ASSESSMENT OF NEPHRON ENDOWMENT IN INFANCY

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OBJECTIVES

• Develop the concept of developmental programming of the nephron endowment and why it is important for individual longevity

• Discuss the genetic and environmental roles on the nephron endowment throughout the life cycle

• Describe a roadmap for identification and treatment of vulnerable populations

• Envision growing collaborations across disciplines to expand translational science and develop early interventions to improve global health.
David Barker and Developmental Origins of Health and Disease

David Barker: “Fetal originals of adult diseases”, renamed “Developmental Origins of Health and Disease—DOHaD”.
Those born after the Dutch famine became obese, developed T2DM, kidney disease, and passed it to 3 generations.

Initially the concept was restricted to intrauterine growth restriction and small for gestational age (<2500 grams)
Evolutionary factors play a central role in determining life history strategy, which spans fetal and postnatal life, and underlies differences between human and mouse kidney development as well as the course of CKD.

**Fetal life**
- 40 weeks gestation
- All nephrons formed before birth at 8% \( O_2 \), 210,000 – 2,700,000 per kidney
- Nephrogenesis

**Postnatal life**
- 70 year life span (global)
  - Adapted to many environments—wide genetic variation.
  - Long postnatal maturation, reproductive period limited by menopause (postreproductive period).
- 2 year life span (laboratory)
  - Specific metabolic rate 7-fold that of human.
  - Most mouse interstitial progenitor cell genes are not conserved in human.

**Evolutionary adaptation (Fitness)**
- Natural Selection ~ 90 million years
- Human
- Mouse
- Evolutionary factors underlying CKD
- Physiologic adaptation (Homeostasis)
- Environmental stressors
- DDHA and Epigenetic modification
- Long-term change in gene expression and metabolism
- Contribution of Natural selection
- CKD

Robert L. Chevalier JASN 2018;29:706-709
The period of the formation of the fetus until the child is 2 years old

CRITICAL PERIOD
First 1,000 Days of Life
THE LIFE CYCLE & LONGEVITY

Risk exposures

Primary intervention & prevention
HYPOTHESIS:

*Preterm birth provides a human model of developmental programming of cardiovascular and kidney disease in adult life.*
POPULATION CONSEQUENCES OF IMPROVED PRETERM SURVIVAL

• ~10% of births each year are preterm; 0.07% Extremely low gestational age newborns (ELGANs) Worldwide
  – 10% of 4 Million births: ~400,000; 98% survive: ~380,000
  – <0.07 % ~35,000
  – ~90% survive: ~30,000 VLBW each year

• 2015: US Population: ~322 million
  – ~32.2 million born preterm; 4.6 million are ELGANs

• Even a “slight” (10-20%) higher risk of ANY illness has a huge population effect
GLOBAL PERSPECTIVE

- Global burden of kidney disease is associated with low birth weight and preterm birth.
- Low birth weight (<2500 grams) is associated with an increase in cardio-renal disease risks in adult life.
- Homogeneous populations have shown that LBW and Preterm birth are associated with decreased longevity and increased risk of ESKD in young adult life (Swedish & Norwegian Birth Cohorts)
- Developmental programming in early life impacts longevity and the development of cardio-renal disease risks.
- Nephron Mass/ Endowment may be the determinant of adult disease.
- Is it discernible during the first 1000 days?
MORTALITY BY GESTATIONAL AGE AT BIRTH

Swedish National Cohort Study
(Crump et al, JAMA 2011; 306:1233-40;
Crump et al, Epidemiol 2013; 24:270-6)

*Adjusted for age, sex, birth order, maternal age, marital status, education
LBW INCREASES RISK OF ESRD: NORWEGIAN BIRTH REGISTRY 1967-2004

- > 2 million births
- LBW (<2500 grams)
  - RR 1.7 for ESRD
  - RR 1.5 (SGA)
- LBW more strongly associated with ESRD during the first 14 years of life (70% more likely) than > 15 years of age.
THE IMPORTANCE OF NEPHRON NUMBER

- Positive correlation of total nephron number in adult humans to health and longevity and the alternative of decreased nephron number, poorer kidney function and hypertension.
- With decreased nephron number and associated decreased kidney function, the cardio-renal syndrome develops with recognized stress and dysfunction of the heart and vascular tree.
- Individuals with low nephron numbers are more likely to develop hypertension.
- Renal allografts with higher nephron numbers have better and longer allograft function compared to smaller kidneys transplanted into larger individuals.
HUMAN RENAL DEVELOPMENT
BRANCHING MORPHOGENESIS
1. Nephrogenesis continued for up to 40 post-natal days; but the extreme preterm infants never achieved a full complement of radial glomerular generations compared to term infants.
2. Many abnormal glomeruli were formed during extra-uterine nephrogenesis, particularly in those with AKI.
3. Hyperfiltration with glomerulomegaly was evident in early infancy.
Human nephron endowment

Nyengaard, 1992
n=37
617,000
(331,000-1,424,000)

Keller, 2003
n=10
1,429,200
(800,000-2,000,000)

Bertram, 2011
n=398
895,711
(210,332-2,702,079)

Slide Courtesy: Jennifer Charlton, MD, MSc
Clinical characteristics of the newborns of white cohort (n = 136).

**A**

Mean = 132.16
S.D. = 29.34

**B**

Mean = 1.93
S.D. = 0.32

**C**

Mean birthweight = 3.62±0.48 (Kg)
Mean body surface area = 0.23±0.02 (m²)
Mean gestational age = 39.44±1.10 (weeks)

Males 53%, Females 47%
Relationship between weight at birth and the number and size of renal glomeruli in humans: A histomorphometric study

REINALDO MANALICH, LEONARDO REYES, MERCEDES HERRERA, CLARA MELENDI and ISABEL FUNDORA

Equation for Ellipsoid

TKV (cm$^3$) = Length (cm) x Width (cm) x AP Diameter (cm)
Neonatal Kidney Size and Function in Preterm Infants: What Is a True Estimate of Glomerular Filtration Rate?

Carolyn L. Abitbol, MD, Wacharee Seeherrunvong, MD, Marta G. Galarza, MD, Chryso Katsoulis, MD, Denise Francoeur, RN, Marissa DeFreitas, MD, Alicia Edwards-Richards, MD, Vimal Master Sankar Raj, MD, Jayanthi Chandar, MD, Shahnaz Duara, MD, Salih Yasin, MD, and Gaston Zilleruelo, MD

Supported by the Gerber Foundation
IS TOTAL KIDNEY VOLUME SYNONYMOUS WITH NEPHRON NUMBER?
Usefulness of Renal Volume Measurements Obtained by a 3-Dimensional Sonographic Transducer With Matrix Electronic Arrays

Usefulness of Renal Volume Measurements Obtained by a 3-Dimensional Sonographic Transducer With Matrix Electronic Arrays
<table>
<thead>
<tr>
<th>Method</th>
<th>Range, mL</th>
<th>Mean ± SD, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D sonography</td>
<td>74.6–236.5</td>
<td>139.7 ± 34.28a</td>
</tr>
<tr>
<td>3D sonography</td>
<td>112.8–270.5</td>
<td>161.8 ± 32.66b</td>
</tr>
<tr>
<td>CT</td>
<td>120.2–270</td>
<td>165.6 ± 33.15</td>
</tr>
</tbody>
</table>
Clinicopathological assessment of the nephron number

38-year-old female
- eGFR: 88 mL/min/1.73m²
- Glomerular density: 4.9/mm²

44-year-old male
- eGFR: 73 mL/min/1.73m²
- Glomerular density: 1.5/mm²
The Substantial Loss of Nephrons in Healthy Human Kidneys with Aging

Aleksandar Denic,* John C. Lieske,* Harini A. Chakkera,† Emilio D. Poggio,‡ Mariam P. Alexander,§ Prince Singh,* Walter K. Kremers,‖ Lilach O. Lerman,* and Andrew D. Rule*

Cationic ferritin was well tolerated in vivo and accurately imaged glomeruli by magnetic resonance imaging.
UNIQUE CHALLENGES WITH NEONATAL KIDNEY FAILURE

- Recognizing and defining the disease
- Collaboration with Neonatologists, Intensivists, Nephrologists, Nursing, the Institutions and Industry
- Adaptation and Innovation
- Education and propagation.
When Kidneys are at Risk ...

- Initiate a plan for monitoring renal status and slowing progression of renal insufficiency.

- Handover of care from pediatric to adult health providers is a critical transition.

COMPREHENSIVE EVALUATION SCHEMA OF THE PRETERM/LBW INFANT FOR EARLY CARDIOVASCULAR AND RENAL DISEASE RISKS

Maternal
- Personal history of prematurity
- Maternal HTN, obesity
- Pre-eclampsia
- Malnutrition
- Socioeconomic factors

Fetal
- Gestational age
- Elastin deposition
- Nephron endowment
- Multiple gestation

Prematurity Low Birth Weight

Cardiac HTN, LVH
- Echocardiography
- cIMT*, LVMI
- Blood pressure monitoring
- ABPM

Metabolic syndrome
- BMI
- Insulin resistance: insulin level, Hgb A1c
- Dyslipidemia
- Vitamin D

Renal CKD
- Renal ultrasound
- Urine protein quantitation
- Renal function
- Cystatin C
- Serum Cr

Vascular stiffness
- Capillary rarefaction*
- PWV*
- Umbilical artery histomorphometry*

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COMPREHENSIVE EVALUATION SCHEMA OF THE PRETERM/LBW INFANT FOR EARLY CARDIOVASCULAR AND RENAL DISEASE RISKS
**Mission Statement:** CHARMS is a comprehensive service clinic devoted to the early detection and treatment of children with conditions that lead to chronic kidney disease in later life.

Childhood obesity and low birth weight is associated with an expanding pediatric population of infants and young children at risk of cardiovascular and renal disease for a lifetime. They develop early hypertension associated with vascular stiffness, hidden microvascular dysfunction and kidney disease. A comprehensive clinical program devoted to early recognition and treatment is essential if we are to provide appropriate medical interventions to alter the disease progression. The following describes a comprehensive pediatric program to diagnose, assess, manage and study hypertension and associated vascular and metabolic disease in children. The goal is to provide early diagnosis and treatment in high risk pediatric populations including those born prematurely and/or of low birth weight and those with early childhood obesity.

**CHARMS** is a comprehensive service clinic devoted to the early detection and treatment of children with conditions that lead to chronic kidney disease in later life. These conditions include the following:

- Elevated blood pressure
- Obesity
- Metabolic Syndrome
- Diabetes Mellitus
- Low birth weight (< 5.5 pounds) and/or prematurity
- Chronic kidney disease

This program establishes a center for children who need early and continued assessment directed at medical, nutritional and motivational interventions. The program also serves as a home for clinical research that can be both investigator-initiated (Faculty & Fellows) as well as sponsor initiated (pharmaceutical trials). It also serves as a potential site for teaching electives for our residency training and fellowship training programs.
### Urine derived kidney cells

<table>
<thead>
<tr>
<th>Markers of Disease Activity</th>
<th>Pathophysiology</th>
<th>Therapeutic Potential</th>
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</thead>
<tbody>
<tr>
<td><strong>Podocytes</strong></td>
<td>Diabetic Nephropathy</td>
<td>Lupus nephritis APOL1</td>
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<td></td>
<td>Pre-eclampsia</td>
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<td></td>
<td>FSGS &amp; APOL1</td>
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<tr>
<td><strong>Proximal Tubular Epithelial Cells</strong></td>
<td>Acute tubular necrosis</td>
<td>Cystinosis</td>
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<tr>
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<td>Diabetes mellitus</td>
<td>Diabetic nephropathy</td>
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<td>Oxalosis</td>
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<td></td>
<td></td>
<td>Lowe’s Syndrome</td>
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<td><strong>Stem/Progenitor Cells</strong></td>
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<td>Nephrogenesis</td>
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<tr>
<td><strong>Extracellular Vesicles</strong></td>
<td>Focal segmental glomerulosclerosis</td>
<td>Not yet studies</td>
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