Glomerular number and size in autopsy kidneys: The relationship to birth weight

MICHAEL HUGHSON, ALTON B. FARRIS III, REBECCA DOUGLAS-DENTON, WENDY E. HOY, and JOHN F. BERTRAM

University of Mississippi Medical Center, Jackson, Mississippi; Department of Anatomy and Cell Biology, Monash University, Clayton, Victoria, Australia; and Centre for Chronic Disease, University of Queensland, Brisbane, Australia

Glomerular number and size in autopsy kidneys: The relationship to birth weight.

Background. In the Southeast United States, African Americans have an estimated incidence of hypertension and end-stage renal disease (ESRD) that is five times greater than Caucasians. Higher rates of low birth weight (LBW) among African Americans is suggested to predispose African Americans to the higher risk, possibly by reducing the number of glomeruli that develop in the kidney. This study investigates the relationships between age, race, gender, total glomerular number ($N_{\text{glom}}$), mean glomerular volume ($V_{\text{glom}}$), body surface area (BSA), and birth weight.

Methods. Stereologic estimates of $N_{\text{glom}}$ and $V_{\text{glom}}$ were obtained using the physical dissector/fractionator combination for autopsy kidneys from 37 African Americans and 19 Caucasians.

Results. $N_{\text{glom}}$ was normally distributed and ranged from 227,327 to 1,825,380, an 8.0-fold difference. A direct linear relationship was observed between $N_{\text{glom}}$ and birth weight ($r = 0.423, P = 0.0012$) with a regression coefficient that predicted an increase of 257,426 glomeruli per kilogram increase in birth weight ($\alpha = 0.050; 0.908$). Among adults there was a 4.9-fold range in $V_{\text{glom}}$ and in adults, $V_{\text{glom}}$ was strongly and inversely correlated with $N_{\text{glom}}$ ($r = -0.640, P = 0.000002$). Adult $V_{\text{glom}}$ showed no significant correlation with BSA for males ($r = -0.0150, P = 0.936$), although it did for females ($r = 0.606, P = 0.022$). No racial differences in average $N_{\text{glom}}$ or $V_{\text{glom}}$ were observed.

Conclusion. Birth weight is a strong determinant of $N_{\text{glom}}$ and thereby of glomerular size in the postnatal kidney. The findings support the hypothesis that LBW by impairing nephron development is a risk factor for hypertension and ESRD in adulthood.

In 1988, Brenner, Garcia, and Anderson [1] proposed that there was an inverse relationship between total renal filtration surface area and the risk of hypertension. It was suggested that the reduced filtration surface area of the kidney resulting from an inherited or acquired deficit of glomeruli impairs the normal adjustment of blood pressure by pressure natriuresis. Persons with the reduced number of nephrons, or low “glomerular endowment,” are thought to be susceptible to developing hypertension because pressure natriuresis curves are shifted and an elevation of blood pressure is required to maintain a balance between normal sodium intake and excretion.

The “low glomerular endowment” hypothesis is supported by several experimental and human studies. Unlike most organs in which cell proliferation occurs primarily before the third trimester, 60% of nephrons are formed in the third trimester with the formation stopping in normal pregnancies at 36 weeks’ gestation [2]. Interference with third trimester fetal growth has been shown to affect nephron development. Intrauterine growth retardation (IUGR) produced in rats by uterine artery ligation, maternal dietary protein restriction, or vitamin A deficiency results in a nephron deficit of up to 30% with a 50% reduction in glomerular filtration rate (GFR) [3–6]. Using guinea pigs, Persson and Jansson [7] found that IUGR induced by uterine artery ligation, maternal dietary protein restriction, or vitamin A deficiency results in a nephron deficit of up to 30% with a 50% reduction in glomerular filtration rate (GFR) [3–6]. Using guinea pigs, Persson and Jansson [7] found that IUGR induced by uterine artery ligation was associated with an elevation of blood pressures after the animals matured.

Low birth weight (LBW) has also been shown to influence human kidney development and the later health of adults. Hinchliffe et al [3] applied stereologic techniques to kidneys obtained at autopsy and observed that infants with asymmetric or type II IUGR had a significant reduction in nephron numbers when birth weights were below the third percentile. In English community surveys, Barker et al [8, 9] and Law et al [10] showed that small infant size at birth predicted an increased risk of elevated blood pressure and cardiovascular disease when combined with obesity in adulthood. It was additionally found that LBW predicted a higher systolic blood pressure at all ages past infancy and that the blood pressure differences increased with age [10]. There are racial groups that have rates of cardiovascular and renal
disease that are greatly elevated above that of the general population in the same geographic areas. These include Australian Aborigines, Native Americans, and African Americans, and all of these have a high prevalence of low-weight infant births and adult obesity [11–17].

Hoy et al [14] investigated urinary albumin excretion as a marker for cardiovascular and renal disease risk in the Tiwi Islanders, an Aboriginal group of the Northern Territory of Australia. The Tiwi Islanders have an unusually high prevalence of premature cardiovascular disease deaths and rates of chronic renal failure that are 20 times greater than the non-Aboriginal population of the Northern Territory. An inverse correlation was found between adult urinary albumin creatinine ratios (ACR) and birth weight, and a direct correlation was seen between ACR and adult weight with the effect of increased adult weight being exaggerated when combined with LBW. The average birth weight of the subjects was 2.79 ± 0.5 kg with 42% of births being below the third percentile of normal birth weight for gestational age. In addition, Spencer, Wang, and Hoy [18] demonstrated by ultrasonography that LBW Aboriginal children had lower body surface area (BSA) adjusted renal volumes than children with “normal” birth weight. A renal biopsy study of Tiwi Islanders with clinical renal disease showed glomeruli up to three times the size of those in donor kidney biopsies from white Australians [19, 20]. The glomerulomegaly was thought to be a marker of the unusually high risk of end-stage renal disease (ESRD) in the Tiwi Islanders and perhaps an indication of low nephron number.

In the 1994 Annual Data Report from the US Renal Data System, the African American to Caucasian ratios for ESRD resulting from diabetes, hypertension, and all causes were 3.1, 6.1, and 3.4, respectively [21]. Lopes and Port [15] surveyed birth certificates in Michigan and found that African American rates of LBW were 2.3 times and severe LBW 3.1 times greater than Caucasians, paralleling the increased risk for ESRD. The African American risk for ESRD appears to be particularly increased in the Southeastern United States. In Mississippi, African Americans have an estimated risk of ESRD that is five times greater than whites [22]. Mississippi also has the highest prevalence of obesity and type 2 diabetes in the country and correspondingly high rates of obesity-associated hypertension [16, 17, 23]. An increasing prevalence of obesity and type 2 diabetes is seen throughout the Southeastern United States and undoubtedly contributes to the disproportionately high rates of hypertensive and diabetic ESRD [16].

Because of the racial disparities in risk for ESRD, Mississippi should provide a study population that is ideal for testing the “low glomerular endowment” hypothesis. This study was therefore undertaken to determine whether there are differences in glomerular size and number related to birth weight that may underlie the increased risk of African Americans for ESRD. In addition, the study examined the influence of body size on glomerular volume.

**METHODS**

Kidneys were collected at autopsy at the University of Mississippi Medical Center (Jackson, Mississippi) from persons without hereditary or congenitally deforming disease and without known renal disease, including diabetic nephropathy. Both kidneys were examined and weighed on an electric balance. If both kidneys were grossly normal and equal or approximately equal in size, the right kidney was perfusion fixed with 10% buffered formalin. Kidneys showing arteriolar nephrosclerosis were included in the study if the subcapsular cortex was only slightly granular. Kidneys were not used if there were coarse pits or any angular or depressed cortical scars. Kidneys were excluded from the study if they microscopically showed evidence of a primary glomerular or tubulointerstitial disease. After perfusion, the kidneys were bisected and immersed in 10% formalin. After 10 days, both halves of the kidney were cut into slices 4 mm thick and every fourth slice of both halves was sampled for stereology beginning with a first slice selected as a random number between 1 and 4. The selected slices were sent to Monash University where they were processed for embedding in glycolmethacrylate for the stereologic estimation of total glomerular number (N^glom^), mean glomerular tuft volume (V^glom^), and mean renal corpuscle volume (V^corp^) using the physical disector/fractionator combination. Total glomerular volume (V^glom^Total^) was calculated as the product of N^glom^ and V^glom^ and total renal corpusscular volume (V^corp^Total^) as the product of N^glom^ and V^corp^.

These methods have been previously described in detail [24–26]. The length of the body was measured and body weight was obtained with a full body scale or from the medical records. BSA was calculated using an Internet Web site (//www.ultradrive.com/bsac.htm).

Representative kidney blocks from upper pole and the midportion of the kidney not sampled for stereology were paraffin embedded. These blocks were cut perpendicular to the cortical surface and contained the full thickness of the cortex and the underlying medulla. Sections were cut 4 μm in thickness, stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS)-hematoxylin, and Masson’s trichrome stains, and examined for renal disease and glomerular obsolescence. The presence and percentage of obsolete glomeruli were determined using PAS-hematoxylin–stained sections. The pattern of obsolescence was classified as ischemic when there was tuft collapse and intracapsular fibrosis and as glomerular solidification resulting from a glomerulopathic disease when there was mesangial expansion, adhesions of the glomerular tuft to Bowman’s capsule, disruption of the
basement membrane of Bowman’s capsule, and pseudodtubule formation [27].

The severity of intrarenal arteriosclerosis was analyzed using the method described by Tracy et al [28–30]. Using PAS-hematoxylin–stained sections, light microscopic fields containing consecutively encountered arteries were captured by digital camera at 100× and 400× and imported as 21.6 cm × 16.25 cm images with Adobe Photoshop 5.5™ into a computer using Scion Image Microscopy System™ software. A 1 mm micrometer scaled at 5 μm was incorporated into the program, and intimal thickening (I) of intrarenal arteries was measured and expressed as a ratio of the thickness of the intima (T) to the outer arterial diameter (OD): I = T/OD. The measurements were divided into those obtained on close arteries 150 to 300 μm in diameter (distal arcuate and proximal interlobular arteries) and remote arteries 80 to 149 μm in diameter (middle and distal interlobular arteries). The elliptic and circular diameters of the arteries were measured. The OD was the least axis of the vessel profile measured at 100× from the outer media of one side of the artery to the outer media of the other side. The thickness of the intima (T) was measured at 400× in the same vessel profile on the same axis as the OD.

The degree of cortical fibrosis was analyzed using Masson trichrome–stained sections. For adults, the cortex was four to five 100× microscopic fields thick, and 16 to 20 images were taken at consecutive, nonoverlapping 100× microscopic fields of subcapsular to juxtamedullary renal cortex over four consecutive, nonoverlapping areas moving laterally along the subcapsular surface. Using Adobe Photoshop 5.5™, the 21.6 cm × 16.25 cm images were imported into a computer with a 64-point counting grid overlay. Cortical fibrosis was measured as the proportion of the number of points overlying blue-stained interstitial tissue divided by the number of points on the grid overlaying nonglomerular and nonvascular cortex.

The decedent’s full name, name of the mother and father, the date of birth, and place of birth were obtained from death certificates. Using this information, birth weights were obtained from the Public Health Statistics Division of the Mississippi State Department of Health. Birth weights on four persons born in Alabama and one person born in Pennsylvania were obtained from the Alabama and Pennsylvania State Departments of Health Statistics. There were 56 cases for which Nglomer and Vglomer had been estimated and on which birth weights were obtained. This consisted of 37 African Americans (21 males and 16 females) and 19 Caucasians (15 males and 4 females) of whom 45 were adults (≥18 years) and 11 were infants and children (five males and six females), including two teenagers at 16 and 17 years old. A detailed obstetric history was available on all infants and children. Infants were used in the data analysis only if they died after a gestational age of 40 weeks. No premature deaths were used in which kidneys had mesenchymal condensates with ongoing nephrogenesis.

The data were collected into Microsoft Excel 97™ and analyzed with SigmaStat™ and SigmaPlot™ software (Jandel, San Rafael, CA, USA). Vcorp and Vglomer were tightly correlated (r = 0.986), so Vglomer and VglomerTotal were the only glomerular size estimates used for data analysis. Gender and race were assigned numerical values (African Americans = 1, Caucasians = 2; male = 1, female = 2), and the relationships between age, gender, race, Nglomer, Vglomer, VglomerTotal, BSA, the percentage of obsolete glomeruli, the proportion of cortical fibrosis, arterial intimal thickening, and birth weight were analyzed using Pearson’s product moment correlation. For relationships that appeared linear, normally distributed, and statistically significant, linear regression was used to predict the changes of one variable in relationship to another. For adults, multiple linear regression was used to investigate the relative influence of age, race, BSA, glomerular obsolescence, cortical fibrosis, arterial intimal thickening, and Nglomer upon Vglomer. Also for adults, adjustment by covariance using multiple linear regression for birth weight and cortical fibrosis was performed to evaluate the independent ability of these variables to predict Nglomer. Differences between groups were analyzed using a t test if data passed normality and equal variance tests and by a Mann-Whitney rank sum test if they did not. In all instances a P value less than 0.05 was considered significant.

RESULTS

Table 1 summarizes for African Americans and Caucasians and males and females the age, Nglomer and birth weights among all cases and Vglomer for adults. No statistically significant racial or gender differences were seen in average Nglomer or adult Vglomer. The causes of death in the 56 cases was as follows: 18 from coronary artery disease (CAD); two from cerebrovascular disease (CVD); five from a pulmonary embolus; 10 homicide victims; eight from accident; two from hemologic/neoplastic conditions; three perinatal deaths; two from neurologic disorders (not CVD); two from cardiovascular events (not CAD); a 3-year-old child with diabetic ketoacidosis; and one each from sudden infant death syndrome, acquired immune deficiency syndrome (AIDS), and chronic lung disease. Among the children, a 1½-year-old African American male accident victim was born at 36 weeks’ gestation with a birth weight of 2.18 kg. In this case, the birth weight was just above the 10th percentile for gestational age [31, 32]. Three of the adult cases had birth weights greater than 4.00 kg, which are at the 90th percentile for a 40-week gestation [31, 32].
Glomerular obsolescence, cortical fibrosis, arteriolosclerosis, \( N_{\text{glom}} \) and \( V_{\text{glom}} \)

Some obsolete glomeruli were seen at all ages. Among infants this was due to congenital glomerulosclerosis in which there was an accumulation of acellular hyaline, eosinophilic and PAS-positive material within the glomerular tufts (Fig. 1). Congenital glomerulosclerosis was seen in six of eight infants up to 1.8 years old and averaged 1.3 ± 1.5% of glomeruli. No statistically significant relationship was found between the percentage of glomeruli involved by congenital glomerulosclerosis and \( N_{\text{glom}} \) \( (r = 0.245, P = 0.474) \) or birth weight \( (r = 0.115, P = 0.736) \). The kidneys of a 3-year-old child revealed rare glomeruli that had a pattern of obsolescence that resembled congenital glomerulosclerosis (Fig. 2). Glomerulosclerosis was not seen in a 16-, 17-, or 18-year-old adolescent, but ischemic obsolescence involved 0.19% of glomeruli of a 19-year-old patient.

Among adults, the percentage of obsolete glomeruli was low averaging 0.36% ± 0.58% between ages 18 to 29 years, 1.17% ± 1.48% between ages 30 to 39 years, and 3.03% ± 2.56% between age 40 years to the oldest person studied at age 50 years. The pattern of glomerular loss was ischemic obsolescence (Fig. 3) in all cases. The greatest degree of glomerulosclerosis was seen in a 42-year-old Caucasian female who died of coronary artery disease and had 8.63% obsolete glomeruli. Five persons had more than 5% glomerulosclerosis. Four were over 40 years old and one was 39 years old. Three of these five persons died of coronary artery or cerebrovascular disease, and two died accidental deaths.

We do not have a detailed blood pressure history on most of our subjects, but Tracy et al [28–30] have shown a close relationship between blood pressure and arteriosclerosis measured as the intimal thickening (I) of the arcuate and interlobular arteries of the kidney. The correlation between I, of the close and remote renal arteries was strong \( (r = 0.745, P < 0.000001) \), and to simplify the presentation of data, I, of close arteries alone was used as a surrogate for hypertension. For adults, no statistically significant correlation was seen between age, race, gender, BSA, I, of close arteries, and \( N_{\text{glom}} \) or \( V_{\text{glom}} \) (Table 2). The I, of close arteries, glomerular obsolescence, and cortical fibrosis were closely related to each other and to age. While the relationship between cortical fibrosis and glomerular obsolescence is highly significant, the correlation coefficient \( (r = 0.628) \) indicates that cortical fibrosis can be present without having a proportional number of sclerotic glomeruli. This probably reflects the disappearance of identifiable obsolete glomeruli from the kidney.

Cortical fibrosis has a correlation with \( N_{\text{glom}} \) and \( V_{\text{glom}} \) that is weak but is much stronger than the relationship between the percentage of obsolete glomeruli and \( N_{\text{glom}} \) and \( V_{\text{glom}} \). The relationship between cortical fibrosis and \( N_{\text{glom}} \) and \( V_{\text{glom}} \) is greatest for \( N_{\text{glom}} \) where the correlation coefficient, showing a decrease in \( N_{\text{glom}} \) with increasing cortical fibrosis \( (r = -0.258, P = 0.0873) \), approaches but does not achieve statistical significance. Among adults, there is a statistically significant correlation between gender and BSA and gender and birth weight with females having significantly lower birth weights and BSA than males. While among all adults, a significant relationship cannot be seen between BSA and \( V_{\text{glom}} \), gender differences may be present in the relationships between birth weight and \( N_{\text{glom}} \) and BSA and \( V_{\text{glom}} \).

Glomerular number \( (N_{\text{glom}}) \) and birth weight

There was an 8.0-fold variation in \( N_{\text{glom}} \) (Table 1) ranging from the lowest number in the 1\( \frac{1}{2} \)-year-old African American male noted above at 227,327 to a 20-year-old African American male who had the highest number at 1,825,380. Females had on average approximately 9% fewer glomeruli than males, but the difference was not statistically significant. The range in \( N_{\text{glom}} \) and birth weight for African Americans was greater than for Caucasians. Four persons, all African Americans, had birth weights under 2.5 kg, and four of six persons that had birth weights over 3.8 kg were African Americans. The average male birth weight was significantly heavier than that of females, and the range in male birth weight was greater than for females.

Among all cases, a significant direct correlation was

---

Table 1. Summary for African Americans and Caucasians and males and females of age, gender, birth weight, and total glomerular number \( (N_{\text{glom}}) \) for all cases and mean glomerular volume \( (V_{\text{glom}} \mu m^3 \times 10^3) \) for adults

<table>
<thead>
<tr>
<th>Age *</th>
<th>Birth weight</th>
<th>Range birth weight</th>
<th>( N_{\text{glom}} )</th>
<th>Range ( N_{\text{glom}} )</th>
<th>( V_{\text{glom}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Americans</td>
<td>29.2 ± 14.2</td>
<td>3.19 ± 0.58</td>
<td>2.61</td>
<td>959,306 ± 328,602</td>
<td>1,572,272</td>
</tr>
<tr>
<td>Caucasians</td>
<td>28.7 ± 17.7</td>
<td>3.34 ± 0.36</td>
<td>1.47</td>
<td>869,959 ± 256,006</td>
<td>1,193,044</td>
</tr>
<tr>
<td>Males</td>
<td>30.4 ± 14.2</td>
<td>3.36 ± 0.48</td>
<td>2.59</td>
<td>959,177 ± 340,658</td>
<td>1,598,053</td>
</tr>
<tr>
<td>Females</td>
<td>26.6 ± 17.2</td>
<td>3.05 ± 0.53</td>
<td>1.81</td>
<td>874,657 ± 262,210</td>
<td>938,100</td>
</tr>
</tbody>
</table>

The values for age, birth weight, \( N_{\text{glom}} \) and \( V_{\text{glom}} \) are mean ± standard deviation.

---

*Among African American subjects there were 21 males, 16 females, 31 adults, and 6 children or infants. Among Caucasians there were 15 males, 4 females, 14 adults, and 5 infants and children. The differences between African Americans and Caucasians for age, birth weight, \( N_{\text{glom}} \) and \( V_{\text{glom}} \) (adults) are not statistically significant. The differences between males and females for age, \( N_{\text{glom}} \) and \( V_{\text{glom}} \) (adults) are not statistically significant.

# The difference between males and females for birth weight is statistically significant, \( P = 0.020 \)
Fig. 1. Congenital glomerulosclerosis in an infant kidney. There is a segmental accumulation of acellular hyaline material within the glomerular tuft. Periodic acid-Schiff (PAS) stain, original magnification x400.

Fig. 2. Glomerular obsolescence in the kidney of a 3-year-old child. An accumulation of hyaline material in a collapsing glomerular segment resembles congenital glomerulosclerosis. Periodic acid-Schiff (PAS) stains, original magnification x400.

Fig. 3. Ischemic glomerular obsolescence in a 41-year-old patient. The glomerular tuft consists of a small hyaline knot surrounded by acellular connective tissue within an intact basement membrane of Bowman’s capsule. Periodic acid-Schiff (PAS) stain, original magnification x400.

The correlation between Nglom and birth weight was strongest for infants and children under 18 years of age (Fig. 5) when they were analyzed separately from adults (r = 0.773, P = 0.0053, N = 11, α = 0.050:0.828). For adults alone, the correlation weakened but remained statistically significant using Nglom unadjusted for cortical fibrosis (r = 0.355, P = 0.0168, N = 45, α = 0.05:0.671). For these adults, using birth weight and cortical fibrosis as covariates, multiple linear regression shows that both birth weight and cortical fibrosis as independent variables contribute to Nglom (r = 0.470, birth weight P = 0.006, cortical fibrosis P = 0.028). The regression predicts a gain of 229,112 glomeruli per kg increase in birth weight and a loss of 160,064 glomeruli per 0.10 increase in cortical fibrosis (α = 0.05:0.911).

Glomerular number (N_{glom}) and glomerular tuft volume (V_{glom})

V_{glom} increased markedly with age and body growth into early adult life with a powerful direct correlation between V_{glom} and BSA among the entire population of 56 cases (r = 0.667, P < 0.00001). Among adults alone, a relationship between V_{glom} and BSA was not apparent (r = 0.0944, P = 0.538). Among adults, there was a 4.9-fold variation in V_{glom}, and V_{glom} showed a significant, statistically significant for males (r = 0.469, P = 0.0039, N = 36) with a regression coefficient that predicted a gain of 333,340 glomeruli per kg increase in birth weight (α = 0.05:0.832). For females the correlation coefficient was weak (r = 0.288, N = 20) and was not statistically significant (P = 0.218), although the power of the test (α = 0.05:0.230) was well below a level that would allow a relationship to be excluded.

The correlation between N_{glom} and birth weight was strongest for infants and children under 18 years of age (Fig. 5) when they were analyzed separately from adults (r = 0.773, P = 0.0053, N = 11, α = 0.050:0.828). For adults alone, the correlation weakened but remained statistically significant using N_{glom} unadjusted for cortical fibrosis (r = 0.355, P = 0.0168, N = 45, α = 0.05:0.671). For these adults, using birth weight and cortical fibrosis as covariates, multiple linear regression shows that both birth weight and cortical fibrosis as independent variables contribute to N_{glom} (r = 0.470, birth weight P = 0.006, cortical fibrosis P = 0.028). The regression predicts a gain of 229,112 glomeruli per kg increase in birth weight and a loss of 160,064 glomeruli per 0.10 increase in cortical fibrosis (α = 0.05:0.911).
Table 2. For 45 adults, Pearson product moment correlation between age, race, gender, body surface area (BSA), N\textsubscript{glomeruli}, V\textsubscript{glomerulus}, birth weight, percent obsolete glomeruli (%GS), proportion of cortical fibrosis (CF), and thickening of distal arcuate, and proximal interlobular renal arteries (I\textsubscript{c}).

<table>
<thead>
<tr>
<th>Race</th>
<th>Gender</th>
<th>BSA</th>
<th>N\textsubscript{glomeruli}</th>
<th>V\textsubscript{glomerulus}</th>
<th>Birth weight</th>
<th>%GS</th>
<th>CF</th>
<th>I\textsubscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.188</td>
<td>0.0876</td>
<td>0.146</td>
<td>–0.184</td>
<td>0.0944</td>
<td>0.237</td>
<td>0.527</td>
<td>0.563</td>
</tr>
<tr>
<td>Race</td>
<td>0.216</td>
<td>0.567</td>
<td>0.339</td>
<td>0.227</td>
<td>0.538</td>
<td>0.117</td>
<td>0.0002</td>
<td>0.00006</td>
</tr>
<tr>
<td>Gender</td>
<td>–0.141</td>
<td>0.196</td>
<td>–0.122</td>
<td>–0.089</td>
<td>0.127</td>
<td>0.138</td>
<td>0.133</td>
<td>–0.622</td>
</tr>
<tr>
<td>BSA</td>
<td>0.357</td>
<td>0.197</td>
<td>0.425</td>
<td>0.701</td>
<td>0.405</td>
<td>0.365</td>
<td>0.384</td>
<td>0.685</td>
</tr>
<tr>
<td>%GS</td>
<td>–0.351</td>
<td>0.0181</td>
<td>–0.156</td>
<td>–0.106</td>
<td>–0.373</td>
<td>0.0477</td>
<td>0.0447</td>
<td>0.0637</td>
</tr>
<tr>
<td>CF</td>
<td>0.0449</td>
<td>0.166</td>
<td>0.282</td>
<td>–0.0661</td>
<td>0.117</td>
<td>–0.0327</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I\textsubscript{c}</td>
<td>0.770</td>
<td>0.276</td>
<td>0.0603</td>
<td>0.666</td>
<td>0.445</td>
<td>0.831</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Within the cells the upper numbers are correlation coefficients and the lower numbers P values. The pairs of variables with positive correlation coefficients and P values below 0.05 tend to increase together. For pairs of variables with negative correlation coefficients and P values below 0.05, one variable tends to decrease while the other increases. For pairs with P values greater than 0.05, there is no significant relationship between the two variables. The variables having a statistically significant relationship are bolded.

Fig. 4. The relationship between birth weight and total glomerular number among all cases that includes infants, children, and adults. Symbols are (●) N\textsubscript{glomeruli} vs. birth weight; (––) N\textsubscript{glomeruli} vs. birth weight regression; (––) 95% regression CI; (…) regression prediction interval. The regression coefficient predicts a gain of 257,426 glomeruli per kg increase in birth weight, \( r = 0.423, P = 0.0012, N = 56 \).

Fig. 5. Relationship between birth weight and total glomerular number (N\textsubscript{glomeruli}) for infants, children, and teenagers under 18 years old. Symbols are (●) N\textsubscript{glomeruli} vs. birth weight; (––) N\textsubscript{glomeruli} vs birth weight regression; (––) 95% regression CI; (…) regression prediction interval. The regression coefficient predicts a gain of 518,038 glomeruli per kg increase in birth weight, \( r = 0.773, P = 0.0053, N = 11 \).

strong inverse correlation with glomerular number \( r = –0.640, P < 0.00001, \alpha = 0.05:1.000 \) (Fig. 6). Among all adults, multiple linear regression using V\textsubscript{glomerulus} as the dependent variable and age, race, BSA, N\textsubscript{glomeruli}, percent obsolete glomeruli, cortical fibrosis, and I\textsubscript{c} of close arteries as independent variables showed that N\textsubscript{glomeruli} was the only factor that significantly predicted V\textsubscript{glomerulus} \( r = 0.700, P < 0.001, \alpha = 0.05:1.000 \). However, the analysis of adult females alone demonstrated a direct correlation between BSA and V\textsubscript{glomerulus} \( r = 0.606, P = 0.0217, N = 14, \alpha = 0.05:0.644 \) as well as a strong inverse correlation between N\textsubscript{glomeruli} and V\textsubscript{glomerulus} \( r = –0.612, P = 0.0199, N = 14, \alpha = 0.05:0.657 \). Among adult males, no relationship was found between V\textsubscript{glomerulus} and BSA \( r = –0.0150, P = 0.936, N = 31 \), but the power of the test was very low \( \alpha = 0.05:0.03 \).

Table 3 shows the average V\textsubscript{glomerulus} and V\textsubscript{glomerulusTotal} for adults in the lowest (1 to 33rd), the middle (34th to 65th), and the highest (66th to 100th) percentiles of N\textsubscript{glomeruli}. V\textsubscript{glomerulus} and V\textsubscript{glomerulusTotal} decreased for each increase in N\textsubscript{glomeruli} with the differences in V\textsubscript{glomerulus} and V\textsubscript{glomerulusTotal} between the lowest and highest percentiles of N\textsubscript{glomeruli} being statistically significant.
Hughson et al: Glomerular number and birth weight

The data also show that the larger glomerular size associated with low number only partly compensated for low Nglomer, and that for kidneys below the 34th percentile of Nglomer, the filtering volume or Vglomer remained low.

**DISCUSSION**

This study demonstrated a direct relationship between total glomerular number (Nglomer) and birth weight in adult and fully developed postnatal kidneys of children. The relationship was linear and spanned an entire range of birth weights from the 10th to the 90th percentile for gestational age. The study further showed that mean glomerular volume (Vglomer) was inversely related to Nglomer with low Nglomer, predicting a large Vglomer. While this increase in glomerular volume to a degree compensated for a decreased Nglomer in the lowest third of Nglomer, the glomerular filtration surface area (FSA), which we estimate as total glomerular volume (VglomerTotal), remained low. The findings support the “Brenner hypothesis” that proposes that low Nglomer, because it reduces FSA, may be an underlying factor in the development of essential hypertension [1]. Because of the reduction in FSA, the larger glomeruli of persons at the lower end of Nglomer would be subjected to increased single nephron filtration rates, thereby increasing the risk of progressive hyperperfusion injury and ESRD as blood pressure rises.

It has been anticipated from experimental studies that intrauterine growth retardation would impair nephron development in humans. This has, in fact, been shown in autopsies of intrauterine fetal deaths and in infants dying after delivery in the first few weeks of life [3, 6, 33, 34]. Although the technical approaches to estimating Nglomer were different, the results of these studies were remarkably similar and demonstrated that infants either dying or being born at weights that were low for gestational age have lower than the average number of glomeruli. Hinchliffe et al [3] by means of the stereologic dissector/Cavalieri stereologic method examined kidneys in six nonmacerated stillbirths with severe IUGR and eight liveborn infants with IUGR dying within 25 weeks of birth. The latter was designated the postnatal group. In both groups, birth weights were below the 10th percentile, and their Nglomer was compared with that of stillbirths or liveborn infants of comparable age whose weights were above the 10th percentile. Nglomer estimates were below the 5th percentile prediction limits in five of the six growth-retarded stillbirths and were 65% of the control mean in the IUGR postnatal group.

Merlet-Benichou et al [6, 33] used the acid-maceration method to count glomeruli in the kidneys of 24 full-term infants that died in utero or within 6 months of birth. A direct linear relationship was found between Nglomer and birth weight. Infants below the 10th percentile of birth weight had an average of 30% fewer glomeruli than infants with birth weights above the 10th percentile. A direct linear relationship between birth weight and glomerular profile density as a measure of Nglomer was also observed by Manalich et al [34] in 35 neonates who died within 2 weeks of birth. Eighteen of the infants had birth weights less than 2.5 kg. In the studies of Merlet-Benichou et al [33] and Manalich et al [34], the correlation coefficients between birth weight and Nglomer (r = 0.772, P < 0.001 and r = 0.870, P < 0.0001) were essentially the same as the correlation coefficient obtained in our study (r = 0.773, P = 0.0053) using data from autopsies on a postnatal group of children 1 week to 17 years old. Our study extended the range of age into adulthood where the correlation remained statistically significant.

In several community studies, LBW has been associated with elevated blood pressure after infancy and with elevated blood pressure and cardiovascular disease in adults. In 1989, Barker et al [35] reported an analysis of the records of persons born in Hertfordshire, England

---

**Table 3.** A comparison of mean glomerular volume (Vglomer, μm³ × 10⁶) and total glomerular volume (VglomerTotal, cm³) among 45 adults (≥18 years old) in the lowest, the middle, and highest third of percentiles of glomerular number (Nglomer)

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Cases</th>
<th>Nglomer</th>
<th>Vglomer</th>
<th>VglomerTotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>To 33th</td>
<td>15</td>
<td>227,327–816,683</td>
<td>9.07 ± 3.11</td>
<td>5.36 ± 1.04</td>
</tr>
<tr>
<td>34th to 65th</td>
<td>14</td>
<td>825,105–1,158,995</td>
<td>7.66 ± 2.62</td>
<td>7.40 ± 2.62</td>
</tr>
<tr>
<td>66th to 100th</td>
<td>16</td>
<td>1,162,345–1,825,380</td>
<td>6.01 ± 1.50</td>
<td>7.57 ± 1.58</td>
</tr>
</tbody>
</table>

The values for Nglomer are total glomerular estimates in the right kidney. For Vglomer and VglomerTotal, the values are mean ± standard deviation.

---

---

**Fig. 6.** Relationship between total glomerular number (Nglomer) and mean glomerular volume (Vglomer) in adults. (●) Nglomer vs Vglomer; (—) 95% regression CI, (——) regression prediction interval, r = −0.640, P < 0.00001, N = 45.
between 1911 and 1930 in which birth weight, weight at 1 year of age, and body mass index (BMI kg/m²) and blood pressure between the ages of 59 to 71 years were recorded. Blood pressure was directly correlated with BMI, and at an average age of 64, men and women within each of four quartiles of BMI had higher systolic blood pressures if they had lower weights at birth. In the male Hertfordshire cohort, death rates from cardiovascular disease were three times higher for persons whose weight at 1 year of age was less than 8.2 kg than for persons who weighed more than 12.3 kg.

Law et al [10] reviewed the data from Hertfordshire; the Brompton study of blood pressure recorded at 4 days, 6 weeks, 6 months, 1 year, and annually until 10 years of age; the Medical Research Council’s national survey of health and development cohort of men and women born in Britain in one week in March of 1946 who had blood pressure measured at 36 years of age; and the Preston records of pregnancy and delivery with blood pressures taken at age 50 years. This consisted of 6825 subjects, all of whom had birth weights recorded. Systolic blood pressure was elevated at all ages past infancy in persons with lower birth weights. The blood pressure difference increased progressively with age, and at 64 to 71 years, systolic blood pressure was 5.2 mm Hg lower for every kg increase in birth weight after adjusting for adult BMI.

These findings show a perinatal influence on blood pressure that was further demonstrated by Levine, Hennekens, and Jesse [36] who examined the relationship between blood pressure, birth weight, and weight gain from birth to 1 year of age in twins. There was an increase in systolic and diastolic blood pressure with increasing body weight throughout the 1-year period. LBW twins had lower blood pressures at birth and showed a more rapid increase in blood pressure than twins weighing more than 3.0 kg. The rapidity of this increase in blood pressure was greater than could be attributed to weight gain alone. Among monozygotic twin pairs there was a significant negative correlation between differences in birth weight and differences in systolic blood pressure at 1 year. The findings implied that blood pressure in infancy was strongly determined by the intrauterine environment even in genetically identical individuals.

On the basis of the published relationships between LBW and elevated blood pressure and LBW and reduced glomerular number, Brenner, Garcia, and Anderson [1] proposed that adult essential hypertension was caused by a nephron deficit acquired in utero. It was further considered that the hypertension was due to a decreased FSA in kidneys with a reduced number of nephrons. A sizable proportion of individuals with high blood pressure have low renin, salt-sensitive hypertension that becomes clinically apparent in midlife and worsens with age [1, 37–39]. It is hypothesized that a reduction in FSA produces salt-sensitive hypertension by shifting pressure natriuresis toward a higher blood pressure in order to maintain normal rates of sodium excretion and a stable blood volume. Physiologic experiments have shown that a decreased glomerular filtration coefficient and loss of nephrons decreases the slope of pressure natriuresis and that small decreases in renal perfusion markedly lower sodium excretion in both acute and chronic conditions [39].

In the human kidney, this alteration of pressure natriuresis may be amplified with age as increasing numbers of glomeruli become structurally and functionally obsolete. The number of sclerotic, obsolete glomeruli in otherwise normal kidneys becomes prominent at about age 40 years and progressively increases with later aging [40]. Among adults in this study, we did not find any statistically significant relationship between glomerular size and age, the percentage of obsolete glomeruli, or the severity of cortical fibrosis. But rather, we found that the main determinant of glomerular size was N_{glom} in which there was a powerful inverse relationship between glomerular size and number that implied an adaptive process, whereby glomerular size increased to compensate for innately low nephron number.

The larger glomerular size found with low N_{glom} creates a situation that may increase the susceptibility of the glomerulus to scarring. Glomerulomegaly is suggested to be a marker of an increased risk of groups of patients or populations for progressive renal disease. An increased glomerular size compared to whites has been seen in Native Americans, African Americans, and Australian Aborigines in regions of the United States and Australia where they have rates of ESRD several times that of the general population [41–44]. In the condition of oligomeganephronia, children are born with a markedly reduced number of nephrons and have very large glomeruli. As a result of progressive glomerulosclerosis, renal function steadily deteriorates into ESRD by the mid-teens [45]. In childhood nephrotic syndrome, Fogo et al [46] identified larger glomerular size as a feature that discriminated focal segmental glomerulosclerosis from minimal change disease even before segmental sclerosis could be found.

The increased single nephron filtration rates in kidneys with low N_{glom} may produce an elevated transcapillary pressure that stretches and promotes scarring of abnormally enlarged glomeruli [47, 48]. Hypertension is a frequent complication of obesity, and with obesity renal blood flow and GFR are elevated [48–50]. The increased renal blood flow associated with obesity may add to glomerular stress that might already be present in kidneys with low nephron numbers and further augment glomerular scarring. Although a significant correlation was not seen between BSA and V_{glom} among all adults or adult males, we did find such a relationship for adult
females in which there was a significant direct correlation between \( V_{\text{glomeruli}} \) and BSA (body surface area) that was independent of the inverse relationship between \( N_{\text{glomeruli}} \) and \( V_{\text{glomeruli}} \). Obesity has been associated with increased glomerular size in other human studies \([51, 52]\). The power of the test that suggested an absence of a correlation between body size and \( V_{\text{glomeruli}} \) in males was very low, and the discrimination of gender differences in this relationship will require an analysis of many more cases.

Nephron number is undoubtedly genetically determined, but there is a growing body of evidence that \( N_{\text{glomeruli}} \) is additionally influenced by social and behavioral factors that affect the intrauterine environment. We have not seen any racial differences in average \( N_{\text{glomeruli}} \) or \( V_{\text{glomeruli}} \). African Americans had a somewhat greater range of \( N_{\text{glomeruli}} \), but they also had a greater range of birth weights than Caucasians. This may mean that in this sample of subjects, there are no substantive genetic differences between African Americans and Caucasians for the determination of \( N_{\text{glomeruli}} \) and that the risk in either race of having low numbers of glomeruli is influenced more by gestational factors.

A notable point about the relationship between birth weight and \( N_{\text{glomeruli}} \) was that the correlation weakened when adults were analyzed separately from infants and children. A part of this difference was probably the result of the loss and under count of glomeruli due to age-related glomerular obsolescence and cortical fibrosis. The correlation between \( N_{\text{glomeruli}} \) and birth weight for adults strengthened when \( N_{\text{glomeruli}} \) was adjusted for glomerular loss associated with cortical fibrosis. The weakened correlation, however, is probably more reflective of the larger number of adult cases analyzed. Among the adults there was a much larger range of \( N_{\text{glomeruli}} \) at all levels of birth weight than was present in infants and children. Very few of either the children (1 of 11) or adults (3 of 45) had birth weights in the moderate LBW range of 1.5 to 2.5 kg. It is this range of birth weights that is proposed to lead to low glomerular endowment-associated hypertension \([3, 9, 33]\). The LBW child had very low glomerular numbers; whereas one of the adults had over a million glomeruli and the other two had over 800,000. We did not have the detailed obstetric histories on the adults that we had on infants and children. The LBW child's birth weight was just above the 10th percentile for gestational age. In the adults, we did not know if births were preterm or how birth weights were related to length of gestation. Although prematurity and intrauterine growth retardation usually occur together, that is not always the case, and Barker and Martyn \([9]\) emphasize that it is intrauterine growth retardation and not prematurity that has been associated with elevated blood pressure.

The substantial variation of adult \( N_{\text{glomeruli}} \) in the lower range of birth weights may indicate that the developing kidney has considerable reserve in its ability to overcome an adverse uterine environment. The extent of that reserve and its consequences for adult health will be important to understand. The implications of an absence of racial differences in average \( N_{\text{glomeruli}} \) and the association of low \( N_{\text{glomeruli}} \) with LBW are obvious. If low \( N_{\text{glomeruli}} \) is a risk factor for hypertension, rates of adult hypertension and its attendant risks of cardiovascular and chronic renal disease should be amenable to intervention that emphasizes prenatal care and reducing the prevalence of LBW deliveries.

Our stereologic studies are ongoing and include Australian Aborigines and Australian Caucasians. As more cases are analyzed, racial differences may be found at the extremes of glomerular size and number that are not now apparent. Although the total numbers of persons entering ESRD programs with a diagnosis of hypertension are large, they represent a small fraction of the entire hypertensive population at risk \([53]\). The identification of differences in renal structure related to that risk may not be found in averages but in changes that are notably deviant from average.

**ACKNOWLEDGMENTS**

This research was funded by grants from the National Health and Medical Research Council of Australia, from Janssen-Cilag Australia Pty., Ltd., from Kidney Care, Inc. Foundation, and from the American Heart Association (Southeastern affiliate).

Reprint requests to Michael D. Hughson, M.D., Department of Pathology, University of Mississippi Medical Center, 2500 North State Street, Jackson, Mississippi 39216-4505.

E-mail: mhughson@pathology.umsmed.edu

**REFERENCES**