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REVIEW

Factors associated with a vicious cycle involving a low nephron number, hypertension and chronic kidney disease

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It has been reported that there is substantial variation in the nephron number between individuals. Previous studies using autopsy kidneys have demonstrated that a low nephron number, in relation to a low birth weight, may result in hypertension (HTN) and/or chronic kidney disease (CKD). However, recent studies have revealed that the association between a low nephron number and HTN is not a universal finding. This observation indicates that a low nephron number is unlikely to be the sole factor contributing to an elevated blood pressure. In addition to the nephron number, various genetic and congenital factors may contribute to increased susceptibility to HTN and/or CKD in a complex manner. Acquired factors, including aging, obesity and related metabolic abnormalities, and various causes of renal injury, may additionally promote further nephron loss. Such a vicious cycle may induce HTN and/or CKD via the common mechanisms of renal hemodynamic maladaptation.
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Keywords: chronic kidney disease; glomerular density; glomerular volume; nephron number

INTRODUCTION

Chronic kidney disease (CKD) is a growing health problem of epidemic proportions worldwide. Numerous randomized clinical trials and epidemiological studies have reported systemic hypertension (HTN) to be strongly associated with renal insufficiency.[1] In addition, it has been established that the kidneys have an integral role in the regulation of arterial pressure. This close interaction between HTN and CKD has long been discussed in relation to the occurrence of cardiovascular disease (CVD) or end-stage renal disease.[2]

Since Brenner *et al.*[3] proposed that a lower nephron number predisposes the individual to both essential HTN and chronic renal disease, the relationship between the nephron number and the adult risk of CVD and CKD has been recognized. These authors also proposed that a congenital or acquired nephron deficit may be associated with glomerular hypertrophy and intraglomerular hypertension, which may cause further nephron loss. A reduction in the nephron number results in a reduced sodium excretory capacity, enhanced susceptibility to HTN and diminished renal functional reserve, thereby limiting the extent of compensation for renal injury and progressive renal insufficiency.[4–6]

It has long been accepted that the human kidney contains, on average, one million nephrons. However, numerous studies conducted in the past 20 years have demonstrated that there is much greater variability in the total nephron number in normal human kidneys than previously suspected. Whereas studies agree that the average number of nephrons is approximately one million per kidney, larger studies have shown a maximal 13-fold variation in the normal human nephron number.[6,7] In addition, a few recent autopsy studies have indicated that the nephron number is lower in the kidneys of patients with hypertension than in the kidneys of normotensive age-matched controls.[8,9] Furthermore, the findings of a low nephron number in Australian aborigines, who exhibit an extremely high rate of renal failure, are consistent with the link between a low nephron number and CKD.[10] These potential differences in the nephron number may underlie the differences in susceptibility to HTN and progression of CKD among individuals.[11]

In this review, we provide an update regarding findings for the nephron number and its association with HTN and/or CKD based on current knowledge and recent studies.

NEPHRON NUMBER

Estimation of the nephron number

The nephron number is estimated via the surrogate of the glomerular number (Nglom) in recent autopsy studies. A range of methods has been used to count the number of glomeruli in the kidneys over the past 100 years. To date, the gold standard method for estimating the

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Nglom is based on the dissector principle proposed by Sterio *et al.*[12] and the fractionator experimental design approach described by Gundersen *et al.*[13] This method ensures that glomeruli are counted with equal probability, regardless of their size, shape or distribution within the kidney. On the basis of this background, the Nglom in human kidneys is now calculated using the unbiased fractionator-sampling/dissector-counting methodology as a surrogate marker of the nephron number.[14,15]

In the first of a series of autopsy studies, Nyengaard *et al.*[16] reported an average nephron number of 617 000 (331 000 to 1 424 000) in 37 normal Danish kidneys. In the second published study, Hoy *et al.* reported similar results, with a mean of 810 646 (228 441 to 1 825 380) glomeruli per kidney, although with ninefold variation among 78 kidneys obtained from black and white Americans and aboriginal and white Australians.[17] Despite the varying ranges of nephron numbers, other studies have shown the similar results (Table 1). Importantly, numerous subsequent studies have suggested that the nephron number is significantly linked to birth weight, race, gender, age and the mean glomerular volume.[18] This suggests that the final nephron number is the result of the complex interplay between genetic and environmental factors that has through out the patient's lifetime (Table 2).

Determining factors of the nephron number

Despite the large variation in the nephron number found in these studies, one consistent observation has been noted: the human nephron number strongly and directly correlates with birth weight. Hughson *et al.*[19] reported that a low birth weight (LBW; defined as a birth weight under 2500 g) is associated with a reduced nephron number in white and African Americans. That study calculated an increase of ~260 000 glomeruli per kilogram increase in birth weight. Meanwhile, Zhang *et al.*[20] found that the nephron number in 15 infants <3 months of age exhibited a range of 4.5-fold, from 246 181 to 1 106 062, suggesting that the range in the adult Nglom reflects not only the degree of variation in nephron loss that occurs with aging, but also the extent of variation in the nephron number at birth.

Barker *et al.*[21] reported the concept of developmental programming of cardiovascular and renal diseases in adults as a result of intrauterine starvation leading to an abnormally LBW in infants. Subsequently, numerous animal experiments and epidemiological studies have demonstrated a similar concept, additionally focused on the association between LBW and a low nephron number.[22,23] In addition, Hodgin *et al.*[24] described the onset of secondary focal segmental glomerulosclerosis (FSGS) as being associated with proteinuria in six adults with a history of extreme prematurity, and Ikezumi *et al.*[25] reported the number of podocytes per glomerulus in LBW-FSGS patients is lower than that seen in MCNS patients born with a normal birth weight. These findings support the hypotheses of both Barker and Brenner that LBW is associated with a reduced nephron number and therefore an increased risk of HTN/CVD and CKD in later life.

In humans, nephrogenesis begins at around the fifth week and ceases at the 36th week of gestation.[26] Although nephrons continue to mature and the kidney increases in size during childhood, the nephron number does not increase. Therefore, it has been assumed that the

Table 1 Nephron number in humans

Population	N	*Age (years)*	*Nglom*	*Fold*	*Range*	*Reference*
Danish	37	58	617 000	4.3	331 000–1 424 000	16
Germany						
HTN (+)	10	45.5	702 379	3.7	531 140–1 959 914	8
HTN (−)	10	46.5	1 429 200			
	25	42.4 ± 13.0	861 205 ± 327 454			17
	37	29.2 ± 14.2	959 306 ± 328 602			19
	39	41.6 ± 13.8	904 412	5.1	395 054–2 026 541	52
African Americans						
HTN (+)	59	46	885 279 ± 333 619	1.8	682 664–1 198 257	38
HTN (−)	48	34	951 807 ± 268 798			
HTN (+)	86	46	953 558 ± 350 054[a]	12.8	210 332–2 702 079	9
HTN (−)	61	35	1 021 582 ± 326 581[a]			
	17	47.9 ± 18.4	858 721 ± 325 579[b]			17
	15	42.5 ± 15.6	861 205 ± 327 454[c]			17
	19	28.7 ± 17.7	869 959 ± 286 006			19
White						
HTN (+)	32	49	841 069 ± 291 903	1.8	651 793–1 146 986	38
HTN (−)	55	41	901 011 ± 298 334			
HTN (+)	44	49	946 339 ± 348 970[a]	12.8	210 332–2 702 079	9
HTN (−)	79	42	1 019 957 ± 319 696[a]			
Aboriginal	10	42.0 ± 13.9	782 671 ± 248 070			17
	17	38.5 ± 12.4	683 174	3.1	364 262–1 129 233	10
Senegalese Africans	28	34.9 ± 19.7	925 485 ± 225 427	2.6	536 171–1 394 010	102
	39	42.3 ± 14.9	937 967	3.3	536 171–1 764 421	52

Abbreviations: HTN, hypertension; Nglom, glomerular number.
[a]Male.
[b]Australian white.
[c]American white.

Table 2 Congenital and acquired factors associated with the nephron number

	Details
Congenital factors	
Genes	*PAX2, RET*
Birth weight	Low birth weight
Gender	Female
Race	Aborigine
Maternal nutrition	Low protein, vitamin A deficiency, hyperglycemia
Acquired factors	
Postnatal nutrition	Low calorie/protein
Medicine	ACE inhibitor, steroid
Age	Older
Kidney disease	Nephropathy, diabetes, cystic disease
Nephrectomy	Trauma, tumor
Obesity/pregnancy	Increased body mass

Abbreviation: ACE, angiotensin-converting enzyme.

nephron number is strongly influenced by the fetal environment. Many animal models have demonstrated an association between a low nephron number and gestational exposure to stimuli of a maternal origin, such as a low-protein diet,[27] dexamethasone,[28] vitamin A deficiency,[29] excessive alcohol consumption,[30] a high vitamin D level,[31] anemia[32] and hyperglycemia.[33] Moreover, Painter *et al.*[34] reported that Dutch individuals exposed to famine in gestation had higher rates of microalbuminuria as adults than those who had not been exposed to famine *in utero*. This effect was not mediated by a reduced maternal weight or small size of the infant at birth. The authors implied that gestational undernutrition results in a reduced nephron number at birth and a consequent increased risk of microalbuminuria.[34] These results suggest that environmental factors, such as the maternal nutritional status and health environment, may affect the determination of the individual nephron number.

Birth weight alone may not be a universal surrogate marker of the nephron number. Other programmed factors associated with the nephron number include race, gender and various genes. As shown in Table 1, the kidneys of Australian aborigines contain significantly fewer nephrons than that observed in other populations. Of note, this population is well known for an extremely high incidence of CKD.[35,36] Meanwhile, there are no differences in the nephron number between white and African Americans.[37,38] A female gender has been shown to be associated with ~12–17% fewer nephrons than that noted in males.[39] This finding is consistent with the fact that females tend to have a lower birth weight than males in the general population. Furthermore, Murphy *et al.*[40] reported that the placental level of 11beta-hydroxysteroid dehydrogenase type 2 is higher in mothers carrying female fetuses. This means that male fetuses may be exposed to higher levels of glucocorticoids than female fetuses.

The process of nephrogenesis is regulated by numerous genes and signaling cascades. Polymorphisms in some of these genes have been investigated in relation to the nephron number in humans. Recently, more than 25 genes in rodents have been shown to result in renal hypoplasia and a low nephron number.[41] These phenotypes involve alterations in the nephron endowment and present as apparent renal malformations, agenesis and/or hypodysplasia. For example, the PAX2AAA haplotype causes a 10% reduction in the kidney volume.[42] Similarly, RET1476A, a polymorphic variant, is associated with an almost 10% reduction in the kidney volume,[20] and mutations in several other genes also result in a reduced nephron number.[43] For example, the glial cell line-derived neurotrophic factor gene (GDNF) allele results in a reduced nephron endowment in the adult kidney, presumably as the result of reduced branching morphogenesis of the ureteric bud.[44] However, a study analyzing polymorphisms in the GDNF genes did not find an association with renal hypoplasia.[45]

Causes of reductions in the nephron number

Conversely, in several previous studies, a low nephron number has been reported in the absence of LBW, and not all LBW individuals display a reduced nephron number.[46] In addition, the variability in the nephron number (Nglom) in the adult kidneys is due to variations not only in nephrogenesis during gestation, but also in the rate of nephron loss during childhood and/or adult life. After birth and throughout adulthood, only loss of the nephron mass occurs. Therefore, the rate of reduction in the nephron number is expected to vary among individuals depending on these factors, including absolute nephron reduction factors (aging, kidney disease and nephrectomy) and factors associated with a relative increase in body mass (catch-up growth, obesity and pregnancy). These factors may additionally increase the single-nephron glomerular filtration rate as a compensatory phenomenon involving exhaustion of the reserved filtration capacity. It has been postulated that glomerular hyperfiltration may be associated with the occurrence of glomerulosclerosis by raising the glomerular wall tension and by also stretching and damaging the glomerular epithelial cells.[47] However, a recent study has shown the development of glomerular hyperfiltration following donor nephrectomy to not be associated with the development of glomerular hypertension or an impairment of the kidney function.[48] Therefore, glomerular hyperfiltration followed by compensatory mechanisms is not considered to be the main risk factor for further nephron loss, but it is likely to increase the risk that a reduction in the nephron number may occur.

Aging is likely the most important factor influencing the nephron number in normal adults. Older individuals have fewer nephrons due to age-related obsolescence. Several studies have also shown that the nephron number progressively decreases due to glomerulosclerosis as a result of intrarenal atherosclerosis and renal ischemia.[49,50] In one study, when four racial groups were analyzed together, the nephron number was found to be inversely correlated with age.[51] The same study demonstrated a decrease in the nephron number of 4179 per year associated with normal aging. In addition, McNamara *et al.*[52] reported an inverse association between the nephron number and age as well as age-associated increases in arteriosclerosis, cortical fibrosis and glomerulosclerosis. These findings indicate that the reduced number of glomeruli observed with increasing age is due to glomerular loss secondary to glomerulosclerosis caused by arteriolosclerosis.

For this reason, a congenitally reduced number of nephrons may increase susceptibility to renal injury later in life. In addition, acquired factors may act as a secondary insult to the kidney and thus further perpetuate disease progression.

Imaging analyses of the nephron number

Current techniques for counting the nephron number are applicable only in autopsy studies. Non-invasive methods for obtaining direct measurements of the nephron number *in vivo* have not yet been established and must be developed to monitor the nephron number in patients at risk of HTN/CVD and/or CKD.

Recent studies have attempted to estimate the nephron number using non-invasive analyses of the fine structure of the kidneys using magnetic resonance imaging (MRI).[53,54] This method is based on the observation that labeling glomeruli with cationic ferritin (CF) *in vivo*

allows for the whole-kidney detection of each labeled glomerulus. Although the total MRI-based count is lower than the stereological count, the error is within 10%. Beeman *et al.*[55] measured the glomerular number and volume in intact human kidneys using this approach. They further demonstrated MRI-detectable changes in the glomerular and vascular morphology in the setting of renal vascular disease and hypertension. These MRI techniques thus have the potential to enable direct measurements of the actual nephron number in living subjects.

Renal pathological changes associated with a low nephron number

Glomerular size. Although the nephron number does not increase after birth, the kidney matches its filtration capacity to the body's demands by increasing the size of nephrons via hypertrophy. Most studies of human Nglom have reported a strong inverse correlation between the Nglom and the mean glomerular volume (Vglom). In an autopsy series, the Vglom showed a 6.7-fold range, exhibiting a close relationship with BMI, Nglom, birth weight and hypertension.[56] Consistently, glomerulomegaly is frequently found in renal biopsies of Australian aborigines with a reduced nephron endowment, whose rates of LBW and renal disease are high.[57] These findings suggest that larger glomeruli may be a sign of compensatory hyperfiltration and hypertrophy in subjects with a fewer number of nephrons. Compensatory hypertrophied glomeruli may be more susceptible to hyperfiltration and glomerulosclerosis. Such hemodynamic changes associated with enlarged glomeruli have been also described in other disorders, such as obesity-related glomerulopathy, diabetes mellitus, polycystic kidney disease and secondary FSGS.[47] In addition, Hughson *et al.*[58] have shown that, in the setting of mild-to-moderate nephrosclerosis, glomerular hypertrophy is identified as an integral feature of hypertensive nephropathy and appears to precede rather than compensate for glomerulosclerosis. The glomerular size may therefore be an additional risk factor predisposing the patient to HTN and CKD.

Glomerulosclerosis. An inverse correlation between the total nephron number and glomerulosclerosis is observed in adult autopsy studies.[57] Glomerulosclerosis also directly correlates with the mean arterial pressure. In renal pathology, the two patterns of glomerulosclerosis may occur in relation to aging and HTN. One pattern involves the onset of glomerulosclerosis that is proceeded by a sequence of ischemic changes. As the glomerular tuft contracts, fibrous connective tissue fills Bowman's space with acellular fibrous tissue. The other pattern of glomerulosclerosis is referred to as glomerular solidification, which consists of an increase in the mesangial matrix, subsequently resulting in either segmental or global solidification of the glomerular tuft.[59] On the basis of these findings, a low nephron number, as a result of glomerular hyperfiltration damage, may lead to arteriolosclerosis in the preglomerular arteries as well as glomerulosclerosis due to ischemia and solidification.

Glomerular density. The significance of the nephron number is now well appreciated. Recently, the concept of the glomerular density

Table 3 Reports on the glomerular density in subjects with a normal renal function

Race	*Objects*	N	*Age*	*GD*	*Methods*	*Findings*	*Reference*
Autopsy Studies							
Slovenian	Accident deaths	20	21.5 years	2.9 mm^{-2}	The number of all glomeruli within the cortical area	A significant correlation between GD and birth weights	61
Cuban	LBW	18	37.0 ± 1.05 weeks	92.9 ± 4.85	The number of glomeruli per 0.6 mm^2 of renal cortex	A strong correlations between glomerular number (direct) and size (inverse) with LBW	62
	NBW	17	38.9 ± 1.29 weeks	105.8 ± 3.91			
Japanese	Disease deaths	89	63 ± 14 years	2.6 ± 0.6 mm^{-2}	The number of non-scleroticglomeruli per 4–8 fields (6 mm^2 /each) randomly selected in the renal cortical area	GD showed maximal 3.5-fold variations between individuals and was inversely correlated with the mean GV	70
Biopsy Studies							
US citizens	Adult living kidney donors	1046	43 ± 12	2.3 ± 0.8 mm^{-2}	The length and width of the biopsy section measured by a ruler.	Decreased GD was associated with kidney function and metabolic risk factors	64
Japanese	IgAN	98	34 ± 13	3.5 ± 1.5 mm^{-2}	The total renal cortical area of the biopsy section measured using a computed imaging analyzer	GD exhibited significant variation in patients with various primary glomerular disease and was a plausible independent predictor of disease progression	65 66
	MN	65	56 ± 14	3.4 ± 1.1 mm^{-2}			67
	MCNS	50	39 ± 18	3.6 ± 1.1 mm^{-2}			68
	ORG	20	40 ± 12	1.7 ± 0.6 mm^{-2}			107

Abbreviations: GD, glomerular density, IgAN, IgA nephropathy; LBW, low birth weight; MCD, minimal change disease; MN, membranous nephropathy; NBW, normal birth weight; ORG, obesity-related glomerulopathy.

(GD; glomerular number per renal cortical area) was introduced, indicating the histological significance of the nephron number[60] (Table 3).

A previous report showed that the GD is correlated with birth weight, a known factor related to the total nephron number.[61] Interestingly, Manalich *et al.*[62] reported that the kidneys of low birth weight neonates contain fewer glomeruli per unit area of cortex than those of neonates with a normal birth weight. In addition, Rothermund *et al.*[63] measured the GD as a surrogate for the nephron number in Munich–Wistar–Frömter (MWF) rats, a well-established model of a genetic reduction in the glomerular number of the order of 50% compared with control rats. At 12 weeks of age, the glomerular density was 12.1 ± 3.1 number/mm^3 *vs.* 7.3 ± 1.6 number/mm^3 in the Wistar and MWF strains, respectively.[63] Furthermore, Rule *et al.*[64] indicated that the GD is associated with the kidney function and other metabolic characteristics, such as body mass index, hypertension and/or high-density lipoprotein cholesterol, based on the findings of renal biopsy samples in healthy adult kidney donors.[64] We also previously demonstrated that the individual value of the GD in renal tissue specimens obtained via percutaneous needle biopsy shows an approximately sevenfold variation in cases of IgA nephropathy (IgAN),[65,66] a fourfold variation in cases of membranous nephropathy (MN) [67] and a fourfold variation in cases of minimal change disease (MCD),[68] even in patients with a preserved renal function. In addition, a low GD on biopsy specimens is associated with a poor long-term renal prognosis and/or blunted response to corticosteroid therapy in these patients.[66–68] Similarly, our study using biopsy samples in patients with hypertensive nephrosclerosis suggested that the GD may reflect the severity of proteinuria in this population.[69] Subsequently, our recent study using autopsy kidneys obtained from 89 individuals without apparent renal disease, which enabled the evaluation of a much larger number of glomeruli than that permitted using biopsy specimens, showed a maximal 3.5-fold variation in the GD.[70] In addition, we previously reported the GD is inversely correlated with the mean glomerular volume (GV) (Figure 1), consistent with our previous findings obtained with biopsy specimens.

These findings led us to hypothesize that the GD, at least in part, reflects the personal nephron number of each individual. This hypothesis should be confirmed in further studies.

NEPHRON NUMBER AND HYPERTENSION

Blood pressure and the nephron number

HTN has been reported to be related not only to renal dysfunction (injury or ischemic), but also to many disorders of the vascular, cardiac and central nervous systems. However, the mechanisms involved in the development and maintenance of HTN have not yet been completely elucidated.

A low nephron endowment has long been identified as a risk factor for the development of HTN in animal experiments and human autopsy studies.[71] In addition, experimental studies have shown the linkage of oligonephronia (a low nephron number) and HTN, to cause an alteration in the tubular sodium transporters expression, vascular function, neuroendocrine adaptation and sympathetic regulation.[72] Although these results indicate that a low nephron endowment is associated with elevation of arterial blood pressure, recent studies have shown that this association is not a universal finding. Our findings therefore suggest that additional factors that lead to the occurrence of a low nephron number cause structural or functional changes in the kidneys that eventually lead to HTN. Further studies are required to unravel the mechanistic links between blood pressure and the nephron number.

Animal experiments

Some animal experiments, using rat fetuses exposed to maternal protein restriction, have suggested a strong link between the nephron number at birth and the postnatal blood pressure.[73,74] For example, Schreuder *et al.*[75] reported that rats born after spontaneous IUGR have a low nephron endowment and become hypertensive. In addition, spontaneous hypertensive rat strains have fewer glomeruli than normotensive rats,[76] and Ots *et al.*[77] showed that a reduced renal mass is the major factor involved in the development and maintenance of arterial hypertension and glomerular injury in 5/6 nephrectomized rats and that these changes can be reversed by supplementing the renal mass. These results provide strong support for the notion that the renal mass is a significant, independent determinant of arterial pressure. Cullen-McEwen *et al.*[78] reported an elevated arterial pressure and glomerular hypertrophy in aged GDNF heterozygous mice. Moreover, Walker *et al.*[79] showed that an augmented nephron endowment in transforming growth factor-β2 heterozygous (Tgfb2 (+/−)) mice protects against the hypertensive effects of a chronic high-salt diet. This finding is consistent with the hypothesis that the

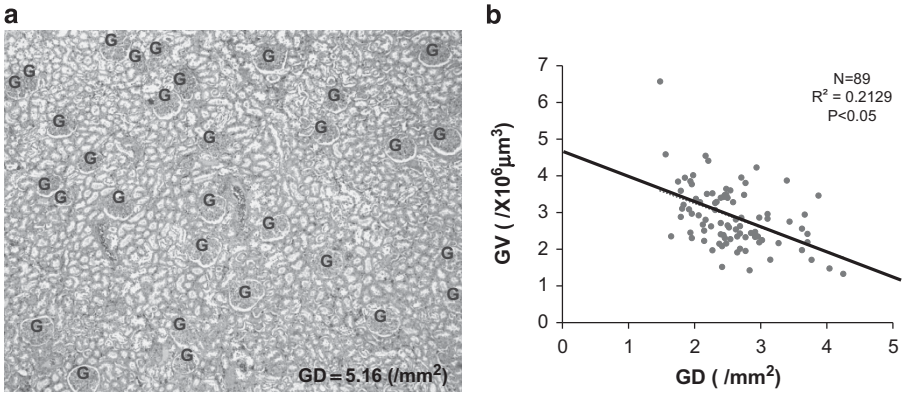

Figure 1 GD in an autopsy study. (**a**) Representative renal histological findings in an autopsy case. Autopsy kidney specimens obtained from a 67-year-old female with an estimated glomerular filtration rate (eGFR) of 89 ml min^{-1} per 1.73 m^2 are shown (original magnification ×100; Masson's trichrome stain). In this case, the GD was estimated to be 5.16 mm^{-2}. G, glomerulus. (**b**) Relationship between the GD and GV in the autopsy kidneys. The GD showed a close inverse correlation with the GV. A full color version of this figure is available at *Hypertension Research* online.

nephron endowment modulates the risk of developing cardiovascular and/or renal diseases.

Meanwhile, several animal studies have suggested that even marked nephron deficiency and hyperfiltration do not always lead to HTN or renal dysfunction. Notably, Ruta *et al.*[80] found that neither moderate (25%) nor severe (65%) reductions in the nephron endowment impact blood pressure (BP) in GDNF heterozygous mice at 1 year of age. Recent studies have also indicated that a low nephron number increases the risk of hypertension in animals exposed to secondary adverse stimuli, such as a high-salt diet. These findings, obtained utilizing a genetic model of a reduced nephron endowment, suggest that deficits in the nephron number alone do not always directly translate to hypertension or renal disease.[81]

Human studies

Keller *et al.*[8] analyzed a consecutive series of subjects who died in accidents and described that the number of glomeruli was lower in the kidneys of the patients with hypertension than in the kidneys of the matched normotensive controls. In particular, the number of glomeruli was diminished by ~46% in the hypertensive individuals, and the mean glomerular volume was markedly increased by ~50%. This study strongly supports the presence of an association between a low nephron number and HTN in humans. Samuel *et al.*[82] also showed that the glomerular number is significantly reduced in subjects with hypertension, in association with a significant increase in the mean glomerular volume, independent of the body surface area. However, the precise mechanisms involved in the increases in blood pressure in individuals with a low nephron endowment have not yet been fully elucidated. One possible effect of a low nephron endowment is a reduction in the number of sodium transporters as well as alterations in renal sodium handling, which may influence blood pressure control.

Similarly, the association between the nephron number and blood pressure has been investigated in several populations, including Germans, aboriginal Australians, white and African Americans and Senegalese Africans. In these studies, however, a low nephron number was not always found to be associated with HTN.[83] In particular, no association between the nephron number and BP has been found in either white Americans, African Americans or Senegalese Africans.[9] This observation indicates that a low nephron number is unlikely to be the sole factor contributing to elevated BP. In addition to the nephron number, other programmed factors associated with an increased risk of hypertension may include salt sensitivity, an altered expression of renal sodium transporters, altered vascular reactivity, modulation of the activity of the RAS, sympathetic nervous system overactivity and dysfunction of the cardiovascular system.[84]

Renal renin–angiotensin system and the nephron number

Nephrogenesis. The renal renin–angiotensin system (RAS) has been identified to have a role in regulating the renal function and arterial pressure in adults as well as promoting the structural and functional development of the fetal kidney.[85] Woods *et al.*[86] showed that perinatal blockade of angiotensin II (AII) angiotensin type1 (AT1) receptors results in fewer, albeit enlarged glomeruli, a reduced renal function and an increased arterial pressure in newborn Sprague–Dawley rats. In addition, AII binding to the AT1 receptor has been shown in culture systems to mediate the process of branching morphogenesis.[87] Therefore, a decreased expression of the AT1 receptor may result in less branching of the ureteric bud and thus a reduction in the nephron number. Similarly, the gestational use of ACE-I may be associated with a high degree of fetal and newborn renal failure or prolonged HTN in humans.[88] Following the completion of nephrogenesis, AT1 receptors appear to be upregulated in the kidneys of offspring. Moreover, Salazar *et al.*[89] showed that AII modulation modifies the renal function and induces the development of AII-dependent hypertension that becomes sodium-sensitive with aging. This finding may provide a mechanistic link with activation of the renal RAS, which may cause sodium retention and elevated blood pressure.[90] On the basis of these findings, a lower expression of RAS components during the active period of nephrogenesis is associated with a lower nephron number and HTN in later life. It has also been shown that AII stimulates the expression of Pax-2 via angiotensin II type 2 receptors and thus affects the onset of nephrogenesis and kidney development.[91]

Treatment of glomerular hyperfiltration caused by a low nephron number. Glomerular hyperfiltration associated with a low nephron number may activate the RAS, which results in maladaptive renal and systemic hemodynamic responses, increased arterial stiffness and endothelial dysfunction. Previous animal studies have also shown that experimental reductions in the nephron number are closely associated with glomerular enlargement, together with increased activation of the intrarenal RAS.[92] The most effective intervention for a low nephron number, therefore, may be to target glomerular hypertension and the RAS.

Of note, it has been demonstrated that a transient decrease in GFR following treatment with an angiotensin receptor blocker (losartan) in patients with diabetic nephropathy is associated with a subsequent reduction in the slope of the renal function.[93] This amelioration of glomerular hypertension in patients with a transient decrease in GFR may indicate dependence pathophysiologically on the RAS. Therefore, a transient decrease in GFR following the administration of RAS inhibitors may be a candidate surrogate marker of a relative reduction in the nephron number.

NEPHRON NUMBER AND CKD

Proteinuria and the nephron number

Numerous studies have reported an increased prevalence of microalbuminuria and proteinuria among adults born with LBW.[94] In a study of Australian aborigines, an odds ratio of 2.8 for albuminuria was found in those with a history of LBW *vs.* NBW.[95] Similarly, among Pima Indians with type 2 diabetes, a U-shaped association has been demonstrated between birth weight and albumin excretion in both LBW and high-birth weight (HBW; defined as a birth weight over 4500 g) adults.[96] Meanwhile, Jones *et al.*[97] described morphological abnormalities in glomerular podocytes in LBW diabetic animals, which may have a role in the development of proteinuria.[97] These findings likely indicate that intrauterine programming of nephron development may be associated with a decreased nephron number and increased risk of albuminuria.

Renal insufficiency and the nephron number

A recent meta-analysis found a 70% increase (odds ratio 1.73) in the relative risk of CKD associated with LBW.[98] In some animal models, congenital nephron deficiency, both genetic and experimental, is associated with renal disease and renal failure in postnatal life. LBW animals with a reduced nephron number have also shown to exhibit abnormal glomerular adaptation and greater renal injury.[99] In contrast, Li *et al.*[100] reported a U-shaped association between birth weight and CKD prevalence among males, but not females, in a screened volunteer population in the National Kidney Foundation's Kidney Early Evaluation. Although it is certainly recognized that the rate of

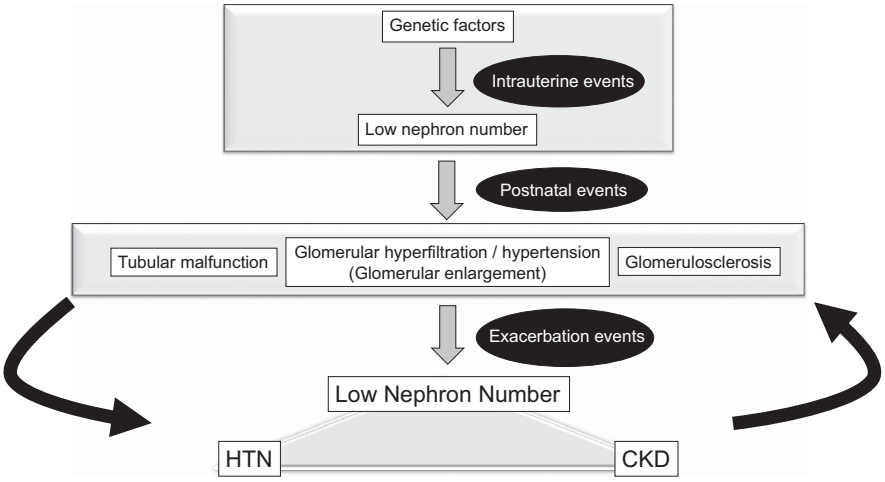

Figure 2 Hypothetical mechanism of nephron number reduction. Three events, intrauterine, postnatal or exacerbation, affect the reduction in the human nephron number. Beginning at the top and moving to the bottom, multiple factors induce further nephron loss, which leads to a vicious cycle among a low nephron number, HTN and CKD via renal hemodynamic maladaptation.

CKD in patients who have undergone partial nephrectomy for renal cell carcinoma is higher than that observed in the general population,[101] few studies have analyzed the direct relationships between the human nephron number and prevalence of CKD.[102]

Researchers have recently suggested that kidneys with a congenitally reduced nephron number, displaying less functional reserve, may also be anticipated to be more susceptible to subsequent renal injury and functional decline.[103,104] In fact, in a model of LBW with the subsequent induction of diabetes, Jones *et al.*[105] demonstrated that LBW animals have a reduced nephron number and that LBW diabetic rats exhibit a greater proportional increase in renal size and glomerular hypertrophy compared with normal birth weight controls after one week of diabetes. That study demonstrated that the renal response to injury in the setting of a reduced nephron number may result in accelerated loss of the renal function. Consistent with this possibility, an LBW status has been shown to be associated with poorer outcomes in patients with chronic glomerulonephritis or diabetic nephropathy.[23] These results suggest that LBW is associated with both the initiation and progression of CKD.

CONCLUSIONS

As previously reviewed,[106] various genetic, congenital and acquired factors have been reported to be associated with a vicious cycle involving a low nephron number, hypertension and chronic kidney disease (Figure 2). Although the association between these three characteristics is not present in all studies, the nephron number is undoubtedly a strong determinant of blood pressure and the risk of renal disease in later life. Therefore, evaluating the nephron number in each patient is currently one of the most important issues in this field. However, counting the nephron number is labor-intensive and expensive and not utilized at most laboratories. Therefore, the development of new methods to non-invasively estimate the individual nephron number would be very useful for evaluating the future CVD/HTN risk and progression of renal disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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