsy, infants of LBW have been found to have reduced glomerular numbers and associated increased glomerular volume. Significantly, as opposed to animals in which nephrogenesis can continue for several days after birth, in humans there is no increase in nephron number postnatally.⁶²

A kidney with a congenitally reduced nephron number, having less functional reserve, may also be anticipated to be more susceptible to subsequent renal injury and functional decline. In fact, in a model of LBW with subsequent induction of diabetes, Jones et al⁶³ demonstrated that LBW animals had reduced nephron numbers and that LBW diabetic rats had a greater proportional increase in renal size and glomerular hypertrophy compared with normal birth weight controls after 1 week of diabetes. This study demonstrates that renal response to injury in the setting of a reduced nephron number may lead to accelerated loss of renal function.

Impact of Nephron Mass on Transplant Outcomes

Although donor age is the most significant nonimmunologic factor impacting allograft outcome, evidence demonstrates that donor kidney size, relative to recipient size, also influences long-term renal allograft function. In a retrospective study examining 32 083 recipients of a first-cadaver kidney, large recipients of kidneys from small donors had a significantly increased risk of late-graft failure compared with medium-sized recipients of kidneys from medium-sized donors.⁶⁴ The suggestion from these data is that a small kidney (presumed, from a small donor, and to have a lower nephron number) transplanted into a large recipient may not have adequate capacity to meet the metabolic demands of the recipient and, thus, would be subject to ongoing glomerular hyperfiltration and renal injury. To investigate this hypothesis, several authors have evaluated the effect of the ratio of donor kidney weight to recipient body weight (DKW/RBW) in transplant outcomes. Among 259 live-donor transplants, a higher DKW/RBW of > 4.5 g/kg was associated with significantly improved allograft function at 3 years compared with a ratio of < 3.0 g/kg.⁶⁵ Similarly, in a cohort of 964 recipients of cadaveric organs, a lower DKW/RBW was associated with a significantly increased incidence of proteinuria,⁶⁶ which suggests more hyperfiltration in the smaller kidneys, which have fewer nephrons.

Additional evidence highlighting the importance of transplanted nephron mass on allograft outcome comes from recipients of 2 “suboptimal” kidneys, for example, from older donors with reduced renal function, in whom outcomes were comparable to single kidney recipients.^{67,68} In these cases, transplantation of more than the usual kidney mass mitigated the impact of the less than optimal nature of the individual kidneys.

Potential Mechanisms Involved in Fetal Programming of Low Nephron Number

Kidney development is a complex process involving tightly controlled expression of several genes and constant remodeling. It has been shown that several factors other than fetal undernutrition can adversely affect nephrogenesis. In general, from animal studies, it is clear that environmental factors have their greatest impact if they are encountered during the period of active nephrogenesis. In humans, kidney development begins in the first trimester around 8 weeks of gestation and continues until 36 weeks. Although approximately two thirds of the nephrons develop during the last trimester of gestation,⁶² earlier insults may have a major impact on subsequent nephrogenesis, that is, in rats, maternal dietary composition can program embryonic kidney gene expression early in the course of gestation, which later impacts nephron number.⁶⁹ Maternal protein restriction during pregnancy is a widely used and studied model. Different types of low-protein diet, however, produce different results. Although the details of these differences and their differential effects are beyond the scope of this review (reviewed in Reference⁷), it is important to emphasize that the relative amount of specific amino acids (eg, methionine or glycine) appears to be more important than the extent of total restriction per se. These effects are proposed to be largely mediated by changes in DNA methylation (CpG methylation, an epigenetic way of regulating gene expression) and gene expression.⁷ The molecular mechanisms whereby nephron numbers may be affected and/or their function altered is not yet completely understood. Several potential mechanisms, however, have been proposed, which are summarized in Figure 2 and are briefly discussed below.

Glial Cell Line–Derived Neurotrophic Factor and c-Ret Receptor Function

Glial cell line–derived neurotrophic factor is a key factor in the initiation of ureteric branching, signaling through its receptor-tyrosine kinase Ret. Whereas mice with homozy-

gous deficiency of Glial cell line–derived neurotrophic factor experience severe renal dysgenesis and die shortly after birth, heterozygous mice have smaller kidneys with $\approx 30\%$ less nephrons and develop spontaneous HTN and glomerulomegaly with time.⁷⁰ Interestingly, retinoic acid (a vitamin A metabolite) stimulates expression of Ret⁷¹ and can reverse the deficiency in nephrogenesis seen in mice lacking retinoic acid receptors.⁷²

Apoptosis

Several studies have shown the importance of regulation of apoptosis in kidney development^{73,74} and explored its potential role in the pathogenesis of fetal programming. Dietary protein restriction during the second half of pregnancy in rats was associated with significantly lower body and kidney weight at birth (15% and 20%, respectively), lower nephron numbers ($\approx 28\%$), higher systolic BP, and increased apoptosis (in glomeruli, interstitial cells, and different tubule epithelial cells).³³ Low-protein diet during pregnancy in rats was specifically associated with increased metanephric apoptosis and reduced number of progenitor cells during embryonic life.⁷⁵ It has been suggested that the observed increase in apoptosis may be because of downregulation of antiapoptotic factors (eg, Pax-2 or Bcl-2) and/or upregulation of proapoptotic factors (eg, Bax, and p53).⁷⁵ Similarly, uteroplacental insufficiency (another model of fetal programming) in pregnant rats was also associated with $\approx 25\%$ lower nephron number and $\approx 180\%$ increase in apoptotic cells. These changes were associated with altered expression of genes in favor of proapoptotic genes (decreased Bcl-2 mRNA expression and increased Bax and p53 mRNA expression). Of note, the change in p53 mRNA expression was related to DNA methylation of its gene (Figure 2).⁷⁶ In addition, authors proposed that uteroplacental insufficiency may lead to oxidative stress and glutathione depletion, shown to be associated with reduced DNA methylation.⁷⁷ Moreover, oligomeganephronia and renal-coloboma syndrome have been associated with Pax-2 gene mutation.⁷⁸ Interestingly, an association be-

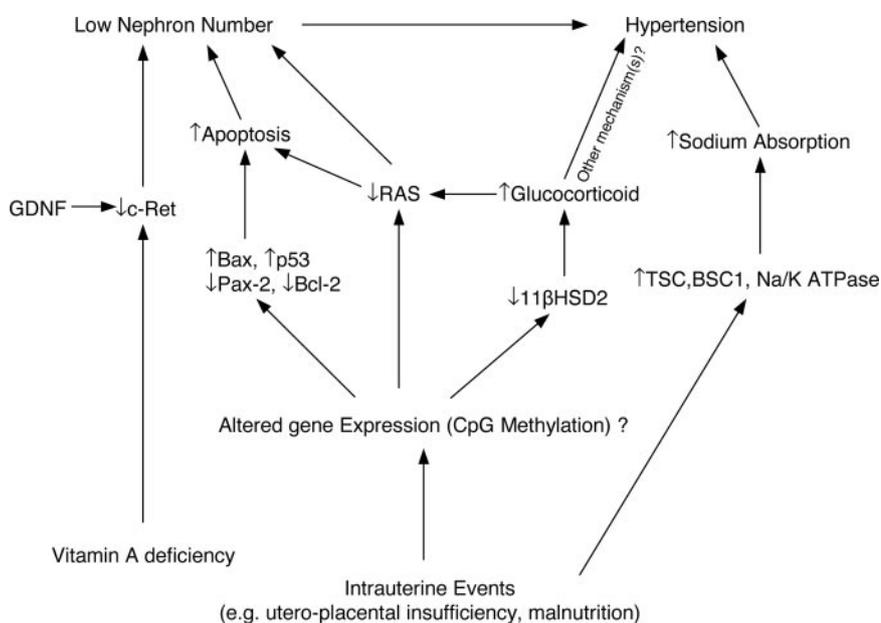


Figure 2. Potential mechanisms through which intrauterine event(s) can mediate low nephron number and hypertension. GDNF, glial derived neurotrophic factor; RAS, renin angiotensin system; 11 β HSD2, 11 β -hydroxysteroid dehydrogenase type 2; TSC, thiazide-sensitive cotransporter; BSC1, bumetanide-sensitive cotransporter.

tween p53 polymorphism and albuminuria (reported in Aboriginal Australians) provides additional evidence for the potential role of apoptosis as a mediator of the fetal programming of nephron number.⁷⁹ Interestingly, the adverse effect of ampicillin and amoxicillin on nephrogenesis may also be mediated through increasing apoptosis.⁸⁰

Renin–Angiotensin System

All of the components of the renin–angiotensin system (RAS) are present in the developing kidney and play an important role in nephrogenesis.⁸¹ Several studies in animal models of fetal programming have shown that lower expression of RAS components during the active period of nephrogenesis is associated with lower nephron number and HTN in later life.^{82–84} In addition, other studies suggest an interaction between glucocorticoids and intrarenal RAS, such that an excess of glucocorticoids can be a negative regulator of RAS components in the fetus.^{32,85} Moreover, it has been shown that angiotensin II can stimulate the expression of Pax-2 through angiotensin II type 2 receptor and, therefore, affect nephrogenesis and kidney development.⁸⁶

Glucocorticoids

In the early 1990s, a relation between increased glucocorticoid exposure in utero and adult HTN was proposed.⁸⁷ Under normal circumstances, the fetus is protected from excess maternal glucocorticoids by activity of the placental enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2). This enzyme converts cortisol to cortisone, allowing for <20% of maternal glucocorticoids to reach the fetus. Maternal exposure to excess glucocorticoids, or a steroid that is not affected by 11 β -HSD2 such as dexamethasone, during pregnancy has been associated with reduced birth weight and HTN.⁸⁸ Similar effects have been seen with lower levels of placental 11 β -HSD2 in rats and humans⁸⁹ and in humans with mutation of 11 β -HSD2 gene.⁹⁰ Interestingly, a low-protein diet has also been associated with significantly lower placental activity of 11 β -HSD2.⁹¹

Altered Sodium Handling by Kidney

In a model of fetal programming, prenatal dexamethasone administration was associated with lower body and kidney weight, lower nephron number, higher BP, increased albuminuria, lower GFR, lower urinary sodium excretion rate, reduced fractional excretion of sodium (FE_{Na}), and higher tissue content of sodium.³² In fact, lower FE_{Na} in the presence of lower GFR is strong evidence of sodium retention by the kidney. Similar findings were seen in IUGR piglets in which low nephron number was associated with a reduced GFR but a normal FE_{Na}⁹² and in the offspring of rats treated with dexamethasone during pregnancy.³² These observations are additionally confirmed by a recent study in rats in which maternal protein restriction during the second half of pregnancy was associated with lower weight at birth, development of HTN at 8 weeks of age, and a significant increase in expression of sodium cotransporters Na-K-2Cl (bumetanide-sensitive cotransporter, BSC1, 302%) and Na-Cl (thiazide-sensitive cotransporter, TSC, 157%) in the offspring.⁹³ Moreover, an increase in glucocorticoid receptor and

glucocorticoid-responsive α_1 and β_1 subunits of Na-K-ATPase has been found in offspring of pregnant rats fed a low-protein diet.⁹¹

Summary

The molecular mechanism(s) through which fetal programming exerts its effects on different organs, including the kidney, remain to be further elucidated. Nevertheless, the fact that even seemingly minor influences, such as composition of maternal diet during fetal life, can have major consequences in the offspring underscores the critical importance of optimization of perinatal care. In addition, catch-up growth significantly enhances the risk of adult disease in LBW individuals, that is, individuals who were born small but catch up or overtake their peers in weight have the highest risk of cardiovascular mortality.^{94,95} Awareness about healthy eating, exercise, and minimization of cardiovascular risk factors, therefore, needs to begin from infancy. BP tracks throughout life, and children with higher BP will continue to distribute at the higher end of the BP curve in adulthood.^{96,97} We suggest that BPs in children should be monitored in centiles, as is growth. Children in the upper centiles of BP deserve close follow-up with early modification of lifestyle factors to improve their overall health and longevity. Managing high levels of BP and renal disease once they become manifest is not optimal, because even patients with well-controlled BP continue to have a significantly higher mortality in comparison with normotensive subjects.⁹⁸ The growing strength of evidence for fetal programming of adult disease highlights an important window of opportunity during gestation in which the growing epidemics of diabetes, HTN, and renal disease worldwide could potentially be curbed.

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