SOLITARY FUNCTIONING KIDNEY

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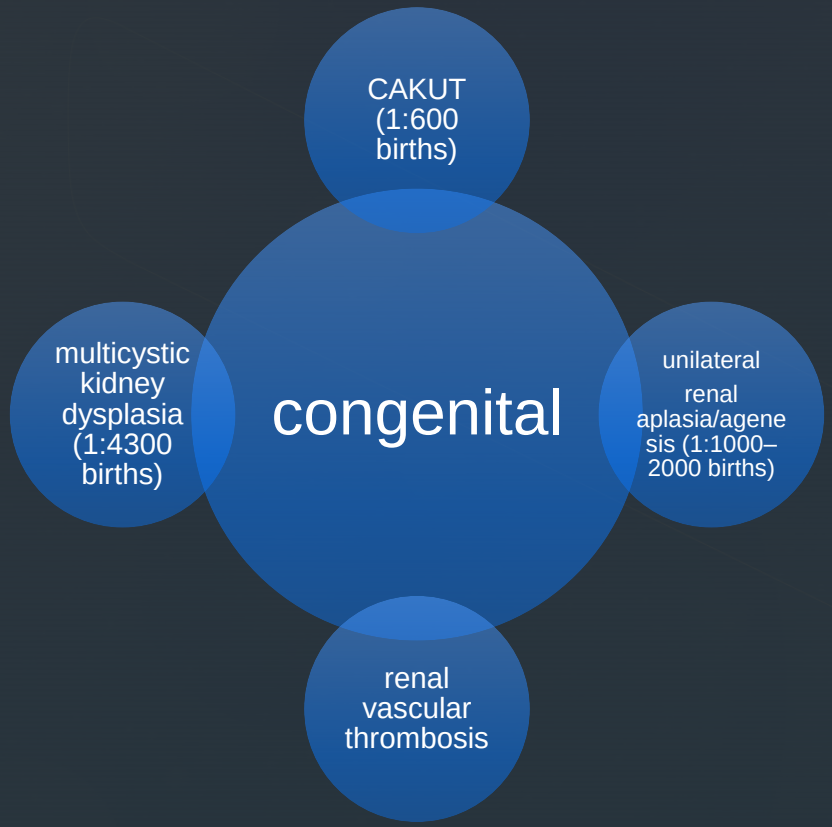
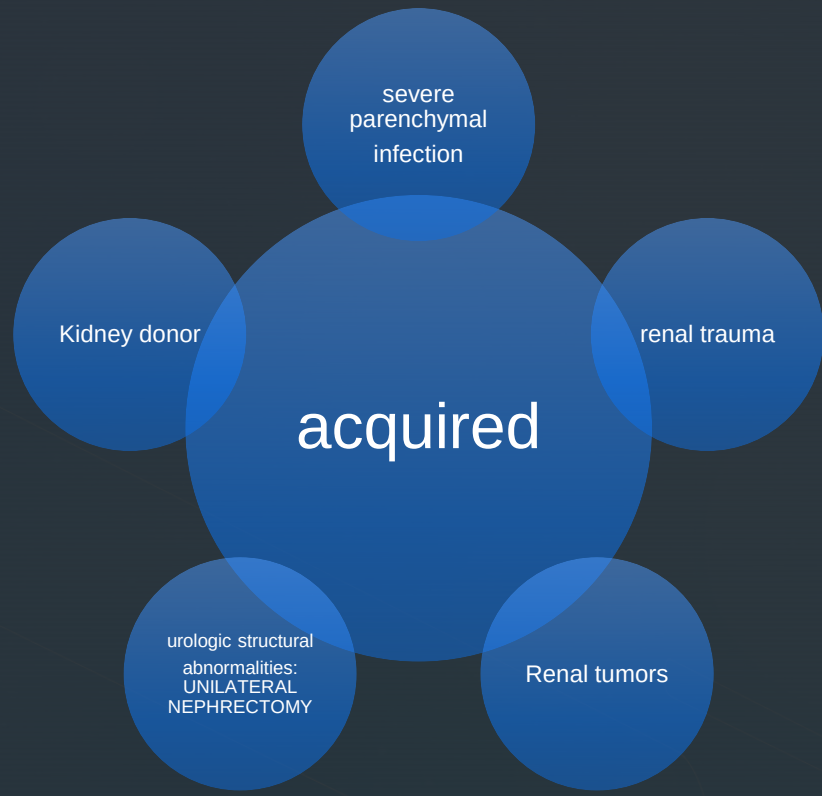
SOLITARY FUNCTIONING KIDNEY

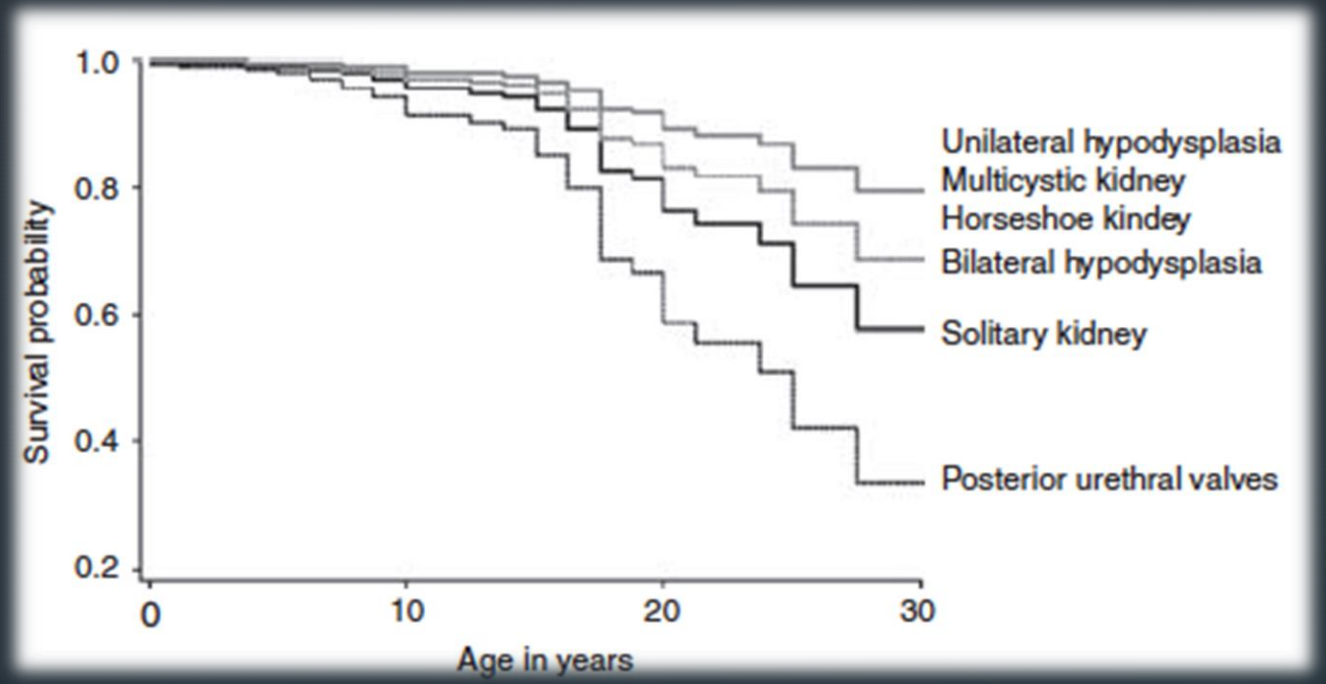
1. Reduction in renal mass. Etiologies
2. Outcome
3. Monitoring
4. Mechanisms of Injury
5. Consequences
6. Prevention and Follow-up

SOLITARY FUNCTIONING KIDNEY. ETIOLOGIES





Renal outcome in patients with congenital anomalies of the kidney and urinary tract



Sanna-Cherchi S, Kidney Int 2009

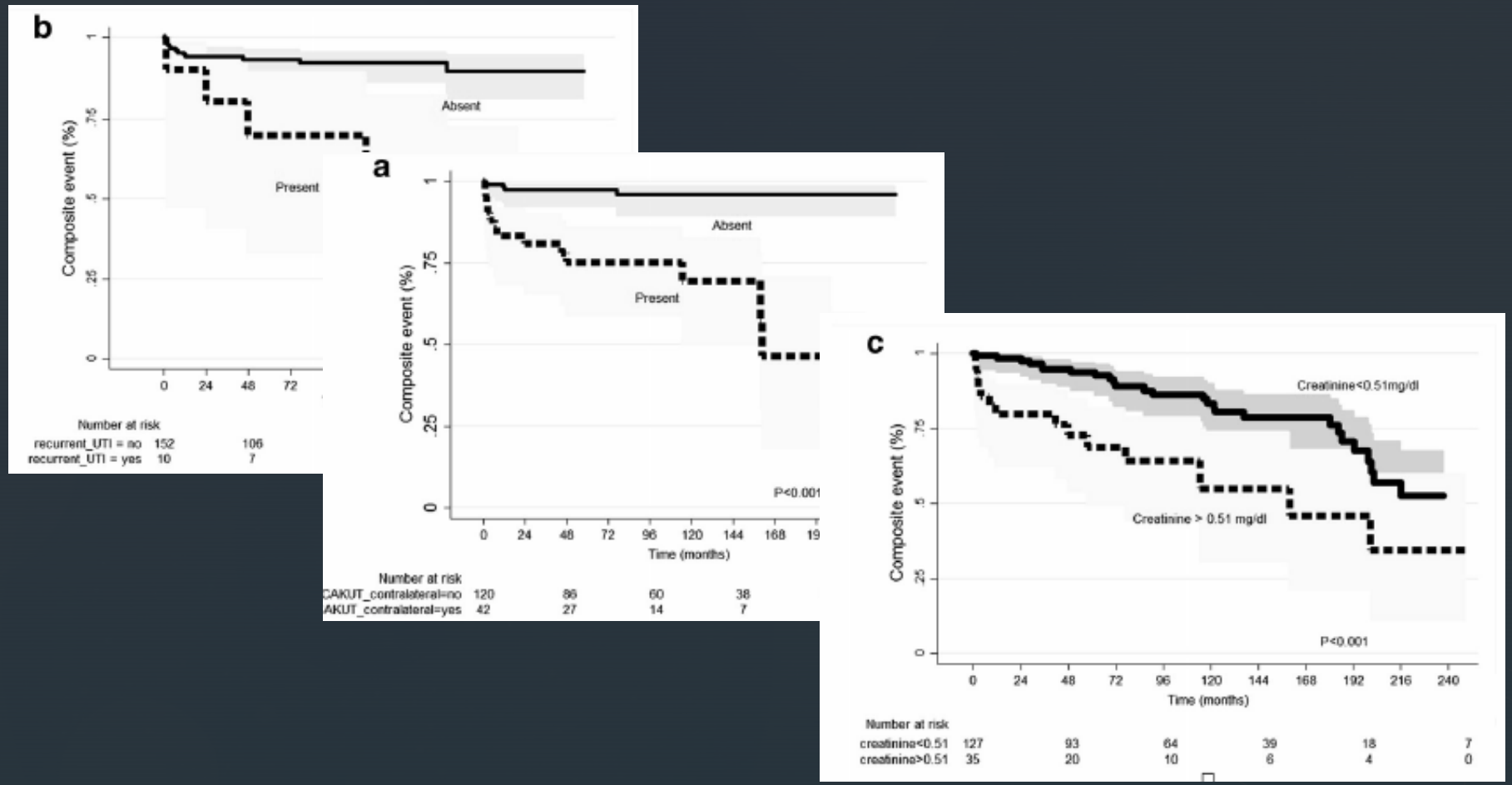
Renal outcome in patients with congenital anomalies of the kidney and urinary tract

- Study group: 190 patients with congenital SFK, 1987- 2015.
- Etiology:
  - renal agenesis,
  - primary renal hypodysplasia,
  - Multicystic dysplastic kidney (MCDK).
- Events of interest:
  - eGFR < 60 ml/min per 1.73 m2,
  - hypertension,
  - proteinuria.
- Primary endpoint : time until the first occurrence of any of the composite events.
- Median follow-up time was 8.5 year

Predictive factors	Proteinuria	Hypertension	CKD	Composite event
Gender	3.15	1.28	2.46	1.45
(male vs. females)	(0.66–14.9)	(0.37–4.4)	(0.51–11.8)	(0.54–3.8)
Birth low weight	2.85	2.44	3.31	2.69*
(< 2500 g vs. > 2500 g)	(0.79–10.2)	(0.71–8.42)	(0.89–12.3)	(1.03–6.98)
Prematurity	0.96	1.55	1.95	2.01
(present vs. absent)	(0.12–7.6)	(0.33–7.2)	(0.40–9.4)	(0.66–6.15)
Birth length (cm)	1.02	1.09	0.76*	0.99
(continuous variable)	(0.74–1.41)	(0.73–1.63)	(0.64–0.92)	(0.76–1.30)
CAKUT contralateral	1.92	6.2*	65.2**	13.3**
(present vs. absent)	(0.96. – 3.81)	(1.78–21.5)	(3.7–115.7)	(4.3–41.2)
Phenotype	2.71	3.00	2.52	2.06
(MCDK vs hypodysplasia)	(0.69–10.5)	(0.87–10.3)	(0.62–10.1)	(0.73–5.8)
Recurrent UTI	7.04*	5.34*	12.7**	6.71**
(present vs. absent)	(2.2–22.4)	(1.38–20.7)	(3.4–47.8)	(2.5–18.1)
pCR L	0.970*	0.99	0.98	0.97*
(percentile continuous)	(0.951–0.98)	(0.97–1.01)	(0.96–1.00)	(0.96–0.99)
Baseline creatinine	2.46**	2.97*	3.5**	3.4**
(continuous variable)	(1.41–4.38)	(1.6–5.61)	(1.98–6.2)	(2.16–5.4)
Baseline eGFR	0.927**	0.95*	0.90**	0.94**
(continuous variable)	(0.890–0.96)	(0.93–0.98)	(0.86–0.94)	(0.92–0.99)

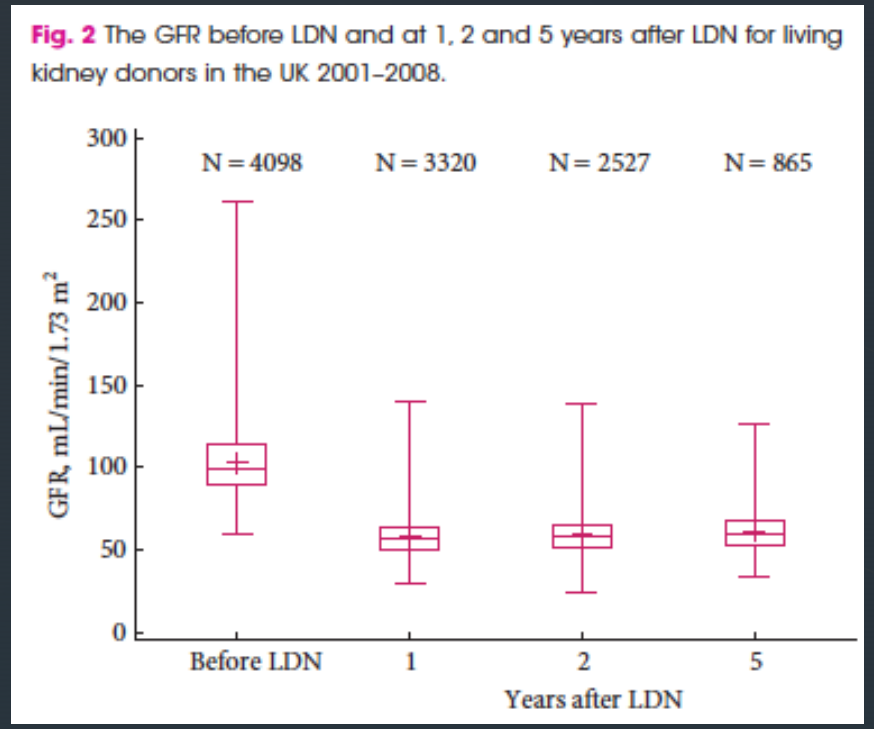
Poggiali I., Ped Nephrol 2018

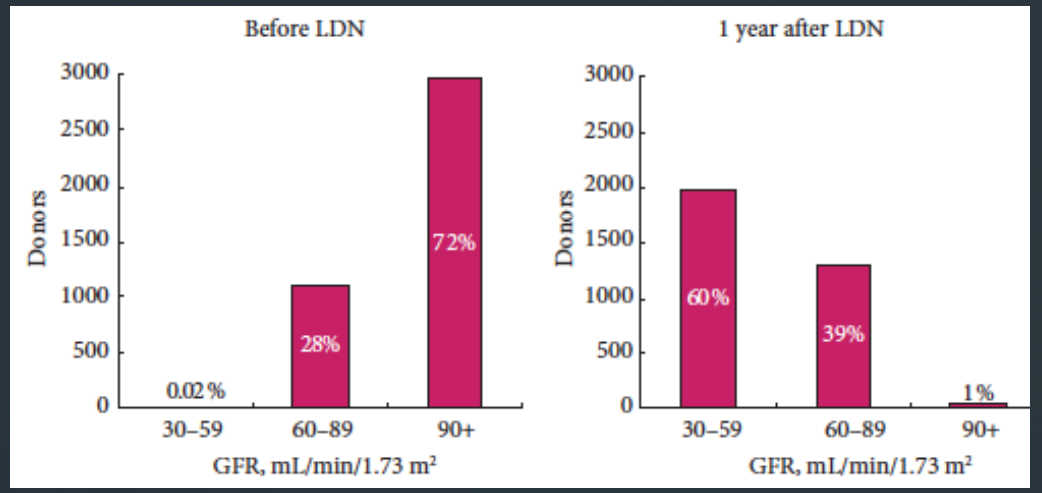
Renal outcome in patients with congenital anomalies of the kidney and urinary tract



Poggiali I., Ped Nephrol 2018

Renal function and cardiovascular outcomes after living donor nephrectomy in the UK: quality and safety revisited





Patel N., 2013 BJU International

Monitoring SFK

- These results prompted recent recommendations to monitor all patients with an SFK from childhood, which includes urine analysis, BP measurements, and a determination of GFR as the best overall measurement of renal function.
- Unfortunately, a gold standard measurement of GFR by inulin clearance is cumbersome, costly, and therefore not commonly available .

GFR MONITORING

- Schwartz formula. (J Am Soc Nephrol 2009;20(3):629-37)
- Cockcroft –Gault (Nephron 1976;16(1):31-41)
- MDRD (Modification of Diet in Renal Disease Study Group. Levey AS, Ann Intern Med 1999)

- Disadvantages of GFR estimation using serum creatinine:
  - The molecule is not only eliminated by glomerular filtration but also secreted in the proximal tubule. Because tubular secretion of creatinine varies widely and increases with declining GFR, the accuracy of the creatinine-based equations is limited when GFR decreases.
  - Serum creatinine concentrations are influenced by muscle mass, which may hamper the interpretation of serum values in the growing child.

Yentonces que ....?

CYSTATIN C

- Cystatin C is a small molecular weight protein that is produced ubiquitously at a regular rate and its reciprocal has been shown to be highly correlated with glomerular filtration rate (GFR)
- This relationship is independent of inflammatory conditions, muscle mass, gender, body composition, and age (after 12 months).
- Cystatin C levels are slightly below 1 mg/l in the blood of healthy individuals.
- The protein is catabolized and almost completely reabsorbed by renal proximal tubular cells, so that little is normally excreted in the urine.
- Inter-individual variations in cystatin C account for 25% of its biological variability compared to 93% for creatinine.
- All currently used estimating equations for GFR have been validated only in children with two kidneys

Precision of Estimating Equations for GFR in Children with a Solitary Functioning Kidney: The KIMONO Study

- The KIMONO (KIdney of MONofunctional Origin) study examined the precision of six common estimating equations in predicting the gold standard GFR, determined by an inulin single-injection method, in 77 children with an SFK.

Two creatinine-based (estimated

two cystatinC–based **(eGFR-**

two cystatin C/creatinine–based (**eGFR-Zappitelli2**, eGFR-CKiD2)

Table 3. P… …ns compared with GFR based on inulin single-injection method in children with a solitary functionin…

Equa…	…	95% Limits of Agreement (ml/min per 1.73 m²)[b]	Proportion of eGFR within ±30% of GFR-Inulin (%)	Proportion of eGFR within ±10% of GFR-Inulin (%)
eGFR…	…	−35.2 to 36.1	90	33
Ccrea…	…	−96.5 to 36.7	55	14
eGFR-Z…	…	−32.9 to 30.5	87	46
eGFR-Zappi…	2.8	−32.3 to 26.7	90	44
eGFR-CKiD1	2.3	−27.1 to 31.8	94	46
eGFR-CKID2	−0.9	−25.1 to 23.3	95	55

Westland R., Clin J Am Soc Nephrol, 2013

The KIMONO Study

$$eGFR\text{-}Schwartz\ (\mathrm{ml/min/1.73m^2}) = 41.3 \times \frac{height\ (m)}{serum\ creatinine\ (mg/dl)}$$

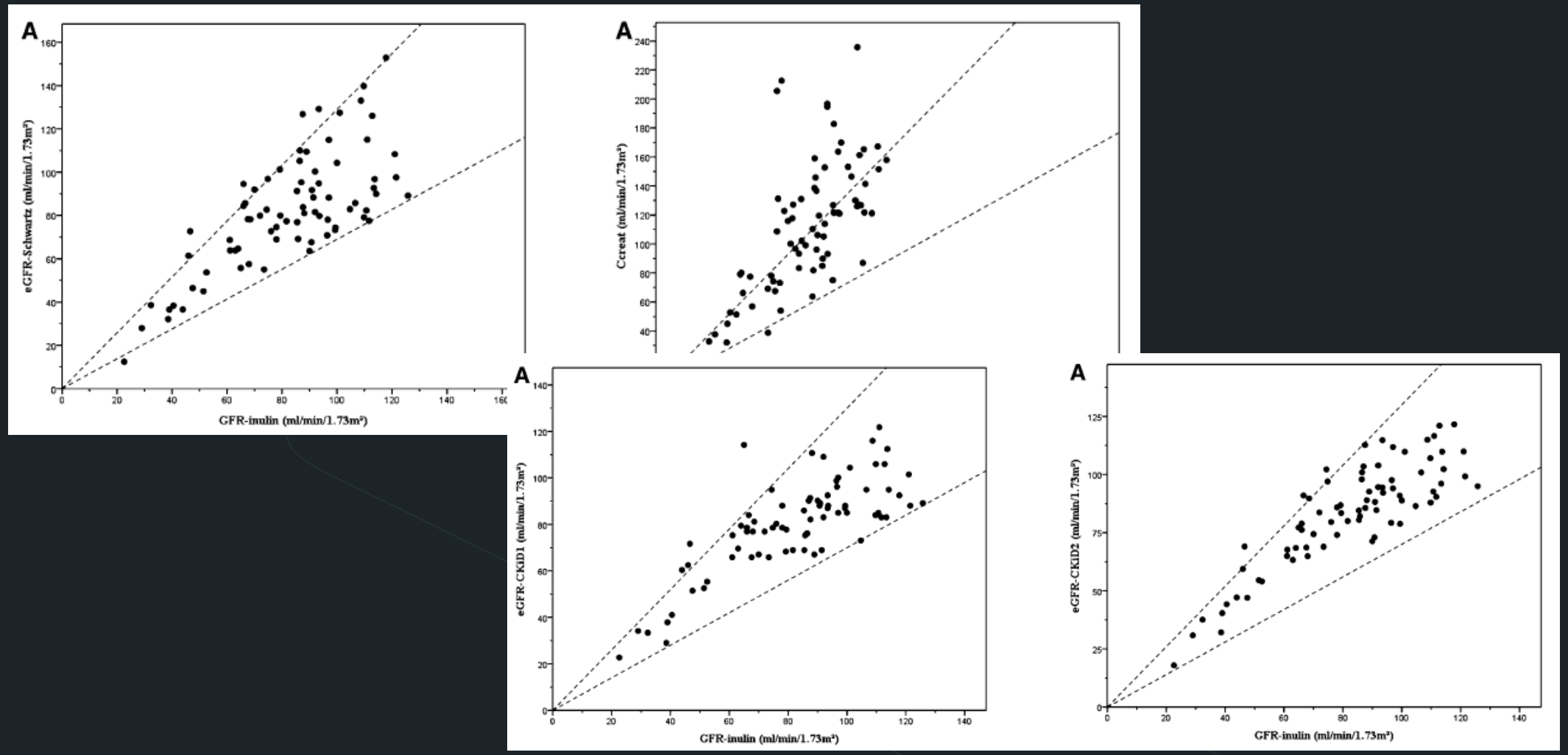
$$Ccreat\ (\mathrm{ml/min/1.73m^2}) = \frac{urine\ creatinine\ (mg/dl)}{serum\ creatinine\ (mg/dl)} \times \frac{urine\ volume(ml)}{time\ (hours) \times 60} \times \frac{1.73}{body\ surface\ area(m^2)}$$

$$eGFR\text{-}Zappitelli1\ (\mathrm{ml/min/1.73m^2}) = \frac{75.94}{serum\ cystatin\ C\ (mg/l)^{1.17}}$$

$$eGFR\text{-}CKiD1\ (\mathrm{ml/min/1.73m^2}) = 40.6 \times \left(\frac{1.8}{serum\ cystatin\ C\ (mg/l)}\right)^{0.93}$$

$$eGFR\text{-}Zappitelli2\ (\mathrm{ml/min/1.73m^2}) = \frac{507.76 \times e^{0.3\ \times\ height(m)}}{serum\ cystatin\ C\ (mg/l)^{0.635} \times (serum\ creatinine\ (mg/dl) \times 88.4)^{0.547}}$$

$$eGFR\text{-}CKiD2\ (\mathrm{ml/min/1.73m^2}) = 39.8 \times \left(\frac{height\ (m)}{serum\ creatinine\ (mg/dl)}\right)^{0.456} \times \left(\frac{1.8}{serum\ cystatin\ C\ (mg/l)}\right)^{0.418} \times \left(\frac{30}{blood\ urea\ nitrogen\ (mg/dl)}\right)^{0.079} \left[\times (1.076)^{male} \times \left(\frac{height\ (m)}{1.4}\right)^{0.179}\right]$$



The KIMONO Study

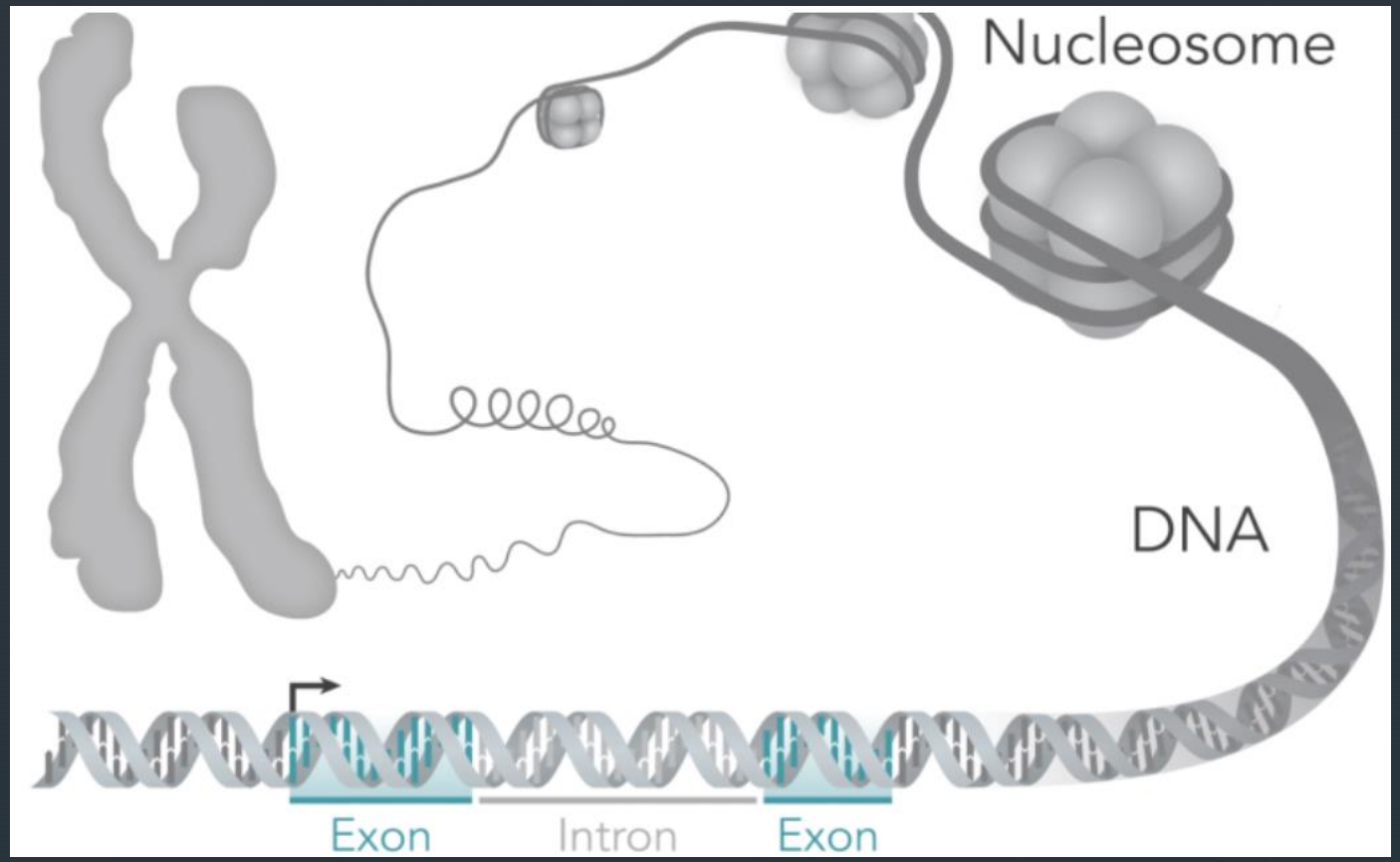
The KIMONO Study

- In conclusion, the KIMONO study s… that the combined serum cystatin C/serum creatinine/BUN CKiD … ion estimates GFR of children with an SFK with superior preci… ence, we recommend the use of this combined equation to … or GFR in children with an SFK.

- If cystatin … surement is not available, eGFR-Schwartz is an acceptable alterna… nd more precise than creatinine clearance, which should be ab… ed.

Westland R., Clin J Am Soc Nephrol, 2013

SFK. Mechanisms of Injury



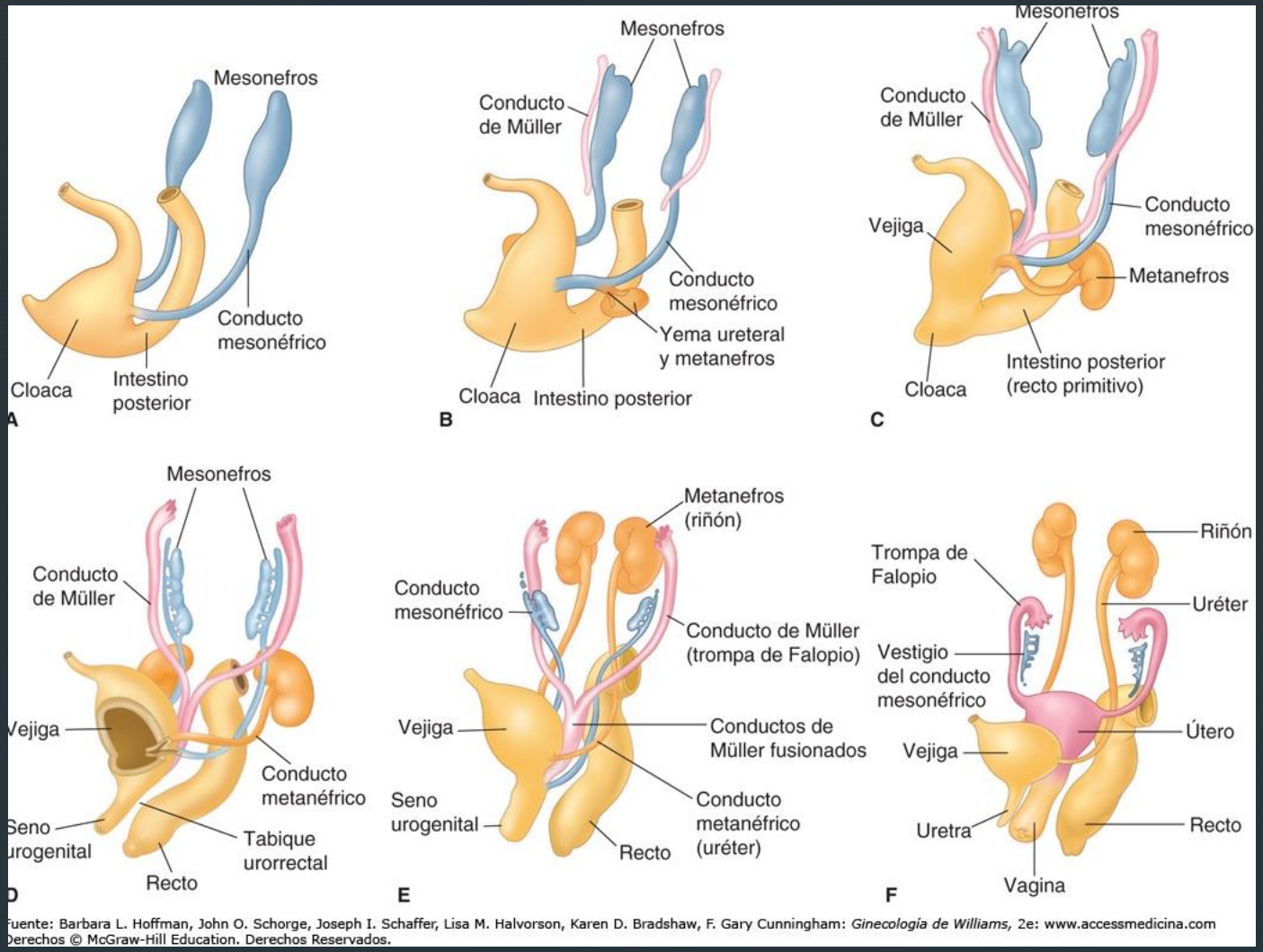
Mechanisms of Injury. Renal Development

- Definitive human renal development is initiated at the fifth gestational week and characterized by complex interactions between the outgrowing ureteric bud of the mesonephric duct, from which the renal pelvis, ureter, and lower urinary tract originate, and the metanephric mesenchyme, from which the renal parenchyma originates. The MM represents a pluripotent stem cell niche which gives rise to the nephron.
- Normal kidney and urinary tract development requires a temporally and spatially coordinated interaction between the Ureteric Bud and the MM.

- Nephrons are formed until the 34th to 36th gestational week, without the possibility of additional nephron formation later in life.
- The total of number of nephrons at birth is approximately 900,000- 1000000 nephrons per kidney, with a high interindividual variability (250.000-2000000), and should last the entire lifespan of an individual.

- Known factors contributing to lower nephron endowment include low birth weight, prematurity, in utero exposure to high-glucose, low-protein diet and in utero growth restriction

Mechanisms of Injury. Renal Development



Environmental factors

- Environmental factors that disturb renal development include medications administered during pregnancy
  - Angiotensin-converting enzyme [ACE] inhibition,
  - dexamethasone,
  - antiepileptic drugs
  - aminoglycosides,
  - maternal diabetes.
- Drug administration in the prematurely born neonate with a solitary functioning kidney can have detrimental effects on nephrogenesis and GFR, especially when administered before the 28th gestational week.
- The most commonly used drugs that disturb nephrogenesis are aminoglycosides and nonsteroidal anti-inflammatory drugs

Genetic factors

- CAKUT are among the most common birth defects in humans (1 in 600 births), and present in over 20% of newborns with chromosomal abnormalities, indicating that kidney development is particularly sensitive to gene disruption.

- The three genes most commonly implicated in nonsyndromic forms of CAKUT are PAX2 (encoding for a nuclear transcription factor involved in early nephrogenesis), HNF1B (encoding for a transcription factor originally implicated in the renal cysts and diabetes syndrome, and DSTYK (encoding for a dual specificity serine/threonine and tyrosine kinase, recently identified as a positive regulator of fibroblast growth factor signaling during kidney development.

Mechanisms of Injury. Hyperfiltration Hypothesis

Cochat P., Ped Nephrol 2018

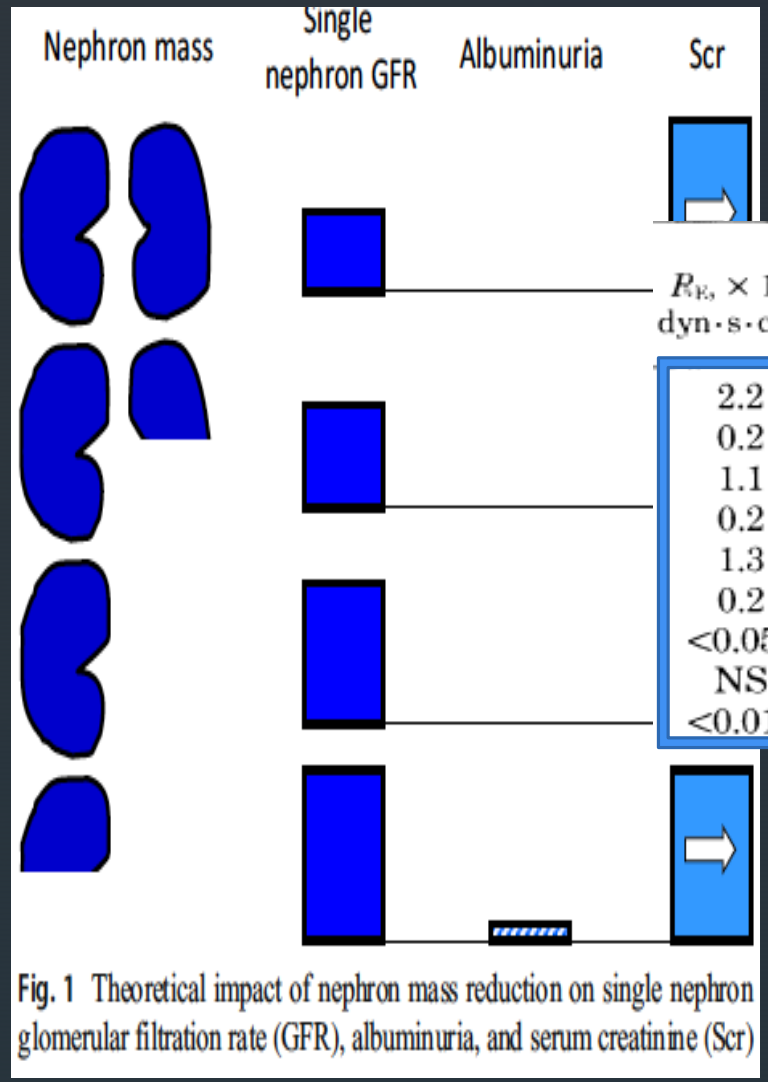


Fig. 1 Theoretical impact of nephron mass reduction on single nephron glomerular filtration rate (GFR), albuminuria, and serum creatinine (Scr)

Glomerular capillary hydraulic pressure

Delta glomerular transcap hydraulic pressure

Single nephron GFR

Glomerular plasma flow rate

R_E, $\times 10^{10}$ dyn·s·cm^{-5}		$\bar{P}_{GC}$, mmHg	P_E, mmHg	$\overline{\Delta P}$, mmHg	SNGFR, nl/min	GFR, ml/min	Q_A, nl/min	R_A, $\times 10^{10}$ dyn·s·cm^{-5}
2.2	*Group I*	49	18	37	27.8	0.72	74	3.5
0.2	($n = 8$)	1	1	1	3.2	0.06	11	0.4
1.1	*Group II*	63	25	44	62.5	0.21	187	1.4
0.2	($n = 9$)	2	2	2	6.4	0.03	20	0.2
1.3	*Group III*	46	19	32	38.2	0.16	92	2.5
0.2	($n = 7$)	1	1	3	6.2	0.01	16	0.5
<0.05	*P, I vs. II*	<0.001	<0.025	<0.025	<0.005	<0.001	<0.001	<0.005
NS	*P, II vs. III*	<0.001	NS	<0.01	<0.025	<0.001	<0.01	NS
<0.01	*P, I vs. III*	NS	NS	NS	NS	<0.001	NS	NS

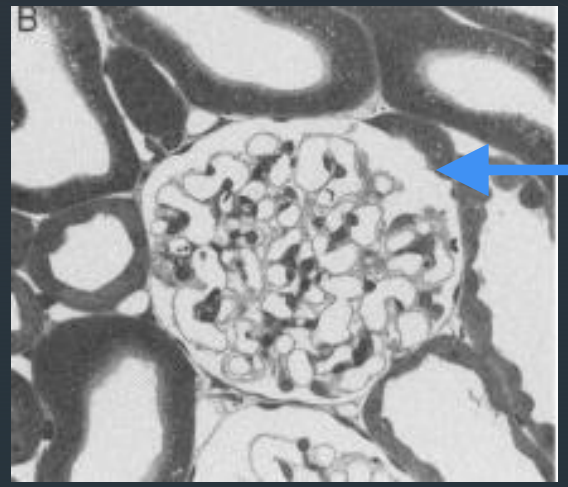
Hostetter T, Am J Physiol. 1981

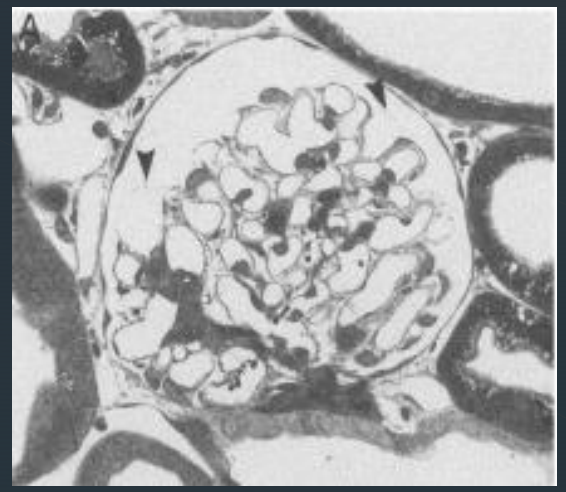
Mechanisms of Injury. Hyperfiltration Hypothesis

TABLE 1. *Summary of renal cortical microcirculation studies in groups I, II, and III*

	PUN, mg/100 ml	Hct, vol/100 ml	$\overline{AP}$, mmHg	P_{BC}, mmHg	P_G, mmHg	P_T, mmHg	$\overline{\Delta P}$, mmHg	C_a, g/100 ml	C_v, g/100 ml	Π_a, mmHg	Π_v, mmHg	SNFF	SNGFR, nl/min	GFR, ml/min	Q_A, nl/min	$R_a \times 10^{-10}$, dyn·s·cm^{-5}	$P_v \times 10^{-10}$, dyn·s·cm^{-5}	$R_{BC} \times 10^{-10}$, dyn·s·cm^{-5}	K_f, nl/(s·mmHg)
Group I	20	52	112	49	12	18	37	5.2	8.3	16	34	0.38	27.8	0.72	74	3.5	2.2	6.0	≥0.041
($n = 8$)	±1	1	2	1	1	1	1	0.2	0.4	1	2	0.02	3.2	0.05	11	0.4	0.2	0.6	0.007
Group II	89	51	128	63	19	25	44	5.3	8.1	17	34	0.33	62.5	0.21	187	1.4	1.1	2.5	0.033
($n = 9$)	±6	2	4	2	1	2	2	0.2	0.3	1	1	0.01	5.4	0.03	20	0.2	0.2	0.3	0.008
Group III	28	52	117	46	14	19	32	5.4	8.7	17	37	0.36	38.2	0.16	92	2.5	1.3	3.9	≥0.085
($n = 7$)	±6	1	4	1	1	1	3	0.2	0.4	1	3	0.02	6.2	0.01	16	0.5	0.2	0.6	0.021
P, I vs. II	<0.001	NS	<0.005	<0.001	<0.001	<0.025	<0.025	NS	NS	NS	NS	NS	<0.005	<0.001	<0.001	<0.005	<0.05	<0.005	
P, II vs. III	<0.005	NS	NS	<0.001	<0.025	NS	<0.01	NS	NS	NS	NS	NS	<0.025	<0.001	<0.1	NS	NS	NS	NS
P, I vs. III	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	<0.001	NS	NS	<0.01	<0.05	

Values are means ± SE. PUN, plasma urea nitrogen. See glossary for other abbreviations.



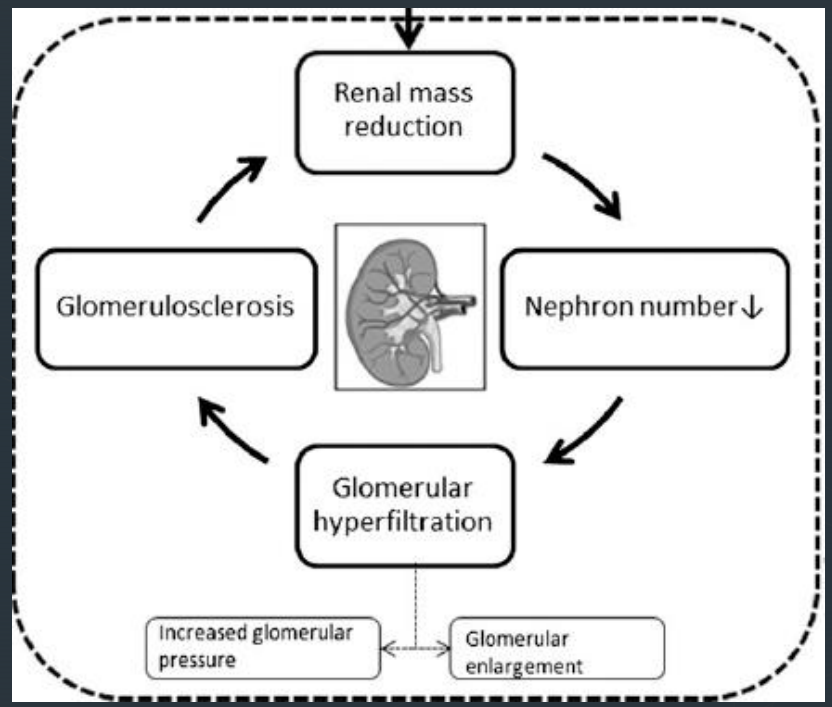


Hostetter T, Am J Physiol. 1981

Mechanisms of Injury. Hyperfiltration Hypothesis

- **Additional CAKUT**
  - Renal hypodysplasia
  - Vesicoureteric reflux
- **Genetic factors**
- **Environmental factors**
  - Intra-uterine growth retardation
  - Premature birth
  - Nephrotoxic drugs (NICU)
  - Increased BMI

Solitary functioning kidney



- **Proteinuria**
- **Hypertension**
- **GFR** ↓

Control of Glomerular Hypertension Limits Glomerular Injury in Rats with Reduced Renal Mass

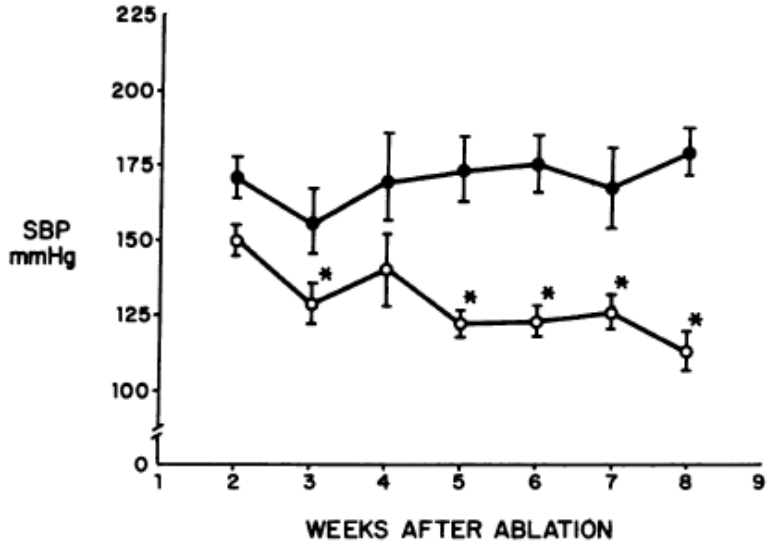


Figure 1. Systolic blood pressure (SBP) measured by the tail cuff method in rats followed for 8 wk after 5/6 nephrectomy. Untreated rats (group 3) (●) exhibited sustained systemic hypertension, while enalapril treatment (group 4) (○) maintained systemic blood pressure at normal levels. Values are means±SEM. *$P < 0.05$ vs. group 3 at the same time point.

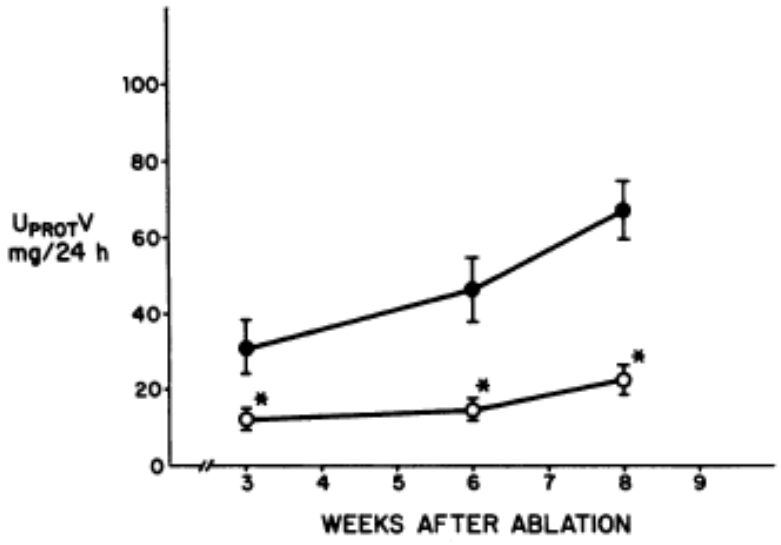


Figure 2. Urinary protein excretion rates. 24-h urinary protein excretion ($U_{PROT}V$) in rats with 5/6 nephrectomy. Untreated rats (group 3) (●) developed progressive proteinuria over the 8-wk course, while treatment with enalapril (group 4) (○) significantly limited proteinuria. Values are means±SEM. *$P < 0.05$ vs. group 3 at the same time point.

Anderson Sh. J Clin Invest 1985

Control of Glomerular Hypertension Limits Glomerular Injury in Rats with Reduced Renal Mass

Single nephron GFR

Glomerular plasma flow rate

Glomerular capillary hydraulic pressure

Table I. Summary of Renal Cortical Microcirculation Studies

	Body wt.	Hct	PUN	GFR	$\overline{AP}$	SNGFR	SNFF	Q_A	$\bar{P}_{GC}$	P_T
	g	*vol/100 ml*	*mg/100 ml*	*ml/min*	*mmHg*	*nl/min*		*nl/min*	*mmHg*	*mmHg*
Group 1 (n = 7)	258±3 SEM	43±1	44±2	0.91±0.04	151±6	93.0±8.0	0.29±0.01	324±26	69±2	17±1
Group 2 (n = 7)	245±7	39±1	49±5	0.77±0.08	101±2	81.6±7.4	0.25±0.02	334±43	54±1	18±1
P	>0.05	<0.02	>0.05	>0.05	<0.001	>0.05	>0.05	>0.05	<0.001	>0.05

Control of Glomerular Hypertension Limits Glomerular Injury in Rats with Reduced Renal Mass

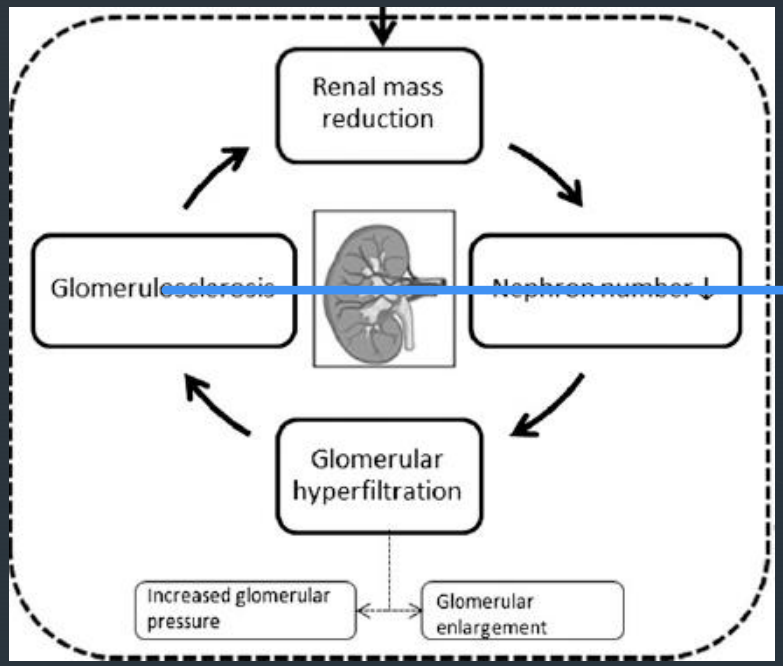
Delta glomerular transcapillary hydraulic pressure

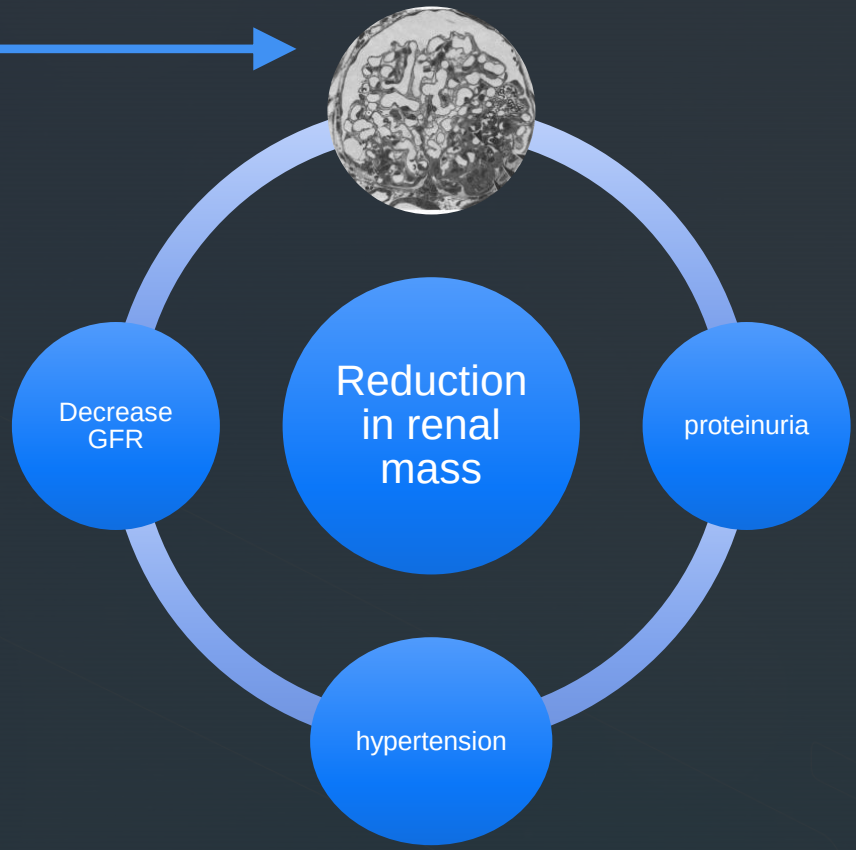
Afferent arteriolar resistance

Efferent arteriolar resistance

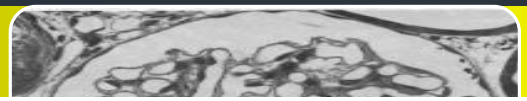
P_E	$\overline{\Delta P}$	C_A	C_E	π_A	π_E	$R_A \times 10^{10}$	$R_E \times 10^{10}$	$R_T \times 10^{10}$	K_f
mmHg	*mmHg*	*g/100 ml*	*g/100 ml*	*mmHg*	*mmHg*	*dyne·s·cm^{-5}*	*dyne·s·cm^{-5}*	*dyne·s·cm^{-5}*	*nl/(s·mmHg)*
18±1	52±2	4.9±0.1	6.9±1	15±0.4	26±1	1.19±0.15	0.87±0.06	2.06±0.18	0.0487±0.0043
19±1	35±1	4.8±0.2	6.4±0.2	15±1	23±1	0.76±0.10	0.65±0.09	1.42±0.19	0.0892±0.0159
>0.05	<0.001	>0.05	>0.05	>0.05	>0.05	<0.05	>0.05	<0.05	<0.05

SFK. Clinical consequences





SFK. Clinical consequences. Proteinuria



Diagnostic test	Normal albuminuria	Microalbuminuria	Albuminuria	Proteinuria
24 hour urine albumin collection	<30 mg/24 hours	30–300 mg/24 hours	>300 mg/24 hours	>300 mg/ 24 hours
Spot urine dipstick	<30 mg/dL	N/A	>30 mg/dL	>30 mg/dL
Spot urine albumin to creatinine ratio	<17 mg/g (men) <25 mg/g (women) <2.5 mg/mmol (men) <3.5 mg/mmol (wom <30 ug/mg		>250 mg/g (men) >355 mg/g (women) >35 mg/mmol >300 ug/mg	N/A
Spot urine protein to creatinine ratio	<200 mg/g <45 mg/mmol	N/A	N/A	>200 mg/g >45 mg/mmol

Microalbuminuria mg/L
Creatininuria mg/dl

Microalb*100/creat= mg/gr

Hypertension ⟷ Proteinuria

SFK. Clinical consequences. Hypertension

Table 1 GFR and proteinuria at time of diagnosis (T0) and after 14 years follow-up (T14)

	GFR ml/min/1.73 m^2		Proteinuria mg/m^2/die	T14	p<
SFK			.13	159.03 ± 234.66	NS
aSFK			.15	140.52 ± 122.26	NS
cSFK			11.78	147.15 ± 247.46	NS

(The middle part of Table 1 is covered by Table 2 on the slide.)

Table 2 Blood pressure at time of diagnosis (T0) and after 14 years follow-up (T14)

	T0	T14	T0 vs T14 *p*<
SFK with BP > 90%thile	12/55 (22%)	42/55 (76.4%)	0.0001
aSFK	5/17 (29%)	14/17 (82.4%)	0.005
cSFK	7/38 (18%)	28/38 (73.7%)	0.0001
PreHyp-SFK	6/55 (10.9%)	22/55 (40%)	0.0008
PreHyp-aSFK	3/17 (17.6%)	5/17 (29.4%)	NS
PreHyp-cSFK	3/38 (7.9%)	17/38 (44.7%)	0.0005
Hyp-SFK	6/55 (11%)	20/55 (36.4%)	0.003
Hyp-aSFK	2/17 (12%)	9/17 (52.9%)	0.025
Hyp-cSFK	4/38 (10%)	11/38 (29%)	NS

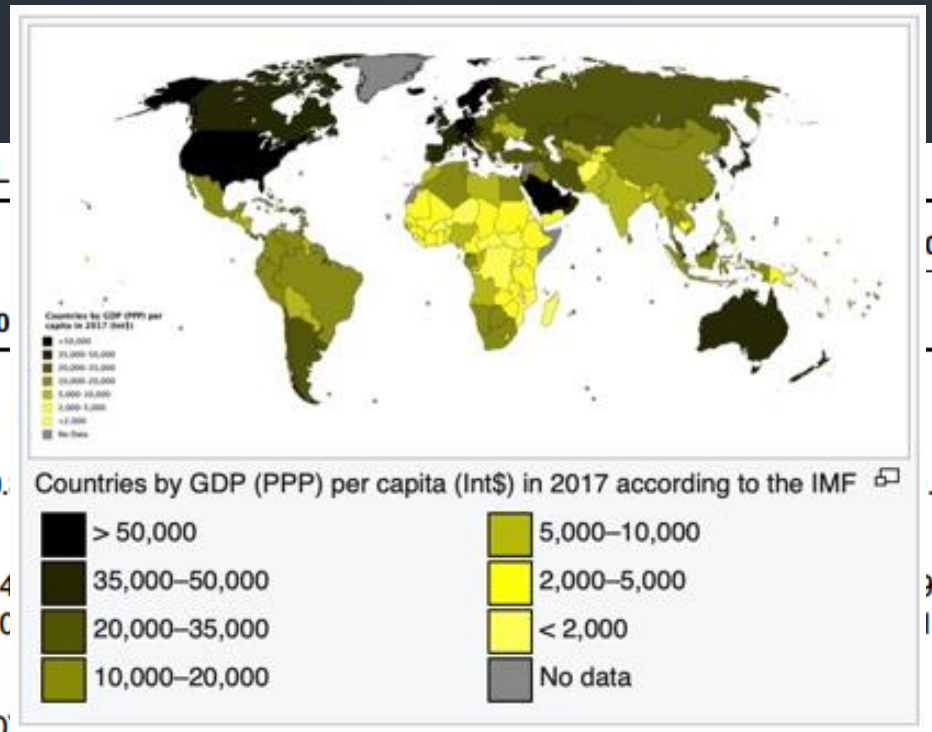
Evolution of blood pressure
in 55 children
with congenital and acquired
solitary
functioning kidney

Lubrano R, Italian Journal of Pediatrics 2017

Association of Income Level With Kidney Disease Severity and Progression Among Children and Adolescents With CKD

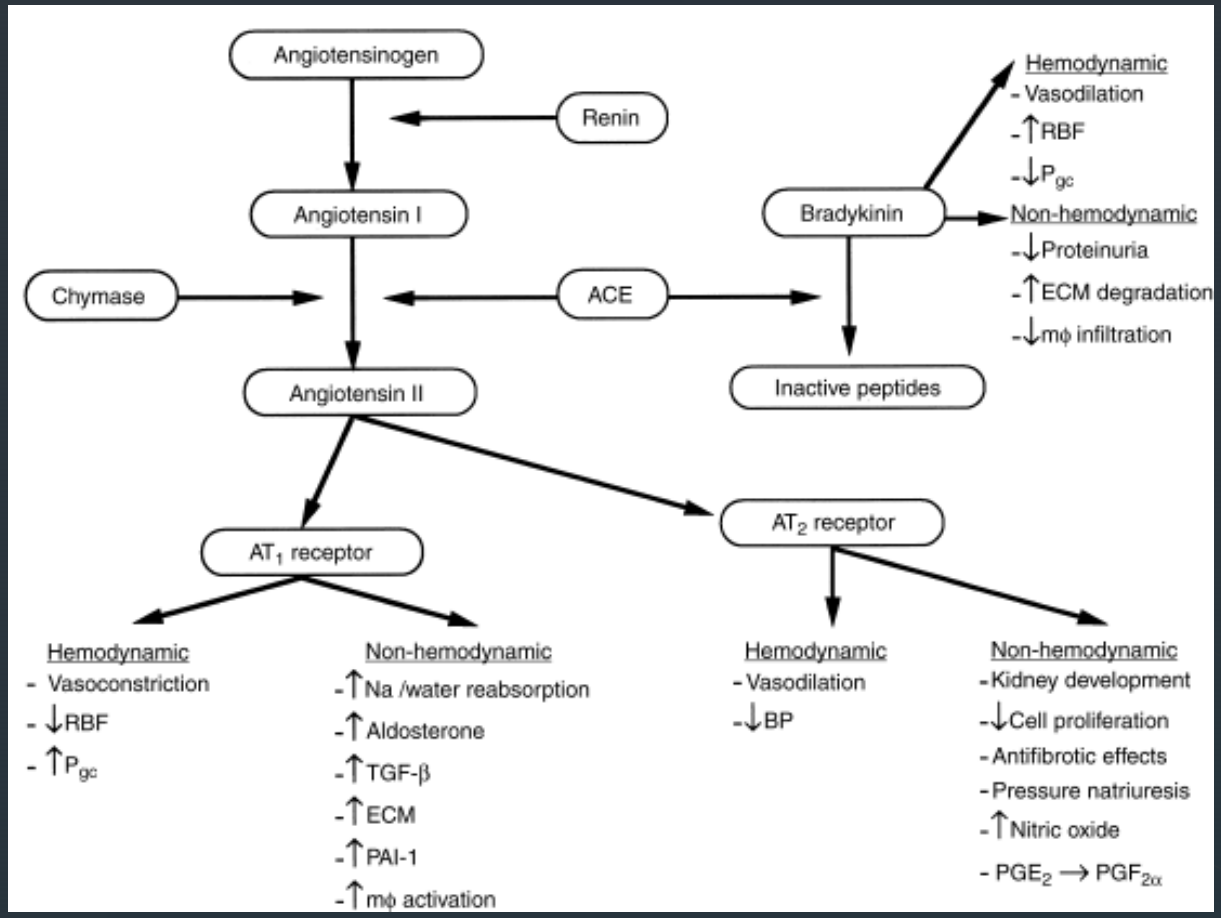
Table 3. Baseline Levels and L

	Income ≥$75,000				P[a]
GFR[b]					
Baseline level (95% CI)	44 (41 to 47)				0.5
Annual change (95% CI)	−1.9% (−4.0% to 0.			.1%)	0.7
SBP *z* scores[c]					
Baseline level (95% CI)	0.20 (−0.01 to 0.4			)	0.9
Annual change (95% CI)	−0.10 (−0.15 to −(			)	0.2
DBP *z* scores[c]					
Baseline level (95% CI)	0.33 (0.17 to 0.50)				0.7
Annual change (95% CI)	−0.10 (−0.15 to −0.05)	−0.06 (−0.10 to −0.01)	0.2	−0.04 (−0.08 to 0.01)	0.05
Height *z* scores[d]					
Baseline level (95% CI)	−0.80 (−1.05 to −0.56)	−0.77 (−1.00 to −0.54)	0.8	−0.98 (−1.23 to −0.73)	0.2
Annual change (95% CI)	0.05 (0.01 to 0.08)	0.01 (−0.02 to 0.03)	0.07	−0.004 (−0.03 to 0.03)	0.03



Hidalgo G. Am J Kidney Dis. 2013

Renoprotective benefits of RAS inhibition: From ACEI to angiotensin II antagonists



MAARTEN W. TAAL and BARRY M. BRENNER KIDNEY INT 2000

Follow-up in SFK. Opinion Guides

Table 3. Opinion-based recommendation for clinical follow-up intervals of children with a solitary functioning kidney

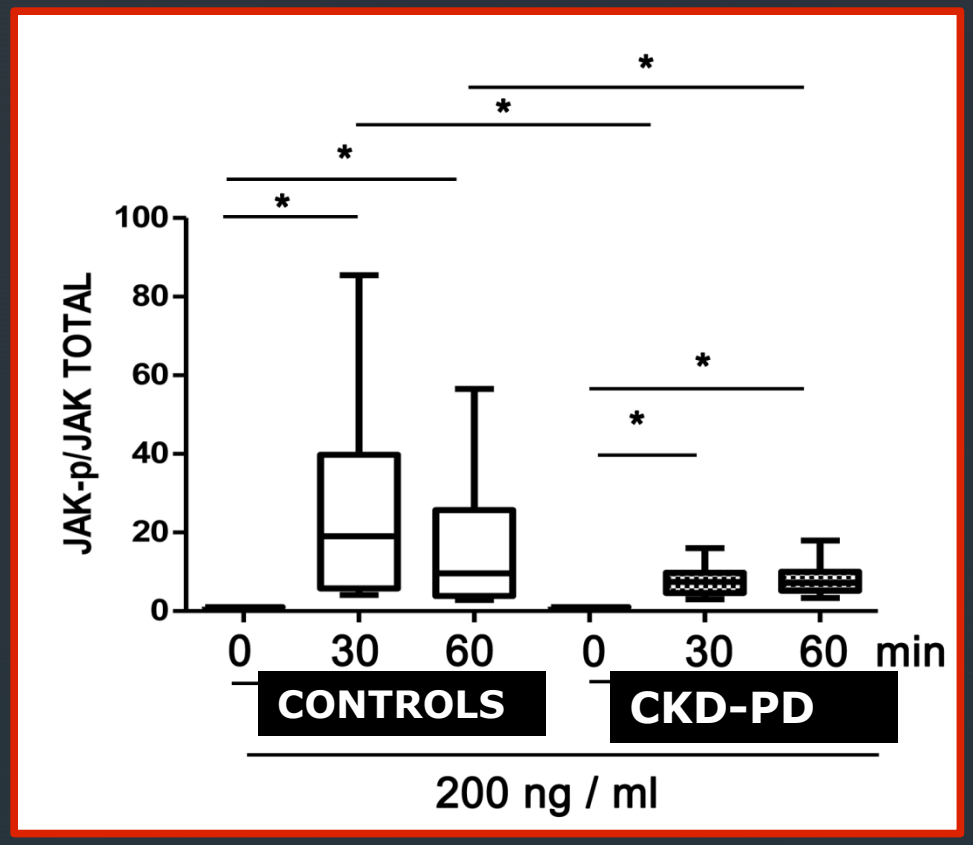
Clinical Parameter/Modality	No Renal Injury		GFR<60 ml/min per 1.73 m^2 or Medication for Proteinuria/Hypertension
	CAKUT −	CAKUT +	
BP	One time per year	Two times per year	Two to four times per year
(Micro)albuminuria	One time per year	Two times per year	Two to four times per year
Serum creatinine/GFR	Every 5 years	Every 5 years	Two to four times per year
Ultrasound	Every 5 years[a]	As indicated	As indicated

Guidelines for the clinical follow-up of children with a solitary functioning kidney. The presented follow-up intervals are based on risk assessment at diagnosis; 24-hour ambulatory BP measurement is preferred in children and adults. Microalbuminuria should be determined in a first fresh morning sample (urinary albumin cutoff value>30 mg/24 h). GFR can be estimated using the commonly used Schwartz formula.

[a]Last ultrasound to be performed at 15–16 years of age.

Cochat P., Ped Nephrol 2018

RESULTS I
pJAK2/JAK2 tot (cyt)



*p < 0,05

Significant decrease in JAK phosphorilation in patients

Significant decrease in JAK 2 phosphorilation in patients

DNA methylation links intrauterine stress with abnormal nephrogenesis

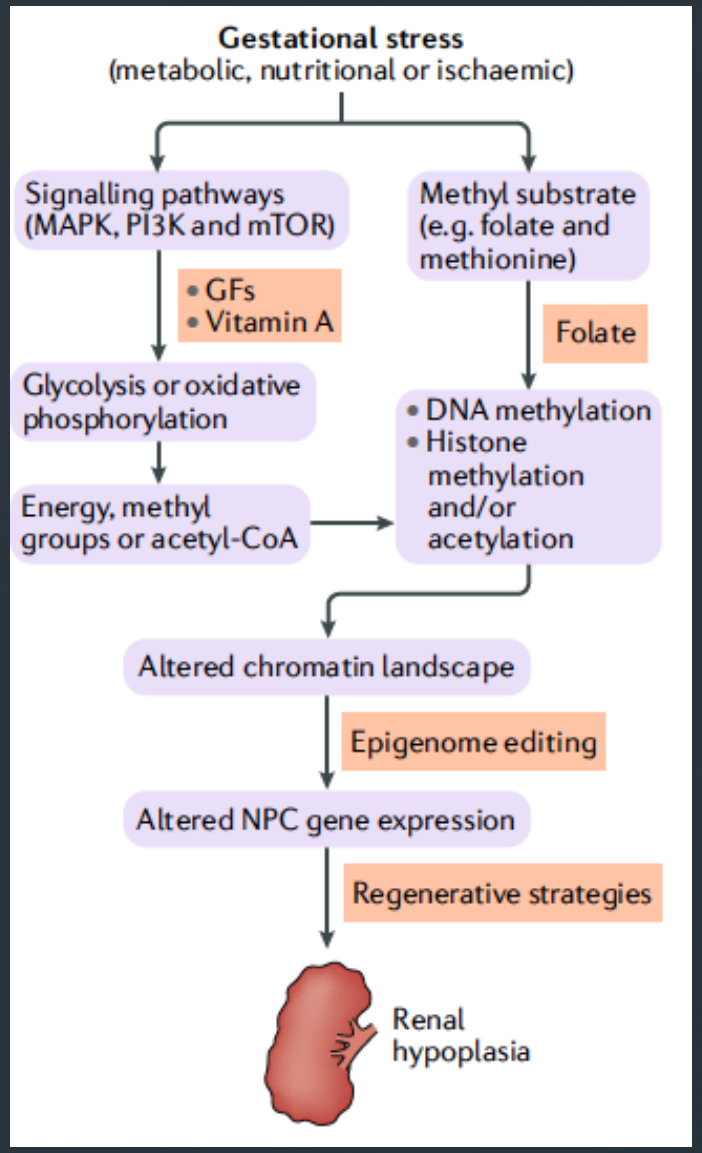
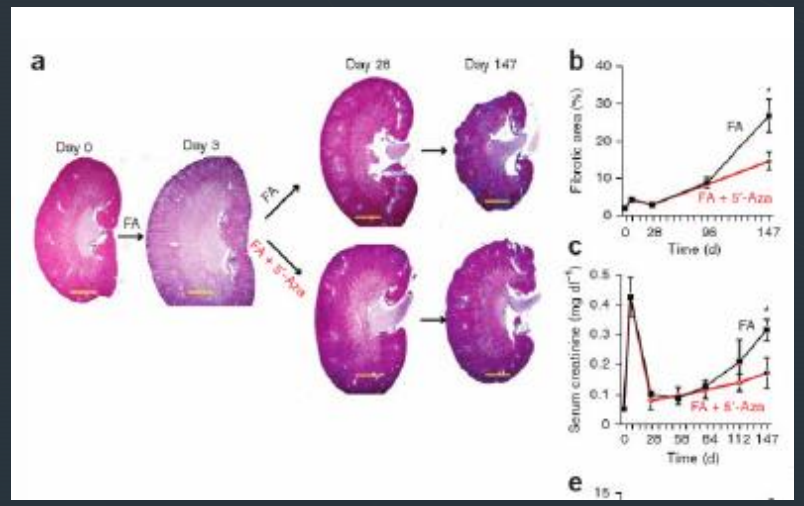


Fig. 1 | **The link between gestational stress, epigenetic mechanisms and congenital nephron deficit.** The renewal of nephron progenitor cells (NPCs), and thus maintenance of the nephrogenic niche, depends on activation of growth and proliferation pathways, such as those involving the mitogen-activated protein kinase (MAPK), phosphoinositide 3- kinase (PI3K) and mechanistic target of rapamycin (mTOR), and their downstream energy-producing pathways. A high level of glycolysis relative to oxidative phosphorylation favours NPC self-renewal. Glycolysis also provides acetyl-CoA and methyl group substrates for DNA and histone modifications. Intrauterine growth restriction (IUGR) can limit the supply of these essential substrates from the mother to the fetus, altering the chromatin landscape and leading to renal hypoplasia. Interventions to enhance availability of these substrates include supplementation with growth factors (GFs) to stimulate glycolysis and folate supplementation. Delivery of targeted epigenome editors might also modulate the accessibility of dynamic developmental enhancers that are affected by IUGR.

El- Dahr S, J. Am.Soc. Nephrol. 2018

Methylation determines fibroblast activation and fibrogenesis in the kidney

Fibrogenesis is a pathological wound repair process that fails to cease, even when the initial insult has been removed. Fibroblasts are principal mediators of fibrosis, and fibroblasts from fibrotic tissues fail to return to their quiescent stage, including when cultured in vitro .



These studies demonstrate that epigenetic modifications may provide a molecular basis for perpetuated fibroblast activation and fibrogenesis in the kidney.

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September 26-27, 2019

DNA Methylation Is Reduced in Models of Environmental and Intrauterine Growth Restriction

DNA Methyltransferases Are Enriched in the Nephrogenic Zone of the Developing Kidney

Dnmt1 Is Required for Efficient Nephron Formation