Clinicopathological assessment of the nephron number

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Abstract

Recent studies have demonstrated much larger variability in the total number of nephrons in normal populations than previously suspected. In addition, it has been suggested that individuals with a low nephron number may have an increased lifetime risk of hypertension or renal insufficiency, emphasizing the importance of evaluating the nephron number in each individual. In view of the fact that all previous reports of the nephron number were based on analyses of autopsy kidneys, the identification of surrogate markers detectable in living subjects is needed in order to enhance understanding of the clinical significance of this parameter. In this review, we summarize the clinicopathological factors and findings indicating a reduction in the nephron number, focusing particularly on those found at the time of a preserved renal function.

Keywords: birth weight; CKD; nephron number; renal biopsy

Introduction

Most types of chronic renal diseases are potentially progressive and irreversible, and once renal functional impairment is established, it is often difficult to retard further disease progression [1,2]. Therefore, it is important to identify subjects at risk of future progression to renal failure as early as possible and take preventative measures before apparent renal dysfunction becomes established [3].

Recent autopsy studies have demonstrated that the total number of nephrons in general populations varies significantly even in the absence of specific renal diseases [4–7]. Such potential differences in the nephron number at the time of a preserved renal function may represent differences in the functional reserve of the kidneys and are currently recognized to be one cause of divergent renal outcomes between individuals with similar clinical background characteristics at the diagnosis of renal disease [8–10]. Therefore, the development of methods to non-invasively estimate the individual total nephron number would be very useful for evaluating the future progression of renal disease. However, at present, the detailed stereology-based analysis of autopsy kidneys is the only available method for accurately determining the human nephron number [11–13]. In addition, due to its microscopic size, it remains difficult to identify the individual fine structure and assess the total number of nephrons in living human subjects using commonly available clinical imaging studies. Therefore, for clinical assessments, it is necessary to integrate information regarding the origin and/or outcome of reductions in the nephron number.

In this review, we summarize currently available markers of a low nephron number that are detectable as clinicopathological information in living human subjects. As a result of current clinical needs, we particularly focused on factors and/or findings indicating nephron number reduction at the time of a preserved renal function.

The human nephron number: the relationship between a low nephron number and the risk of renal diseases

The human nephron number can be estimated by the stereology-based analysis of autopsy kidneys [11–13]. Recent studies have demonstrated much larger variability in the total nephron number in normal populations than previously suspected. As shown in Table 1, the variations among reported autopsy series are up to 8-fold. Of note, it has consistently been reported that there is a close relationship between the birth weight and the total nephron number [4,5]. Recent investigations have revealed that nephron number increases by ~260 000 per kg increase in birth weight [4]. The correlation between the birth weight and total nephron number is likely based on the fact that the final number of human nephrons is determined at 34–36 weeks of gestation and does not increase thereafter [17,18].

A low birth weight can result from intrauterine growth restriction or preterm birth. In general, a low-birth-weight infant is defined as an individual born weighing <2500 g, while a preterm birth infant is defined as an individual born before 36 weeks of gestation. Sutherland et al. [19] conducted a study of the autopsied kidneys of preterm human neonates born between 24 and 35 weeks of gestation who lived for 2–68 days after birth. Compared with
the gestational control tissues, the preterm kidneys exhibited a reduced width of the nephrogenic zone and a greater percentage of morphologically abnormal glomeruli. These observations suggest that preterm kidneys have fewer functional nephrons. This hypothesis is further supported by a series of experimental studies, including analyses using a baboon model of preterm birth [20].

Importantly, it has been suggested that a low birth weight, in association with a low nephron number, is a plausible risk factor for progression to renal failure in adult life [21]. The progressive loss of functioning nephrons is the hallmark of most types of renal disease. Therefore, increased severity and acceleration of renal disease is likely when the number of nephrons is already reduced prior to disease onset. On the other hand, studies have also suggested relationships between birth weight and the incidence of hypertension/cardiovascular diseases, which are closely related to the pathogenesis of chronic kidney disease (CKD) [22]. Therefore, the concept of 'nephron number reduction in individuals with a normal renal function' is fully consistent with that of CKD, which aims to prevent health hazards by observing renal and cardiovascular complications, not only in patients with end-stage kidney disease (ESKD), but also in subjects at risk of ESKD, from the time of a normal renal function. Therefore, the hypothesis of 'developmental origins of health and disease', first described by Barker et al., is attracting much attention from nephrology researchers, as this theory has the potential to elucidate the complex pathophysiological cascade of CKD [23–25].

**Clinical surrogates for a low nephron number**

As shown in Table 2, clinical surrogates for a low nephron number include parameters related to the origin and/or the outcome of nephron number reduction.

**Maternal nutrition and behavior**

Maternal malnutrition during gestation has been shown to be associated with a low birth weight and low nephron number [26, 27]. In particular, it has been demonstrated that protein restriction reduces the nephron endowment during nephrogenesis in animals [28, 29]. Likewise, it is known that vitamin A deficiency influences kidney development and is related to a low nephron number [30, 31]. Other factors that have been found to be related to alterations in the nephron number in animals include a low or high salt intake and iron or zinc deficiency [32–34]. Maternal diabetes has also been shown to be associated with a risk of renal agenesis and dysplasia in animals [35]. In addition, maternal smoking and alcohol consumption are related to a low nephron number as well as defects in nephrogenesis in animal experiments [36, 37]. The use of medications by a pregnant female may also influence fetal kidney development. For example, it has been shown that the maternal use of steroids or renin–angiotensin–aldosterone system (RAAS) inhibitors affects fetal renal development [38, 39].

**Fetal birth weight**

Maternal social, environmental and nutritional factors during pregnancy are quite important in determining the ultimate number of fetal nephrons. In particular, because...
a low birth weight has been established to be an indicator of an insufficient gestational environment, it is the most reliable and useful parameter of a low nephron number [4, 5]. In addition, a recent study showed an odds ratio for a low-birth-weight infant of 1.8 among mothers born with a low birth weight, indicating the potential role of genetic factors other than fetal environmental factors in the occurrence of a low birth weight [40].

Genetic factors
Specific monogenic mutations in certain genes have been shown to be responsible for phenotypes of congenital abnormalities of the kidneys and urinary tract. Many of these phenotypes involve alterations in the nephron endowment, recognized as apparent renal malformations, agenesis or hypodysplasia. More subtle changes are inherited as variants in the DNA sequence, termed genetic polymorphisms. For example, the RET 1476A polymorphism [41] or PAX2AAA haplotype [42] are frequently identified in the general population. These gene polymorphisms have been shown to be associated with a 10% reduction in kidney size for each genotype without apparent morphological abnormalities in the kidneys, with a 23% reduction in kidney size in the presence of both genotypes [41].

Race and gender
Comparisons of the mean total nephron numbers in the African Americans and the Caucasian Americans did not show differences among the races [4]. It has been shown that the nephron number in certain Australian aboriginal communities is significantly low compared with that observed in other populations [16]. Of note, this population is well known for an extremely high incidence of CKD [43, 44].

Female gender has been shown to be associated with 12% fewer nephrons than that observed in males [5, 45]. This finding is consistent with the fact that females tend to have a lower birth weight than males in the general population.

Age
Among the physiological factors that can occur during an individual’s lifetime, aging is probably the most important factor influencing the nephron number [46, 47]. As an individual ages, the nephron number progressively decreases due to ischemia as a result of intrarenal atherosclerosis, even in the absence of any specific renal diseases. An estimate from one study demonstrated a decrease in the nephron number of 4500 per year associated with normal aging [48]. As a result, the kidney size decreases to ∼50–60% of that observed at the maximal level on average [49].

Adult height and body weight
The total nephron number has been shown to be strongly related to height in adults, a characteristic predicted by birth weight [50]. A low adult height has also been reported to be associated with the incidence of hypertension and diabetic nephropathy [51, 52]. Although adult obesity is associated with glomerular hypertrophy in general, its relationship with the total nephron number is unclear.

Kidney size
The nephron number exhibits a weak correlation with kidney size until 3 months after birth [41, 42]. The total nephron number in adults has been shown to be correlated with kidney weight in adult human autopsy series [14]. However, the relationship between the total number of nephrons and the kidney size measured on imaging analyses remains undetermined, although a relationship between the renal size on ultrasonography and the incidence of hypertension or slope of the renal function has been reported [53–55].

Hypertension
It was recently reported that the nephron number in patients with essential hypertension is lower than that observed in age-matched subjects without hypertension in an analysis of autopsy kidneys among a German population with sudden death [15]. In addition, a low nephron number is associated with hypertension in Australian Aborigines and Caucasian Americans. However, the relationship between a low birth weight and hypertension is not apparent in African Americans [5]. The precise mechanisms involved in 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 [56].

Proteinuria
In a study of Australian Aborigines, the odds ratio in subjects with a low birth weight was 2.8 (95% CI 1.26–6.31) for the appearance of microalbuminuria in comparison with those without a low birth weight. This result suggests that a low birth weight is associated with both the initiation and progression of CKD [57].

In routine clinical examinations, it is technically difficult to distinguish between proteinuria associated with primary immunological or non-immunological glomerular injury and proteinuria induced by the secondary compensatory failure of glomeruli due to a reduction in the functional nephron number. Therefore, the appearance of proteinuria per se is not always a marker of nephron number reduction. This finding is more probable when proteinuria is detected together with microscopic hematuria or various casts in urinary sediment.

Response to therapy
In a post hoc analysis of the Reduction of End Points in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan trial, it was demonstrated that a transient fall in glomerular filtration rate (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 [58]. These results suggest that the progression of renal tissue injury is attenuated, at least in part, by the amelioration of glomerular hypertension in patients with a transient decrease in GFR. Perhaps the kidneys in patients exhibiting a relatively large decrease in GFR following the initiation of the losartan therapy are pathophysiologically more dependent on the RAAS and therefore more sensitive to RAAS inhibitors. Previous studies have
shown that experimental reductions in the nephron number are closely associated with glomerular enlargement together with increased activation of the intrarenal RAAS [59, 60]. Therefore, it is conceivable that maladaptive glomerular injury due to a subtle reduction in the nephron number is involved in the pathogenesis of certain renal diseases, such as diabetic nephropathy. Therefore, a transient decrease in GFR and subsequent reduction in proteinuria following the administration of RAAS inhibitors is a candidate surrogate marker of a relative reduction in the nephron number, even at the time of a preserved renal function.

**Histopathological surrogates of a low nephron number on renal biopsy specimens**

As shown in Table 3, the following factors may be associated with a reduction in the nephron number at the time of a preserved renal function. However, because renal biopsies are generally performed in patients with signs of renal injury, such as persistent urinary abnormalities, it is difficult to evaluate these histopathological factors in clinically ‘normal’ patients without any signs of renal injury.

**Glomerular hypertrophy**

In autopsy studies, it has been clearly demonstrated that the total nephron number is inversely correlated with the glomerular volume [4–7]. This finding indicates the presence of renal compensatory changes in order to maintain the GFR at the ideal level in response to nephron number reduction. Under such compensatory processes, the GFR of single nephrons increases among the remaining glomeruli and the glomeruli become enlarged. Therefore, glomerular hypertrophy is a finding indicative of a relative reduction in the nephron number. Consistent with this idea, previous reports have demonstrated a relationship between the detection of glomerular hypertrophy on a diagnostic renal biopsy and the subsequent progression to renal failure [61–65].

Currently, the glomerular size can be evaluated by measuring the maximal glomerular diameter or the glomerular surface area and estimating the glomerular volume based on these data using biopsy or autopsy specimens [61–66]. However, no consensus exists regarding the size of glomeruli defining glomerular hypertrophy and/or glomerulomegaly [67]. Accordingly, glomerular enlargement can be evaluated only when the glomerular size is compared among the specimens of certain patient cohorts.

Renal tubules are also postulated to become enlarged in response to reductions in the nephron number.

However, it is technically difficult to estimate the tubular size on biopsies because the axis of the slices of the specimens is not always constant. In addition, the size of the tubules largely depends on each nephron segment, which further complicates quantitative evaluations.

**Glomerular capillary number**

In a rat heminephrectomy model, it was recently demonstrated that the glomerular capillary number increases during the process of compensatory glomerular enlargement [68]. Consequently, certain angiogenesis-promoting factors are secreted to increase the glomerular capillary number and maintain the total glomerular filtration rate under conditions of nephron number reduction. Consistent with this idea, increases in the glomerular volume in this animal model are abolished by treatment with a neutralizing antibody to vascular endothelial growth factor (VEGF) [69, 70]. The increased secretion of angiogenesis-promoting factors, including VEGF, has also been reported in tissue microarray analyses of renal biopsies in patients with obesity-related glomerulopathy, whose glomeruli are markedly increased in size [71]. These results suggest that an increase in the glomerular capillary number is indicative of a relative decrease in the nephron number.

**Focal segmental glomerulosclerosis**

Focal segmental glomerulosclerosis (FSGS) is a renal pathological finding that is believed to result from glomerular podocyte injury [72]. The mechanisms underlying glomerular podocyte injury include those induced by immunological injury, as well as transformation by direct viral infection, drug-induced cytotoxic effects and/or non-immunological hemodynamic or pressure loading [73]. Under conditions of nephron number reduction, FSGS may be established as a result of glomerular scarring due to the failure to maintain the physiological function when stressors on glomerular podocytes induced by excessive glomerular enlargement exceed a certain upper limit.

Such hemodynamic changes may also be found in subjects with massive obesity in which a ‘mismatch’ between body size and the nephron number exists. Indeed, glomerulomegaly and FSGS are characteristic histopathological findings in patients with obesity-related glomerulopathy and are occasionally found in massively obese individuals [74–76]. In this disease entity, the glomerular filtration rate increases to meet the increased metabolic demands of the kidneys [77, 78]. Accordingly, massive obesity may be a finding indicative of a relatively low nephron number. Likewise, the detection of FSGS in very-low-birth-weight infants or body builders with a large muscle mass is consistent with the ‘mismatch’ hypothesis [79, 80].

Histopathologically, FSGS induced by hemodynamic stress is often associated with the perihilar variant, which accompanies segmental sclerotic lesions near the vascular pole of the glomeruli [72]. In electron microscopic studies, the frequency of podocyte foot process effacement is relatively low compared with that observed in patients with FSGS induced by other mechanisms [75].

**Glomerular density**

We recently demonstrated that the individual glomerular density (the number of non-sclerotic glomeruli per renal cortical area on a needle biopsy specimen) exhibits significant variation in patients with various primary glomerular
diseases, although all biopsies were performed when the renal function was within the normal range [81–83]. The maximal differences in glomerular density were 6.8-fold among 98 patients with IgA nephropathy (IgAN), 4.3-fold among 65 patients with idiopathic membranous nephropathy (IMN) and 4.3-fold among 50 patients with minimal change disease (MCD). Figure 1A shows the representative renal biopsy findings in a patient with a high glomerular density and Figure 1B shows a patient with a low glomerular density. Of note, the glomerular density was found to be inversely correlated with the mean glomerular volume in these patient cohorts (Figure 2). Furthermore, a low glomerular density at the time of a preserved renal function is a plausible independent predictor of progression in patients with IgAN or IMN. The analyses of patients with MCD revealed that the patients with a low glomerular density tended to have similar clinicopathological characteristics to patients with a histological diagnosis of FSGS. During the initial treatment with corticosteroids in the patients with MCD, the number of patients achieving complete remission was significantly lower among the subjects with a low glomerular density than among those with a high glomerular density. These results suggest that the glomerular density on renal biopsy specimens is an important determinant of the variability in glomerular size and can influence the clinical phenotype, such as the response to therapy and the long-term renal outcome. Based on these findings, we suggest that the glomerular density observed on renal biopsy specimens reflects, at least in part, the personal number of nephrons in an individual. In support of this idea, a previous report showed that the glomerular density is correlated with the birth weight, a known factor related to the total nephron number [84].

On the other hand, there is an issue regarding the evaluation of the glomerular density on renal biopsy specimens with respect to the limitations of morphological measurements using small tissue specimens obtained via needle biopsies. In fact, 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 analyses of both superficial and juxtamedullary cortices between individuals; this result was smaller than that observed using biopsy specimens [85]. In addition, it is uncertain whether the glomerular density observed on a renal biopsy specimen truly represents the total number of nephrons in the entire kidney, since data on the total cortical volume of the kidneys were not available in our study. Accurately determining the origin of the variation in glomerular density observed in renal biopsy specimens therefore requires further investigation.

**Imaging assessments of the nephron mass and future perspectives**

Although the least invasive and most standardized marker of kidney size in living human subjects is that measured on ultrasonography, the obtained value is 2D and dependent on the technique of the operator [86–88]. In contrast, X-ray computed tomography (CT) and/or magnetic resonance
imaging (MRI) are 3D and can provide more accurate values of the human kidney volume [89–91]. However, in response to nephron number reduction, renal compensatory changes, including hypertrophy of the glomeruli and tubules, may occur; thus, the kidney does not necessarily exhibit a remarkable difference in size in the absence of apparent renal dysfunction. Therefore, it can be difficult to estimate the total nephron number using only information obtained from imaging studies in living human subjects.

A new method using MRI to measure the number of glomeruli and individual glomerular volume in perfused rat kidneys has recently been reported [92, 93]. This method is based on the observation that labeling glomeruli with cationic ferritin in vivo allows for whole-kidney detection of each labeled glomerulus using MRI. The total MRI-based count is lower than stereological counts; however, the error is within 10%. Therefore, this new MRI method has the potential to enable measurement of the total nephron number.

Multiphoton microscopy of the kidneys in animals is a powerful technique for renal research. This imaging technique enables the dynamic 4D analysis of organ structures in vivo. Recent advances in research have resulted in not only the ability to detect molecular changes in the glomerulus, but also monitor the progression of renal disease. For example, the labeled human monoclonal antibody (F1.1) directed against the NC1 domain of α3(IV) collagen can be used to assess structural changes in the glomerular basement membrane during the course of glomerular disease, which potentially allows for quantitative estimators of the structural viability of glomeruli [94].

Conclusions

Variations in the nephron number endowment among the general population may determine the future risk of renal failure. Therefore, evaluating the nephron number in each individual is currently one of the most important issues in clinical nephrology. Surrogates for the total nephron number include fetal environmental factors, genetic factors and the presence of certain clinical or histopathological findings at diagnosis. However, due to its complex and multifactorial nature, it is often difficult to evaluate the nephron number. Therefore, the establishment of new technology to accurately estimate the nephron number in living human subjects is required.

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