SOLITARY FUNCTIONING KIDNEY

RIÑON UNICO

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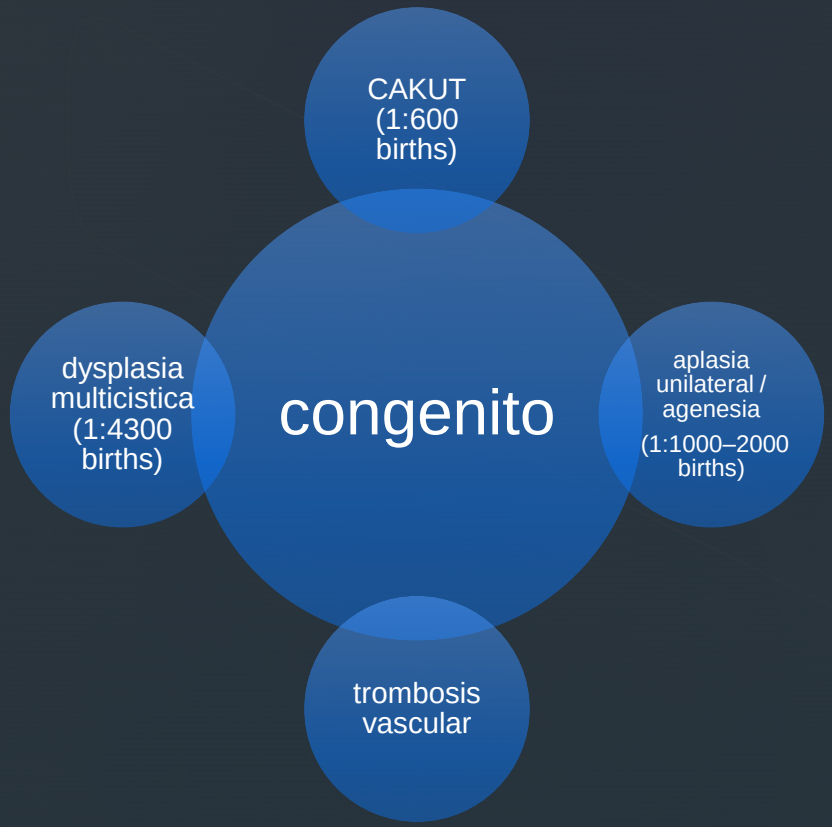
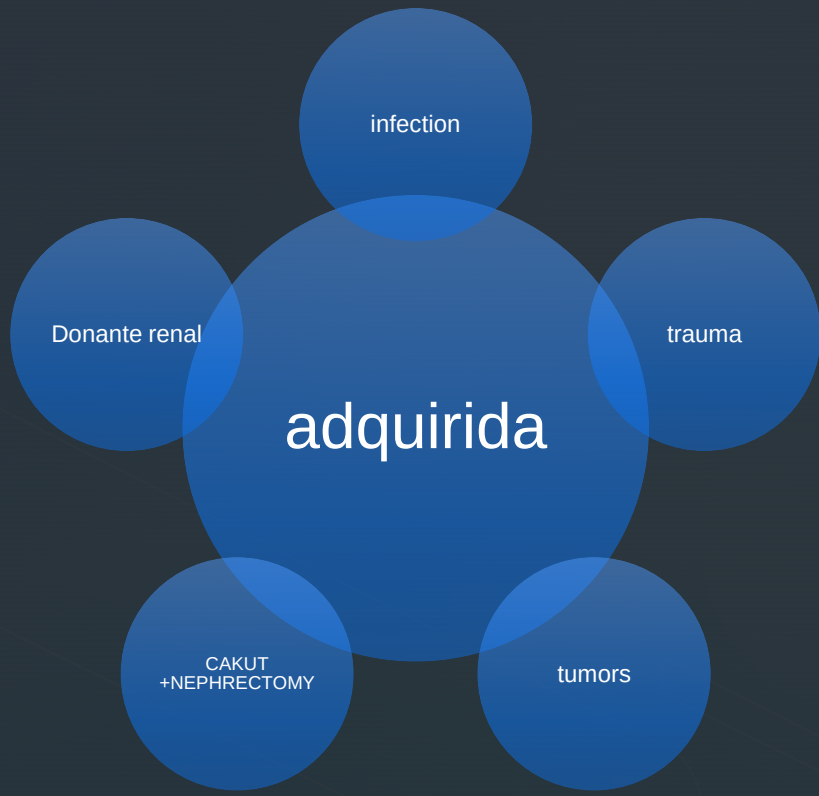
RINON UNICO FUNCIONANTE

1. Reduccion de masa renal. Etiologias
2. Pronostico
3. Monitoreo
4. Mecanismos de dano
5. Consecuencias
6. Prevencion y seguimiento

SOLITARY FUNCTIONING KIDNEY

1. ETIOLOGIES





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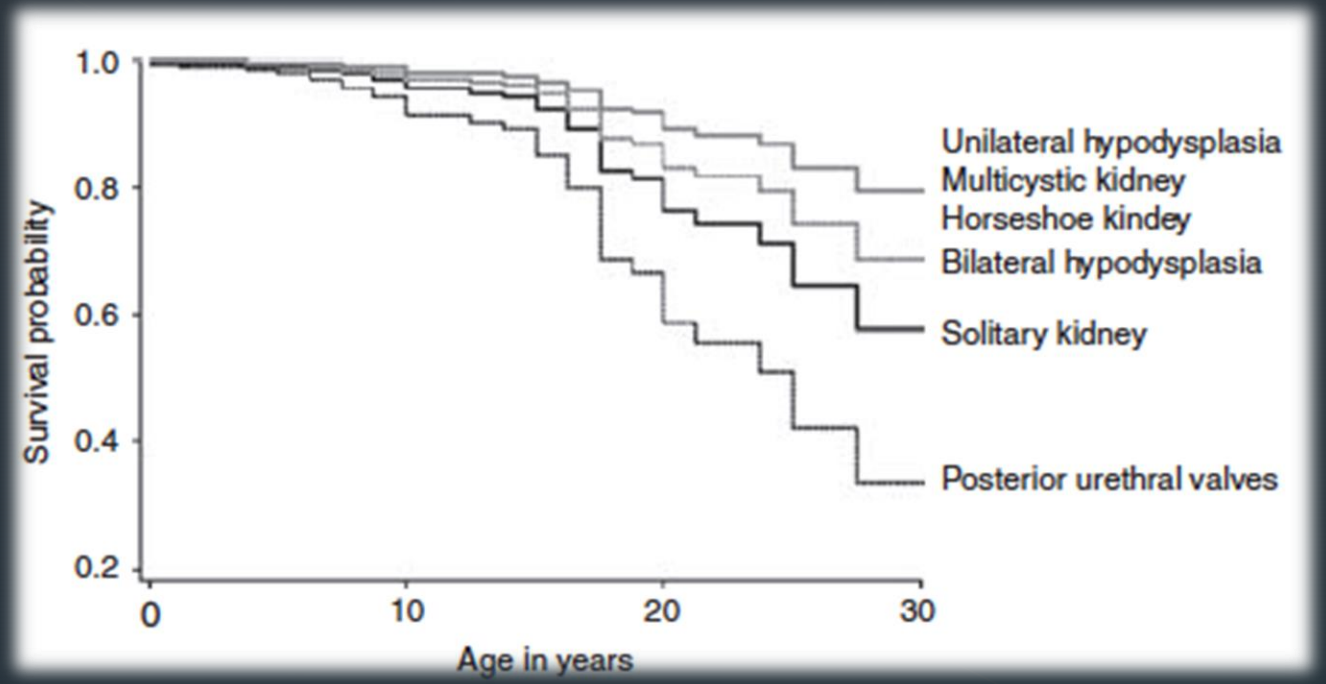
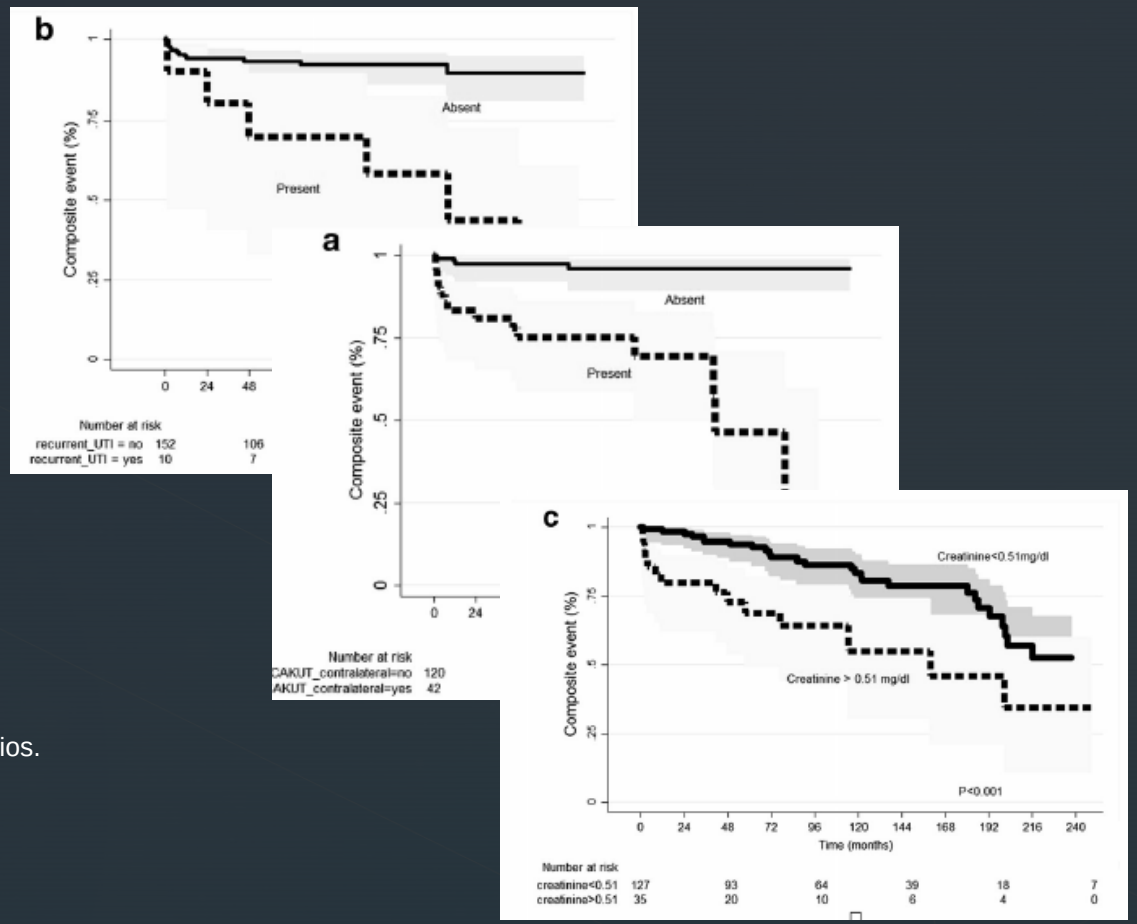
2. PRONOSTICO. 312 pacientes controlados desde RN hasta los 30 anos de edad. Endpoint: dialysis



Sanna-Cherchi S, Kidney Int 2009

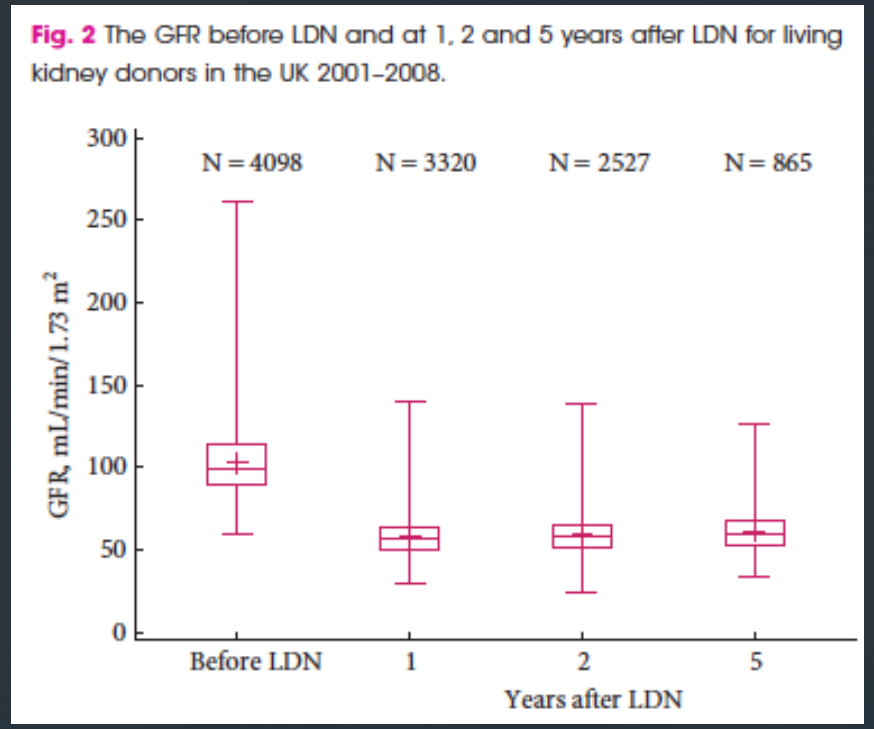
Renal outcome in patients with congenital anomalies of the kidney and urinary tract

- Grupo de estudio: 190 pacientes con SFK congenito, 1987- 2015.
- Etiologia:
  - Agenesia renal, 6.2%
  - hipodisplasia, 12.3%
  - Rinon multicistico (MCDK) 81.5%.
- Eventos de interes:
  - eGFR < 60 ml/min per 1.73 m2,
  - hipertension,
  - proteinuria.
- Primary endpoint : tiempo hasta la ocurrencia de uno de los eventos primarios.
- Seguimiento promedio: 8.5 anos
- Predictores de un evento primario:

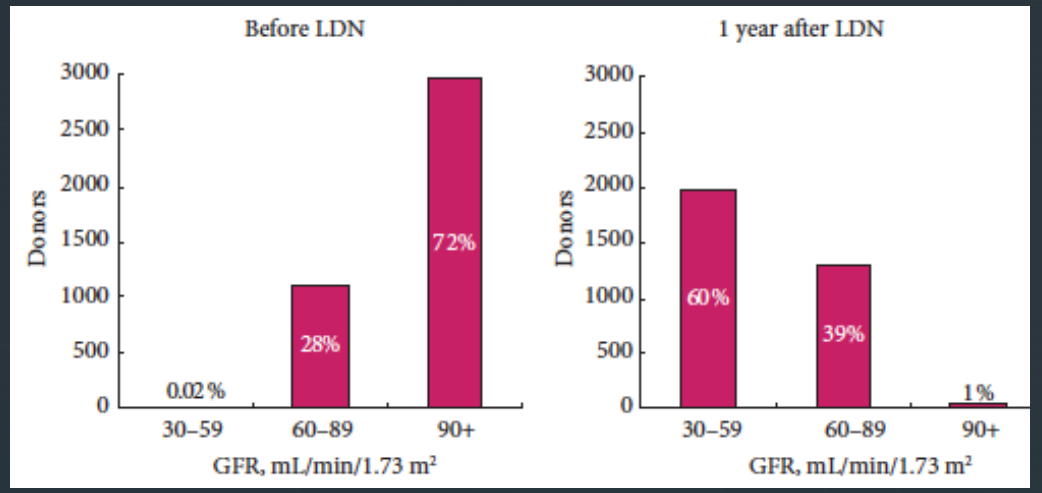


Poggiali I., Ped Nephrol 2018

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



UK Transplant Registry (UKTR)
NHS Blood and Transplant (NHSBT) Kidney and Pancreas Research Group
Donantes periodo 2001 and 2008.



Patel N., 2013 BJU International

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3. MONITORING

- Estos resultados han originado la recomendacion de monitoreo para todo paciente con SFK desde la infancia, lo cual incluye examen de orina, presion arterial, y monitoreo de Filtracion Glomerular.
- Desafortunadamente, el gold standard para evaluar la GFR por clearance de inulina no es practicable en la rutina clinica.

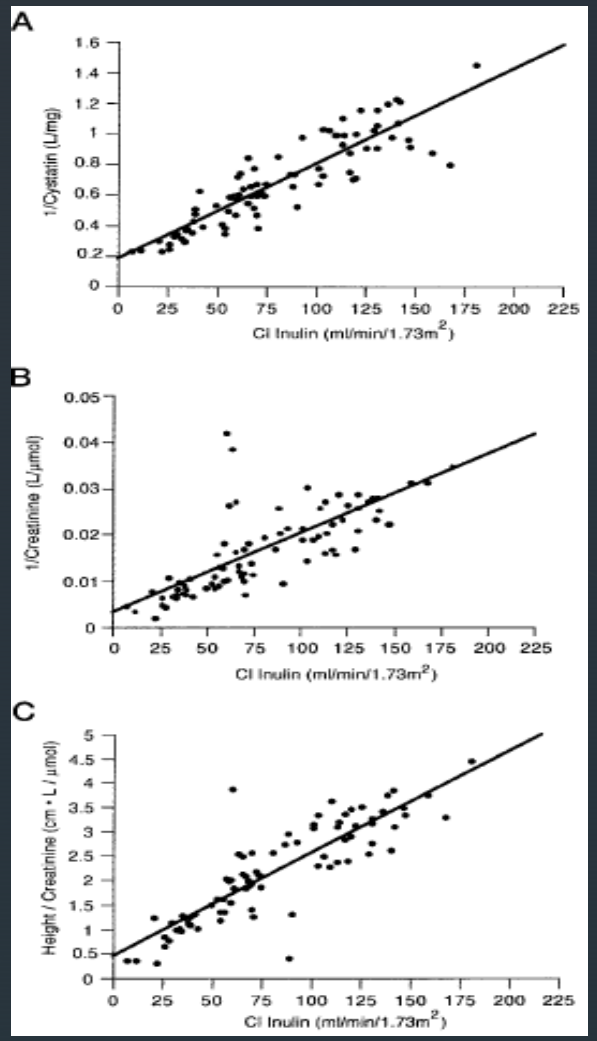
MONITOREO DE VFG

- 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)

- DESVENTAJAS DE LA MEDICION VFG MEDIANTE CREATININA
  - La molecula no se elimina solo por filtracion glomerular, sino que existe secresion tubular proximal. La secresion tubular es muy variable, y aumenta con la disminucion de la function renal. Lo cual limita la exactitud del calculo a medida que declina la velocidad de filtracion glomerular.
  - La concentracion de creatinine serica esta fuertemente influenciada por la masa muscular, lo cual implica un constant cambio durante el crecimiento.

Y entonces que…?

Cystatin C—A New Marker of Glomerular Filtration Rate in Children Independent of Age and Height



Bivariate plots of CIn versus 1/Cys, 1/Crea, and Ht/Crea.
Linear regression analysis:

1/Cys (r 0.88; P <0001),

1/Crea (r 0.72; P <0001),

Ht/Crea (r 0.86; P <0001)

Bokenkamp A., Pediatrics 1998

CYSTATIN C

- Cystatin C es una proteina de bajo PM, de produccion ubicua a un ritmo regular en el organismo, y su valor reciproco ha mostrado una alta correlacion con la velocidad de filtracion glomerular (GFR).
- Su produccion es independiente de condiciones agudas, inflamatorias, masa muscular, genero, composicion corporal y edad (despues de los 12 meses).
- Los niveles plasmaticos de Cystatin C son aproximadamente 1 mg/l en individuos sanos.
- La proteina se catabolize y es completamente reabsorvida en el tubule proximal, con un minimo de excresion urinaria.
- Las variaciones inter-individuales de cystatin C son aprox un 25%, comparado a un 93% de la creatinina. Todas estas ecuaciones han sido validadas en sujetos con 2 rinones.

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 a SFK, edades 1.5-19.8 anos.

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

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

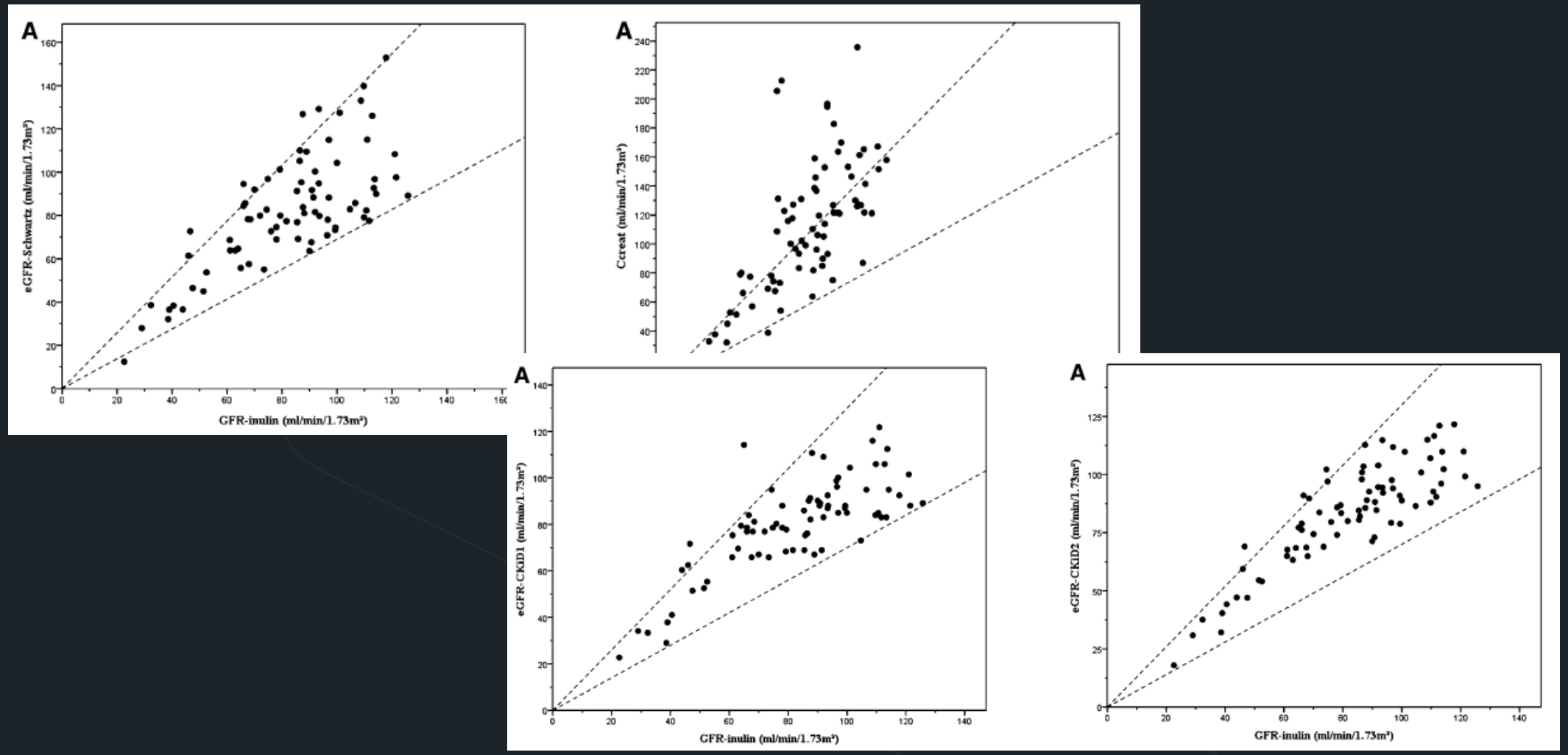
$$Ccreat\ (\mathrm{ml/min/1.73m^2}) = \frac{urine\ creatinine\ (mg/dl)}{serum\ creatinine\ (mg/dl)} \times \frac{urine\ volume(ml)}{time\ (hours) \times 60} \times \frac{1.73}{body\ surface\ area(m^2)}$$

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

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

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

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



The KIMONO Study

The KIMONO Study

www.kidney.org/proffesionals/KDOQI/gfr_calculatorPed

- El studi[illegible]MONO evidencio que la ecuacion combinada de cystatin C/c[illegible]tine/BUN (CKiD) estima la VFG con la mas alta precision. Por ello [illegible]ecomienda el uso de esta equation para monitoreo en pediatria de pacientes con SFK.

- En caso de que la medicion de cystatin C no este disponible, eGFR-Schwartz es una aceptable alternative, mas precisa que el clearance de creatinina, el cual debe ser abandonado.

Westland R., Clin J Am Soc Nephrol, 2013

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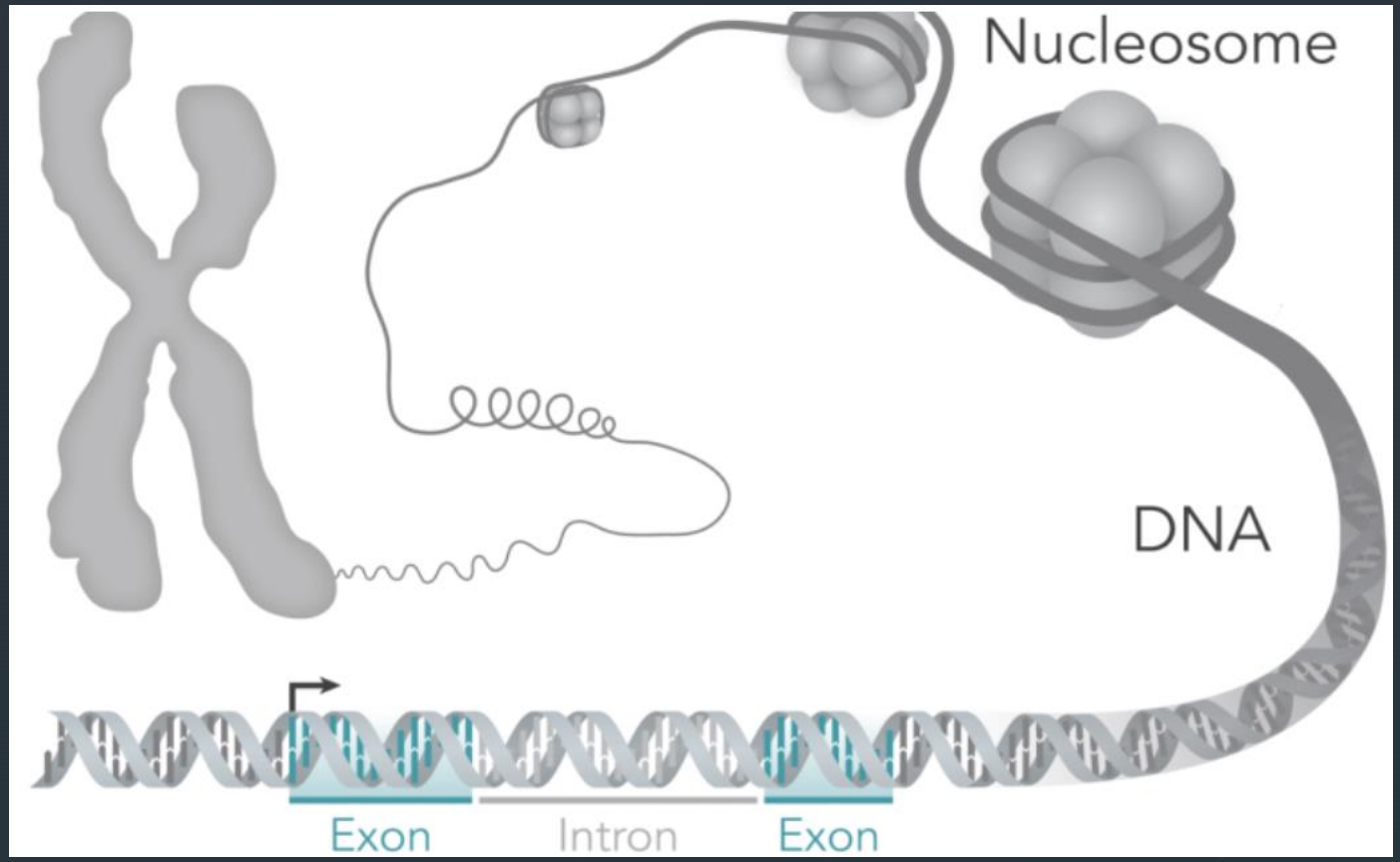
4. MECANISMOS DE DAÑO



Mechanisms of Injury. Renal Development

- Definitive human renal development is initiated at the fifth gestational week and characterized by complex interactions between the 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.

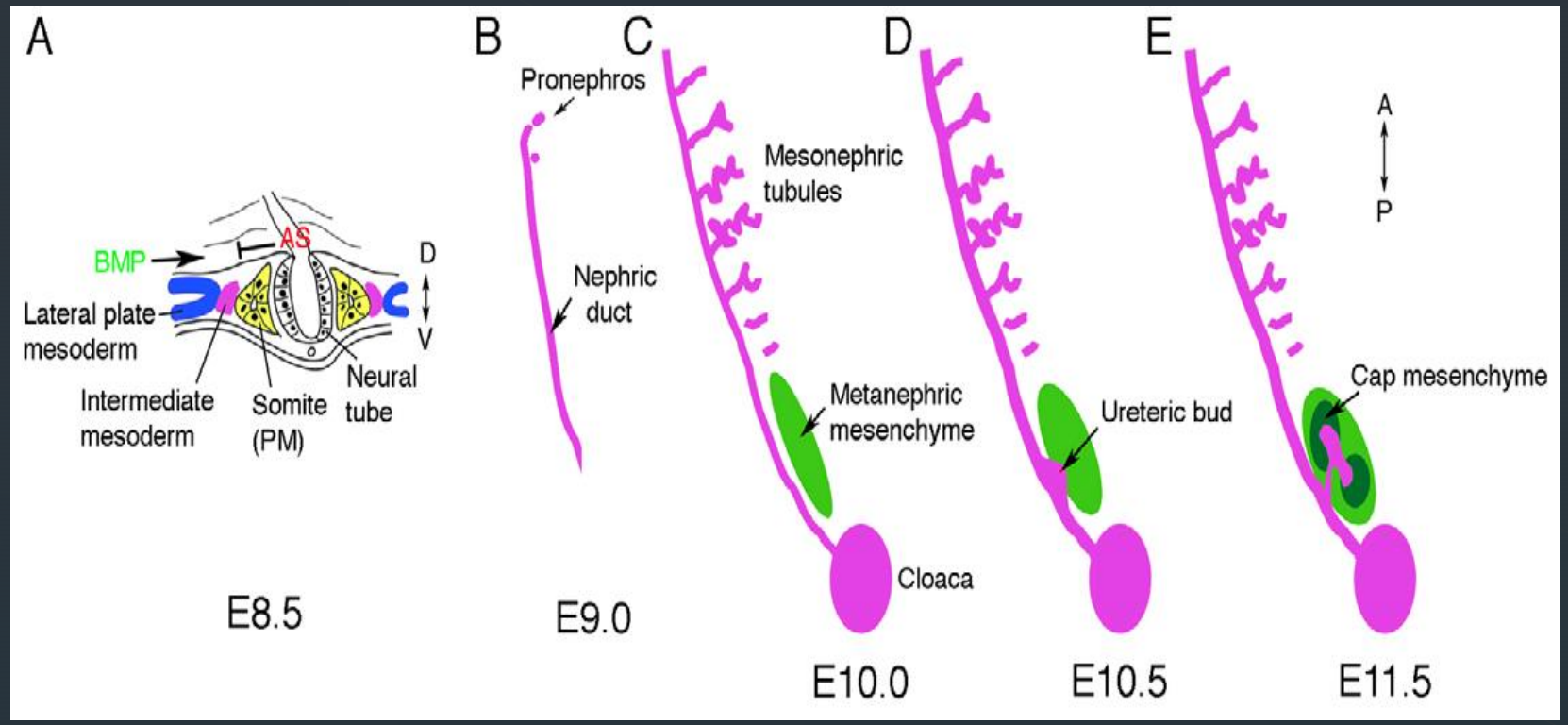
Mechanisms of Injury. Renal Development

In amniotes, the kidney arises from the intermediate mesoderm, between the paraxial somatic mesoderm and the lateral plate mesoderm

Mesonephric tubules are developed as the nephric duct reaches the cloaca

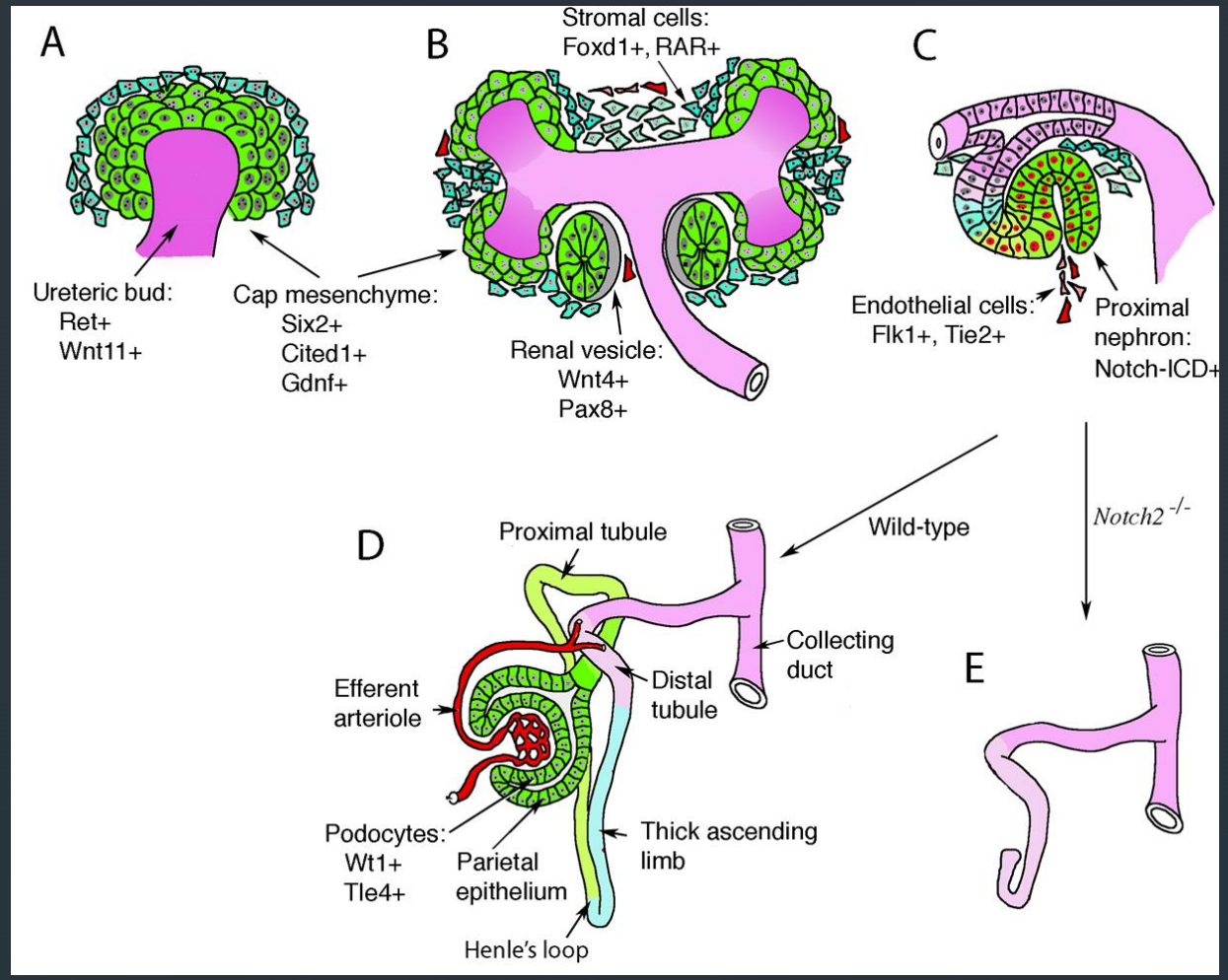
Posterior cells adjacent to the duct form an aggregate called the metanephric mesenchyme

an outgrowth of the duct, the ureteric bud (UB), invades the metanephric mesenchyme.



Mesenchymal cells are the epithelial stem cells of the nephron and generate the glomerular podocyte cells, the parietal epithelium, the proximal tubules, and the distal tubules.

Mechanisms of Injury. Renal Development and Genetics



The ureteric bud of the mesonephric duct, from which the renal pelvis, ureter, and lower urinary tract originate,

The metanephric mesenchyme, from which the renal parenchyma originates.

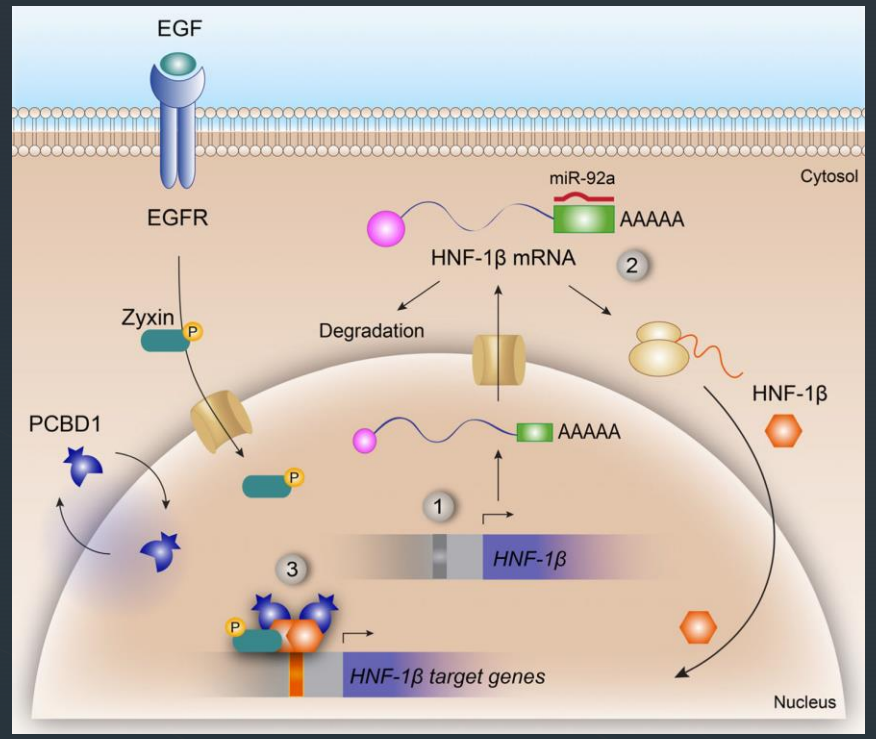
Genetic factors

- 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, Int. J. Dev. Biol, 1999), 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.

New insights into the role of HNF-1β in kidney (patho)physiology

- Hepatocyte nuclear factor-1β (HNF-1β, vHNF1) is a developmentally regulated transcription factor required for tissue-specific gene expression in the epithelial cells of many organs, including kidney, pancreas, liver, and genitourinary tract.
- HNF-1β is an essential transcriptional regulator of renal epithelial organization and differentiation.
- HNF-1β is expressed in the WD, UB, RV, comma-shaped bodies, S-shaped bodies, and developing renal tubules.
- HNF1B mutations cause congenital anomalies of the kidney and urinary tract.
- Humans who carry HNF1B mutations develop heterogeneous renal abnormalities, including multicystic dysplastic kidneys, glomerulocystic kidney disease, renal agenesis, renal hypoplasia,and renal interstitial fibrosis

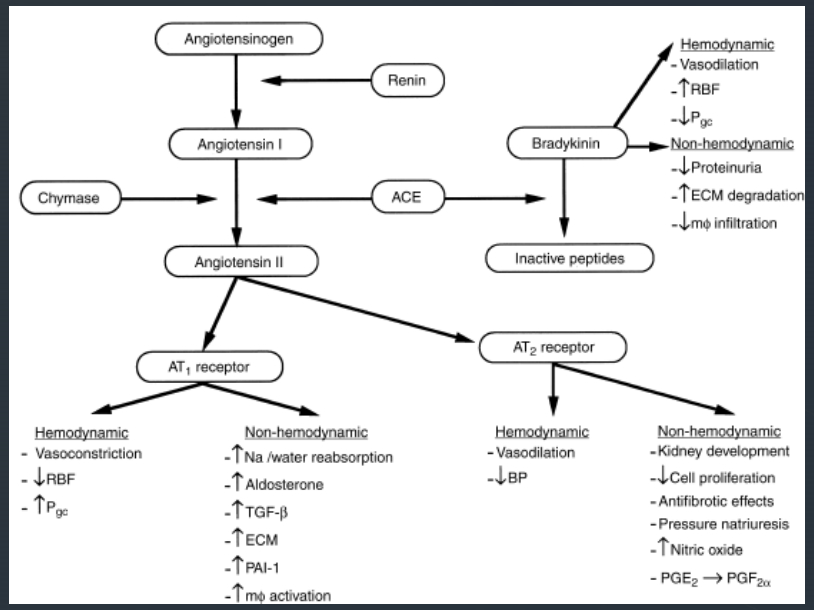


Ped Nephrol 2018

Mechanisms of Injury. Renal development and Environmental factors

- Environmental factors that disturb renal development include medications administered during pregnancy
  - Angiotensin-converting enzyme [ACE] inhibition,
  - dexamethasone,
  - antiepileptic drugs
  - aminoglycosides,
  - maternal diabetes.
  - prematurity
- 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

Mechanisms of Fetal and Neonatal Renal Impairment by Pharmacologic Inhibition of Angiotensin



Chevalier R., Current Medicinal Chemistry, 2012

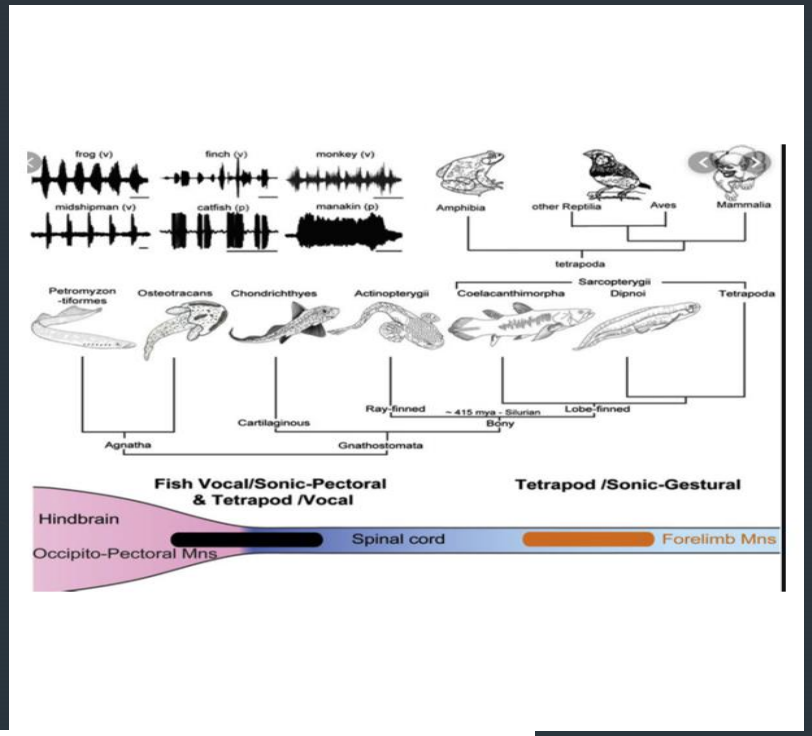
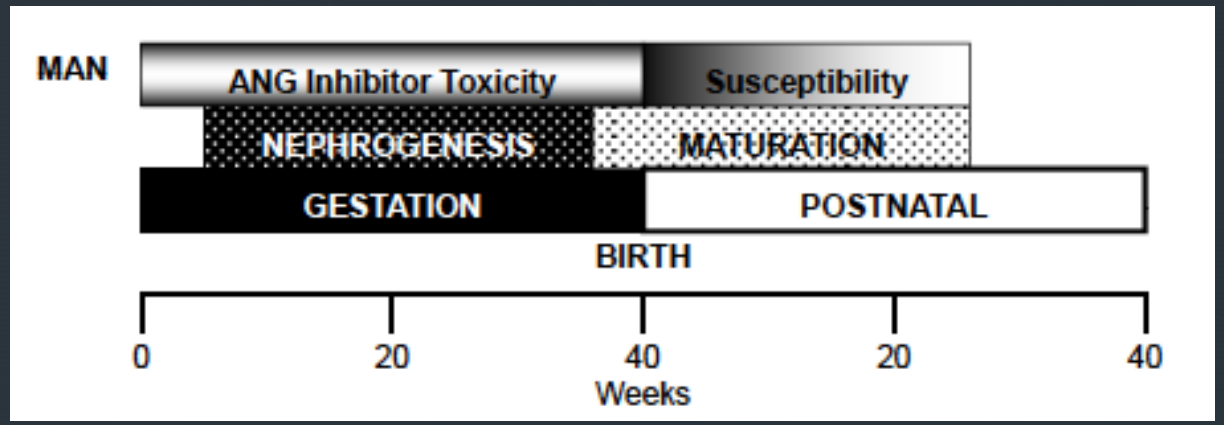


Table 2. Comparison of Maturation of the Renin-Angiotensin System in Metanephros of Rat, Mouse, and Man (Data from Reference [30])

Species	Gestational Age	Gestation Duration	Renin	ACE	AT1 Receptor	AT2 Receptor
		Days	Gestational Age of First Appearance, Days (% Total Gestation)			
Rat	Day 12 to PP day 7-10	21	17 (80)	PP-1	15 (70)	17 (80)
Mouse	Day 11 to PP day 20	20	14 (70)		14 (70)	14 (70)
Man	Days 30-245	268	56 (21)	56 (21)	56 (21)	56 (21)

Mechanisms of Fetal and Neonatal Renal Impairment by Pharmacologic Inhibition of Angiotensin



Chevalier R., Current Medicinal Chemistry, 2012

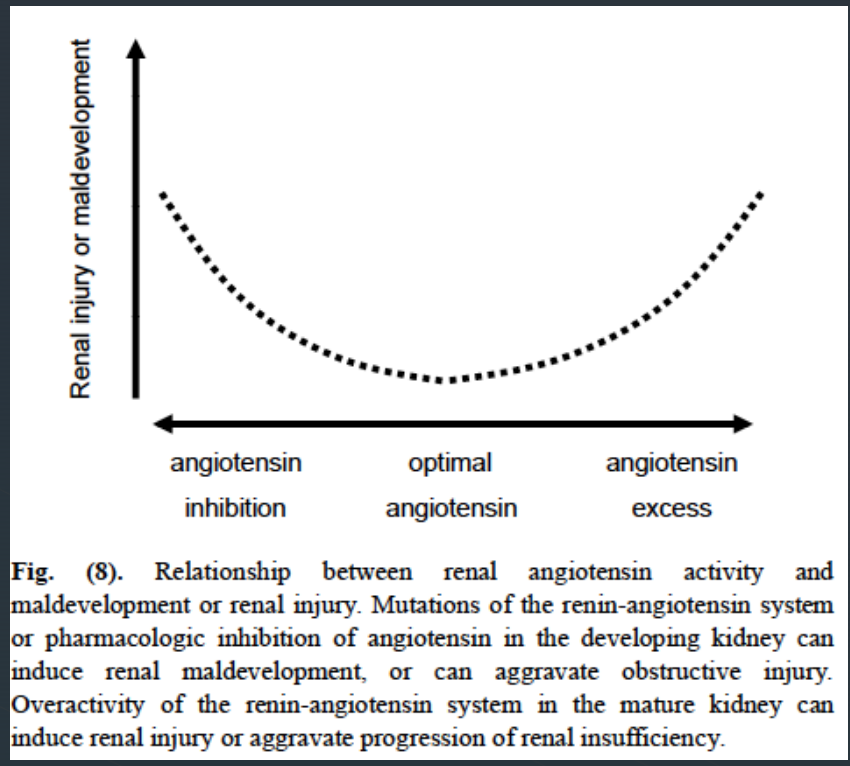


Fig. (8). Relationship between renal angiotensin activity and maldevelopment or renal injury. Mutations of the renin-angiotensin system or pharmacologic inhibition of angiotensin in the developing kidney can induce renal maldevelopment, or can aggravate obstructive injury. Overactivity of the renin-angiotensin system in the mature kidney can induce renal injury or aggravate progression of renal insufficiency.

Mechanisms of Injury. Hyperfiltration Hypothesis

Dietary Protein Intake and the Progressive Nature of Kidney Disease:

The Role of Hemodynamically Me… Glomerular Injury in the Pathogen… Progressive Glomerular Sclerosis in… Renal Ablation, and Intrinsic Renal…

BARRY M. BRENNER, M.D.,
TIMOTHY W. MEYER, M.D.,
AND THOMAS H. HOSTETTER, M.…

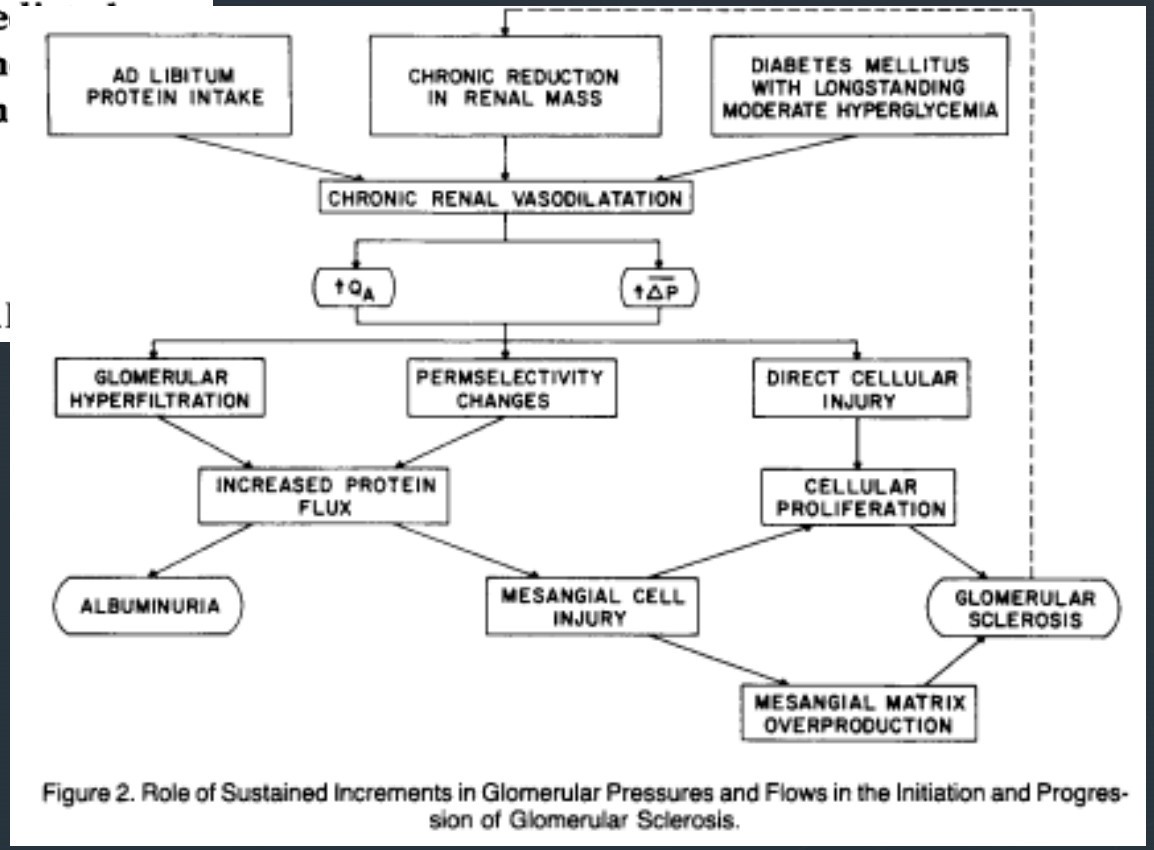


Figure 2. Role of Sustained Increments in Glomerular Pressures and Flows in the Initiation and Progression of Glomerular Sclerosis.

Mechanisms of Injury. Hyperfiltration Hypothesis

Group I: 8 control rats that underwent laparotomy and were fed a normal diet;

Group II, 9 rats that underwent right nephrectomy and segmental infarction of five-sixths of the left kidney and were fed a normal diet;

Group III, seven rats that underwent the same renal ablative procedure and were fed a low protein diet.

SNGFR | **Whole GFR** | Glom plasma flow rate | Resist AA | Resist AE | Glom capillary hydraulic pressure | **Delta glom transcap hydraulic pressure**

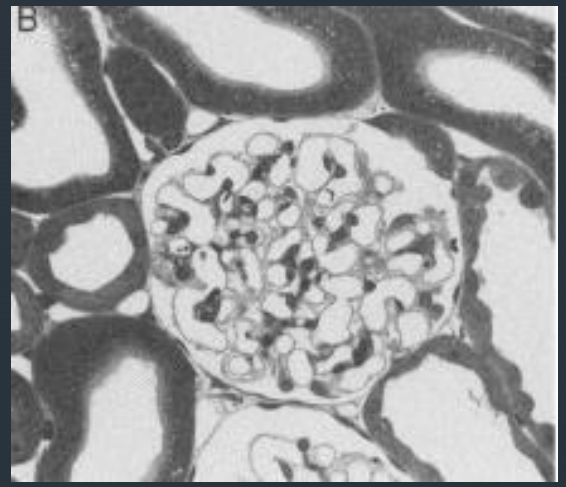
	SNGFR, nl/min	GFR, ml/min	Q_A, nl/min	$R_A \times 10^{10}$ dyn·s·cm^{-5}	$R_E \times 10^{10}$ dyn·s·cm^{-5}	$\bar{P}_{GC}$, mmHg	$\overline{\Delta P}$, mmHg
Group I	27.8	0.72	74	3.5	2.2	49	37
($n = 8$)	3.2	0.06	11	0.4	0.2	1	1
Group II	62.5	0.21	187	1.4	1.1	63	44
($n = 9$)	6.4	0.03	20	0.2	0.2	2	2
Group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

Hostetter T, Am J Physiol. 1981

Mechanisms of Injury. Hyperfiltration Hypothesis

This functional hypertrophy is generally considered beneficial in the sense that it minimizes the reduction in total glomerular filtration rate that would otherwise occur. However, a number of workers have shown that a pathological process of sclerosis eventually occurs in the glomeruli of these residual nephrons

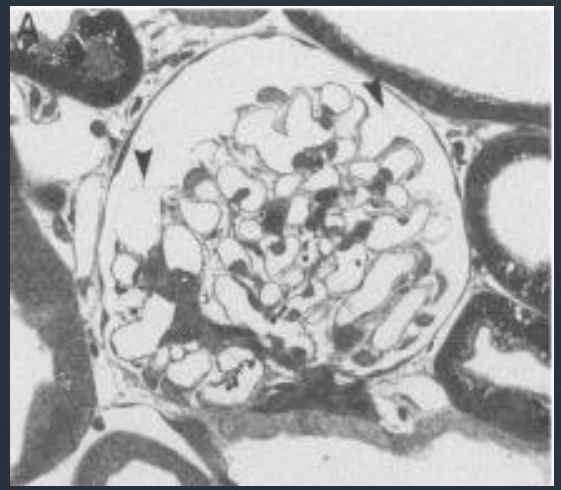
Group III



Delta glom transcap hydraulic pressure

$\overline{\Delta P}$, mmHg
37
1
44
2
32
3
<0.025
<0.01
NS

Group II

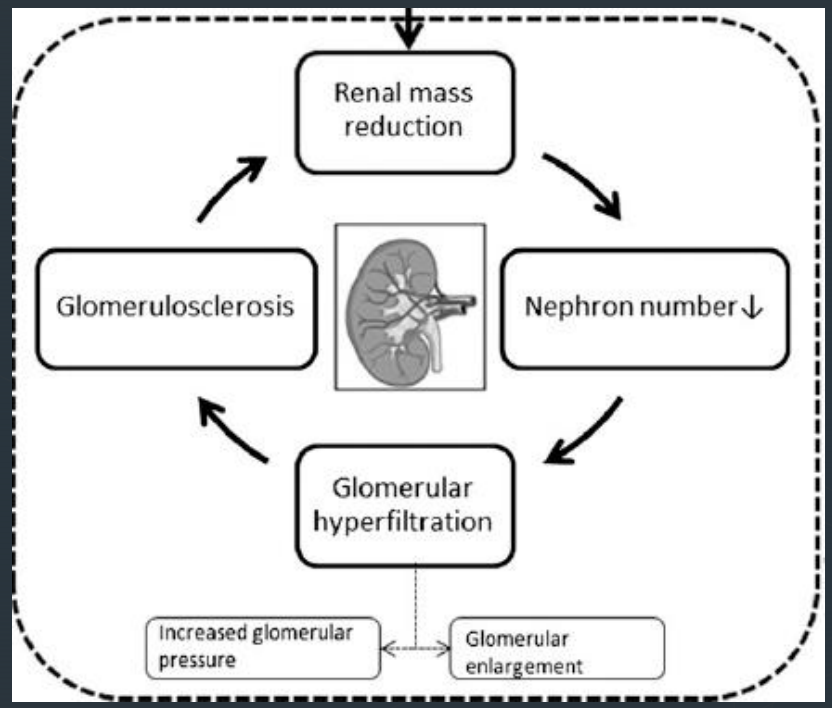


Hostetter T, Am J Physiol. 1981

Mechanisms of Injury. Consecuencias

- **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** ↓

Westland R, Clin J Am Soc Nephrol 2014

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

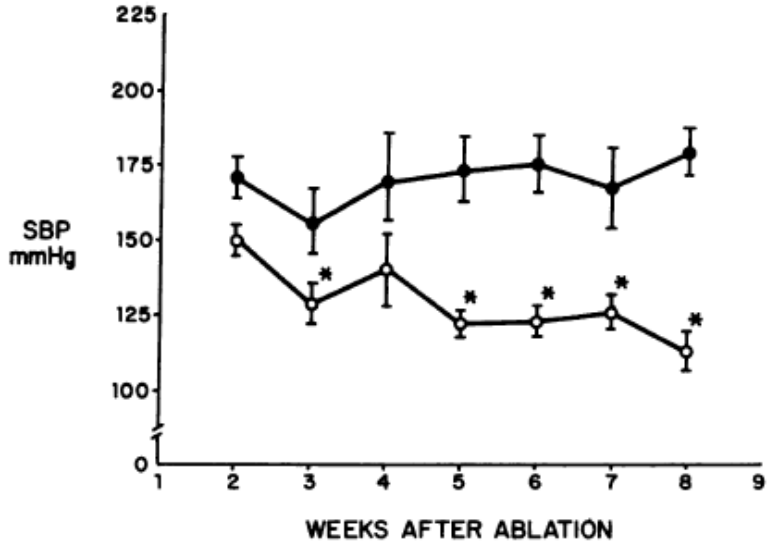


Figure 1. Systolic blood pressure (SBP) measured by the tail cuff method in rats followed for 8 wk after 5/6 nephrectomy. Untreated rats (group 3) (●) exhibited sustained systemic hypertension, while enalapril treatment (group 4) (○) maintained systemic blood pressure at normal levels. Values are means±SEM.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

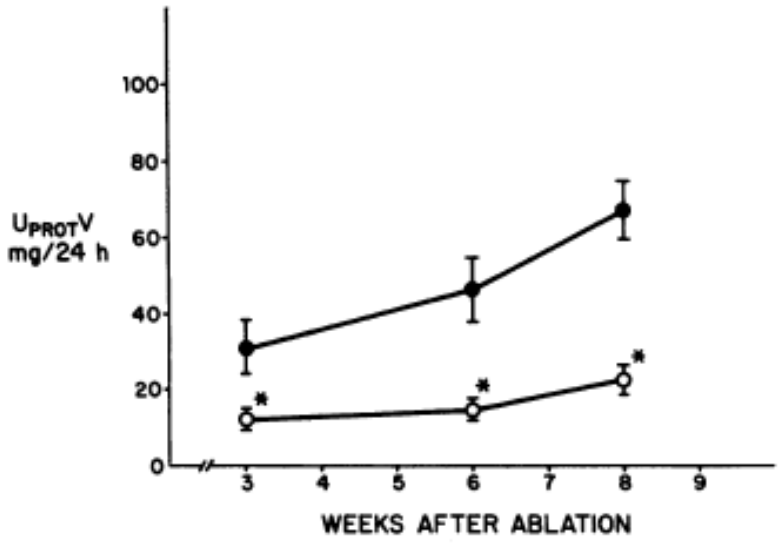
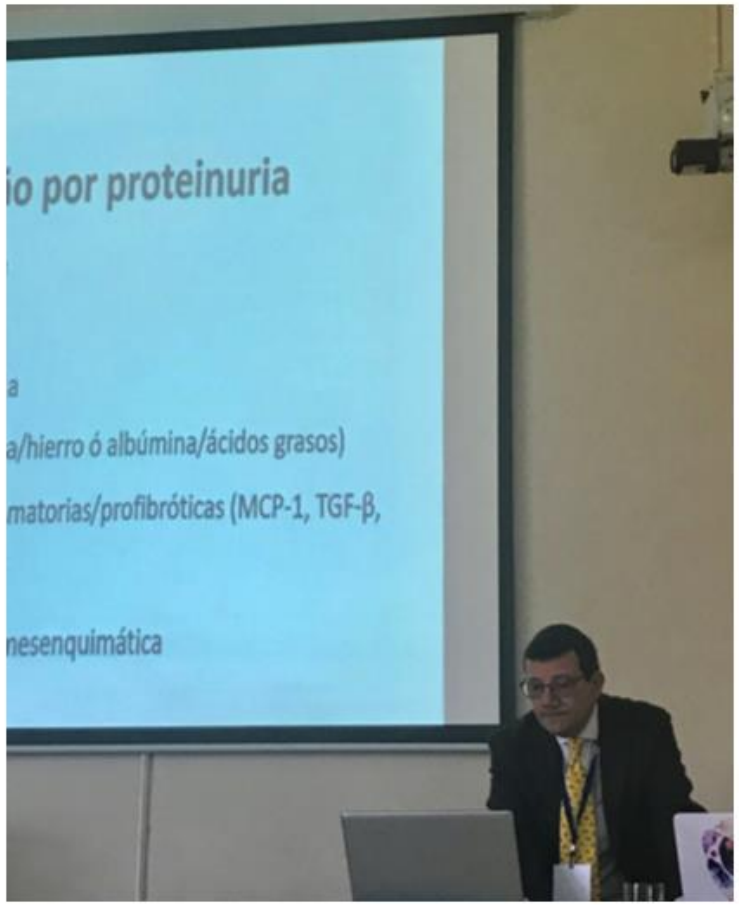


Figure 2. Urinary protein excretion rates. 24-h urinary protein excretion ($U_{PROT}V$) in rats with 5/6 nephrectomy. Untreated rats (group 3) (●) developed progressive proteinuria over the 8-wk course, while treatment with enalapril (group 4) (○) significantly limited proteinuria. Values are means±SEM.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

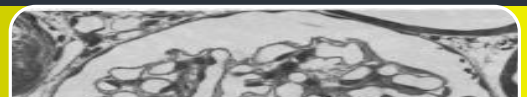
Anderson Sh. J Clin Invest 1985

SFK. Clinical consequences. Proteinuria

Para mayor información remitirse a…….



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

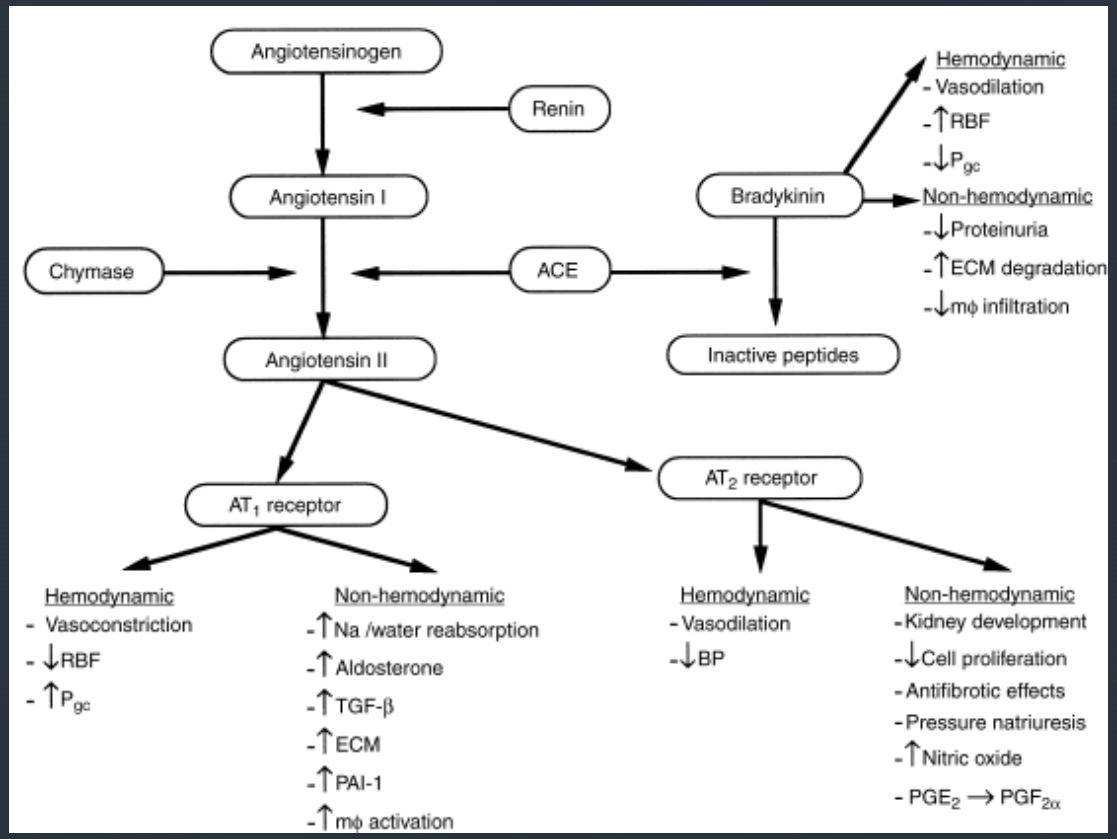
Table 2 Blood pressure at time of diagnosis (T0) and after 14 years follow-up (T14)

	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

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



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

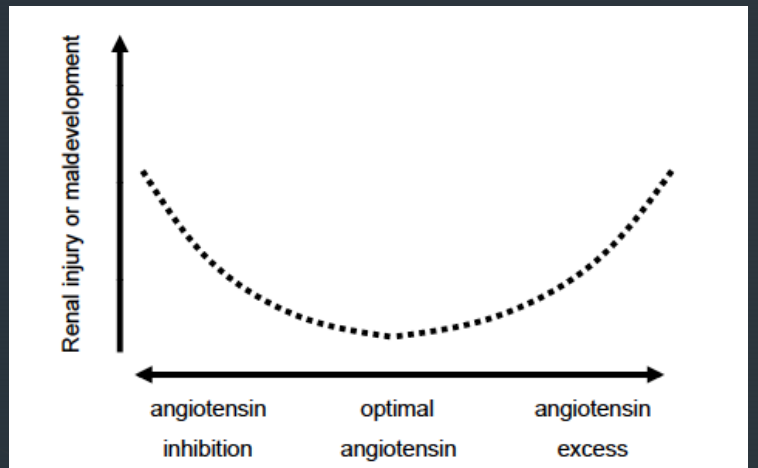


Fig. (8). Relationship between renal angiotensin activity and maldevelopment or renal injury. Mutations of the renin-angiotensin system or pharmacologic inhibition of angiotensin in the developing kidney can induce renal maldevelopment, or can aggravate obstructive injury. Overactivity of the renin-angiotensin system in the mature kidney can induce renal injury or aggravate progression of renal insufficiency.

Follow-up in SFK. Clinical Implications of the Solitary Functioning Kidney

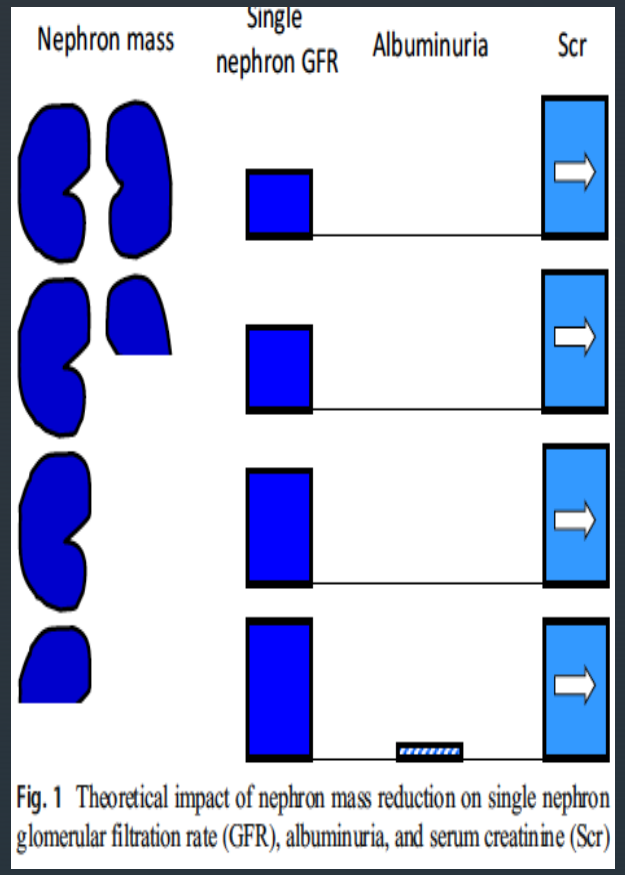


Fig. 1 Theoretical impact of nephron mass reduction on single nephron glomerular filtration rate (GFR), albuminuria, and serum creatinine (Scr)

Cochat P., Ped Nephrol 2018

RECOMENDACIONES

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

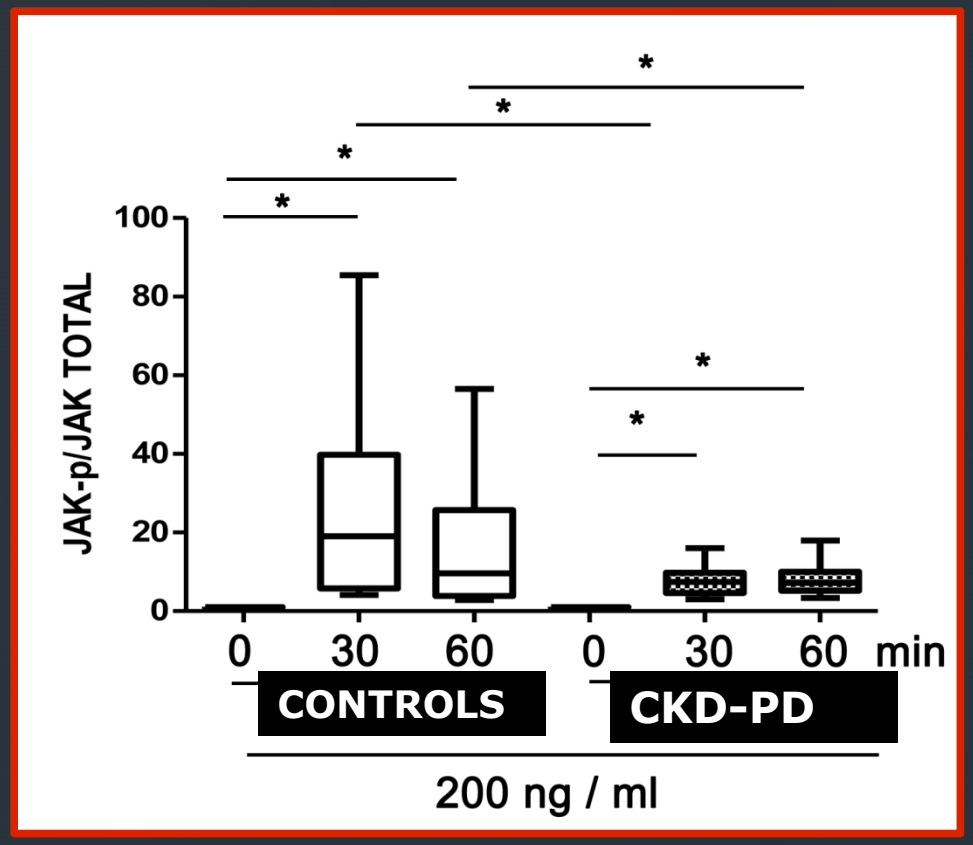
Guidelines for the clinical follow-up of children with a solitary functioning kidney. The presented follow-up intervals are based on risk assessment at diagnosis; 24-hour ambulatory BP measurement is preferred in children and adults. Microalbuminuria should be determined in a first fresh morning sample (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.

Westland R, Clin J Am Soc Nephrol 2014


HOSPITAL LUIS CALVO MACKENNA

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

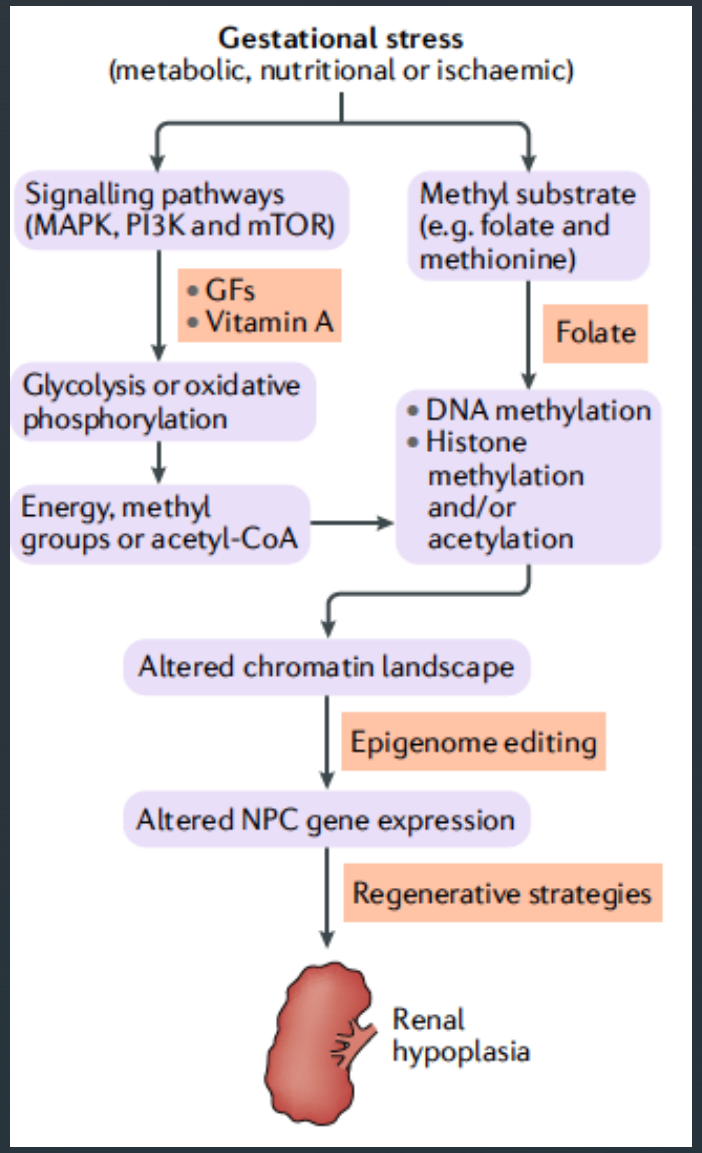
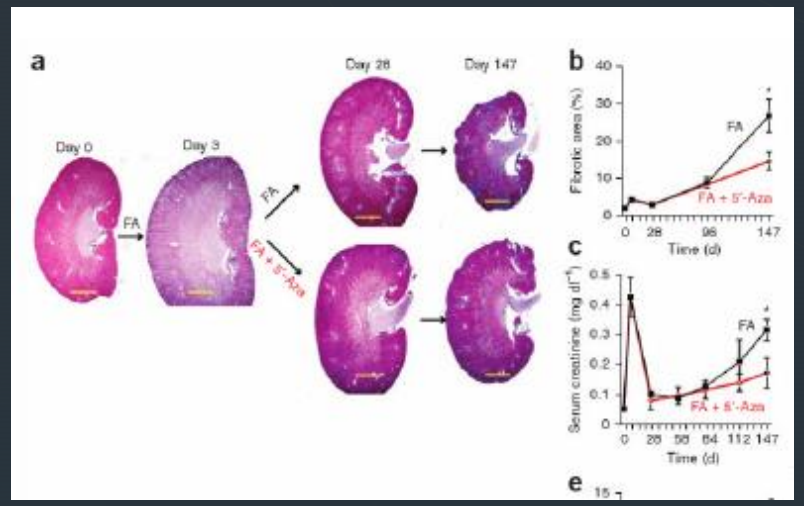


Fig. 1 | **The link between gestational stress, epigenetic mechanisms and congenital nephron deficit.** The renewal of nephron progenitor cells (NPCs), and thus maintenance of the nephrogenic niche, depends on activation of growth and proliferation pathways, such as those involving the mitogen-activated 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