Human Nephrogenesis and Nephron Endowment at Birth

Nephrogenesis begins in week 9 of human gestation, and ends at approx. week 36.

Nephron endowment is set shortly before term birth, and therefore any deficit is permanent.

Strong correlation between increased birth weight and increased nephron number in adults – 230,000 more nephrons/kg birth weight (Hughson et al. Kidney Int 2003).

Children born preterm or small for gestational age have low nephron endowment and increased risk for adult hypertension and CKD (Rodriguez et al. Ped Nephrol 2005; Abitbol and Rodriguez Nat Revs Nephrol 2012).

Nephron endowment in children and nephron number in adults varies widely.

4.5-fold range in nephron number in 15 children <3mo
Nephron Number in Adults = Nephron Endowment Minus Nephron Loss

<25 studies, mostly small samples, all require biopsy/autopsy tissue

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Clinical Kidney Disease Present</th>
<th>Technique</th>
<th>Mean Nephron No. per Kidney</th>
<th>Sample Size</th>
<th>Clinical Characteristics Associated with Low Nephron Number</th>
<th>Year of Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsy series</td>
<td></td>
<td>Acid maceration</td>
<td>908,333</td>
<td>18</td>
<td>Age</td>
<td>1973^43</td>
</tr>
<tr>
<td>Traumatic accidents</td>
<td>no</td>
<td>Acid maceration</td>
<td>1,309,280</td>
<td>32</td>
<td>Age</td>
<td>1977^44</td>
</tr>
<tr>
<td>Autopsy cases</td>
<td>no</td>
<td>Acid maceration</td>
<td>1,107,000</td>
<td>28</td>
<td>Low birth weight, low vitamin A levels</td>
<td>1999^21</td>
</tr>
<tr>
<td>Autopsy of full term infants</td>
<td></td>
<td>Acid maceration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy cases</td>
<td>no</td>
<td>Disector/fractionator</td>
<td>617,000</td>
<td>37</td>
<td>Age</td>
<td>1992^6</td>
</tr>
<tr>
<td>Traumatic accidents</td>
<td>yes</td>
<td>Disector/fractionator</td>
<td>702,379</td>
<td>10</td>
<td>Hypertension</td>
<td>2003^8</td>
</tr>
<tr>
<td>Autopsy cases</td>
<td>no</td>
<td>Disector/fractionator</td>
<td>1,429,200</td>
<td>10</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Autopsy cases</td>
<td>no</td>
<td>Disector/fractionator</td>
<td>992,353</td>
<td>39</td>
<td>N/A</td>
<td>2010^11</td>
</tr>
<tr>
<td>Autopsy cases</td>
<td>no</td>
<td>Disector/fractionator</td>
<td>901,902</td>
<td>420</td>
<td>Age, low birth weight, short height, Australian Aboriginal race, hypertension</td>
<td>2010^22</td>
</tr>
</tbody>
</table>

| Autopsy cases Living patients        |                                 | MRI with cationized ferritin | 1,236,667                  | 3           | N/A                                                        | 2014^38             |
| Stable renal transplants             | some                            | MRI and protocol biopsy (Weibel–Gomez model) | 730,000                  | 39          | Age, low GFR                                              | 2003^18             |
| Older and younger kidney donors      | no                              | Whole-kidney $K_t$         | 631,500                    | 34          | Age, low GFR                                              | 2010^15             |
| Healthy kidney donors                | no                              | Whole-kidney $K_t$         | 641,730                    | 19          | Age                                                        | 2015^16             |
| Normotensive and hypertensive kidney donors | no                            | Whole-kidney $K_t$         | 605,592                    | 51          | Age, hypertension                                          | 2015^17             |
| Healthy kidney donors                | no                              | Renal CT angiogram and implantation biopsy (Weibel–Gomez model) | 873,696                  | 1638        | Age^* female sex, short height^* family history of ESRD^* high serum uric acid^* and low GFR^* | This study |

^*Characteristic was an independent predictors of low nephron number in the study.

Denic et al. JASN 2017
## Large Range in Nephron Number in Normal Kidneys

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Mean</th>
<th>Range</th>
<th>Fold-Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nyengaard &amp; Bendtsen Anat Rec 1992</td>
<td>Danish</td>
<td>37</td>
<td>617,000</td>
<td>331,000 - 1,424,000</td>
<td>4.3</td>
</tr>
<tr>
<td>Merlet-Bénichou et al. Lab Invest 1999</td>
<td>French</td>
<td>28</td>
<td>1,107,000</td>
<td>655,000 - 1,554,000</td>
<td>2.4</td>
</tr>
<tr>
<td>Keller et al. NEJM 2003</td>
<td>German normotensive</td>
<td>10</td>
<td>1,429,200</td>
<td>884,458 - 1,959,914</td>
<td>2.2</td>
</tr>
<tr>
<td>Bertram et al. Ped Nephrol 2011</td>
<td>Caucasian Americans</td>
<td>147</td>
<td>924,981</td>
<td>227,327 - 1,956,973</td>
<td>8.6</td>
</tr>
<tr>
<td>Bertram et al. Ped Nephrol 2011</td>
<td>African Americans</td>
<td>190</td>
<td>904,864</td>
<td>210,332 - 2,702,079</td>
<td>12.8</td>
</tr>
<tr>
<td>McNamara et al. NDT 2008, NDT 2010</td>
<td>Senegalese Africans</td>
<td>47</td>
<td>988,263</td>
<td>536,171 – 1,764,421</td>
<td>3.3</td>
</tr>
<tr>
<td>Kanzaki, Puelles et al. JCI Insight 2017</td>
<td>Japanese – normotensive</td>
<td>9</td>
<td>666,140</td>
<td>419,282 - 960,756</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Human Nephron Number, Hypertension and Renal Pathophysiology

- Relatively few studies to date due to current need for kidney tissue (biopsy/autopsy)
- Most studies have relied on surrogate markers of nephron number
  - Low birth weight
  - High birth weight
  - Preterm birth
  - Being born small for gestational age
  - Reduced kidney volume on ultrasound
  - Enlarged glomeruli on kidney biopsy
Human Nephron Number and Hypertension

- **Nephron number in adult Aboriginal Australians**

- Probability of hypertension (95% CI)

- Nephron number and estimated glomerular filtration rate (eGFR) and numbers of nonsclerosed glomeruli (Nglomeruli), respectively, were completely sclerosed. The mean glomerular volume in these two patients was 6.50 mm². The percentage of periglomerular area (i.e., intact plus sclerosed glomeruli) was 25 percent and 30 percent of the glomeruli, respectively. Therefore, the renal cortex.

- Our findings, obtained in a consecutive series of patients with hypertension (and affected up to 19 percent of the periglomerular area) but was significantly found in all the patients with hypertension.

- To this end we examined the kidneys of two elderly subjects who died in accidents, suggest that the number of glomeruli is lower in the kidneys of patients with hypertension than in the control group.

- Recently, Bertram et al. reported preliminary insight.jci.org results.

- Our study has several limitations. The first is the small number of subjects with the attendant risks of random statistical error. The small sample size was imposed by the need to have age-matched and sex-matched subjects.

- Measures of association were tested by Spearman rank coefficient. The total volume of all nonsclerosed glomeruli (Vglomeruli) per kidney, for the 3 Japanese groups. NT, normotensive; HT, hypertensive; CKD, chronic kidney disease. Bold lines indicate means ± SD. In this study, we found that nephron number decreases with age owing to the accelerated loss of glomeruli after the age of 60 years. Consequently, the number of glomeruli is lower in the kidneys of patients with hypertension than in the control group. The percentage of periglomerular area (i.e., intact plus sclerosed glomeruli) was 25 percent and 30 percent of the glomeruli, respectively, were completely sclerosed. The mean glomerular volume in these two patients was 6.50 mm². The percentage of periglomerular area (i.e., intact plus sclerosed glomeruli) was 25 percent and 30 percent of the glomeruli, respectively. Therefore, the renal cortex.

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Nephron Number and Renal Pathophysiology

Low nephron number associated with increased glomerulosclerosis (Douglas-Denton et al. Ethnic Dis 2006; Hughson et al. Kidney Int 2006; McNamara et al. NDT 2008; Denic et al. JASN 2017)

Low nephron number associated with increased nephrosclerosis (Hughson et al. Kidney Int 2006; Denic et al. JASN 2017)

Low nephron number associated with low measured and estimated GFR and SNGFR (Fulladosa et al. JASN 2003; Tan et al. JASN 2009, Kidney Int 2010; Denic et al. JASN 2017; Kanzaki, Puelles et al. JCI Insight 2017)

Numerous studies showed birth weight inversely associated with microalbuminuria, decreased GFR, FSGS and ESKD.

Kanzaki, Puelles et al. JCI Insight 2017
Towards the Glomerular Size Distribution for a Whole Kidney

(US white males; 6 subjects/group, 30 gloms/subject - 1,440 gloms; Cavalieri)

Hoy et al. Clin Nephrol 2010
Why Estimate Glomerular Number and Size *In Vivo*?

Obtain a measure of functional nephron/glomerular mass.

Enable more accurate estimation of SNGFR.

Estimate functional nephron mass in patients newly-diagnosed with CKD – baseline value.

Determine the effectiveness of therapy in patients with CKD – progression rates, is nephron mass stabilised or decreasing? What is happening to SNGFR?

Count/size perfused (non-sclerosed) and non-perfused (sclerosed) glomeruli.

Better understand temporal relationships between decreasing nephron number and changes in blood pressure, GFR and pathology

In animal studies, perform longitudinal studies on effects of potential new therapies on glomerular number, size and SNGFR.

Estimate nephron number in children born small or premature and identify those to monitor closely (proteinuria, blood pressure). Detect problems early and treat accordingly.
Summary

Reports of human nephron (glomerular) number

- <25 studies to date – we have a lot to learn
- Only approx. 10 racial groups studied to date
- Generally small samples
- All used kidney tissue

Nephron number

- Varies >10-fold in normal human kidneys – some of this variation present at birth
- Is lower in premature and low birth weight babies
- Is lower in some racial groups than others
- Low nephron number is often associated with
  - hypertension
  - lower estimated and measured GFR
  - glomerulosclerosis, cortical fibrosis, nephrosclerosis
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