Nefropatía Diabética

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Review

Diabetic nephropathy: Time to withhold development and progression - A review

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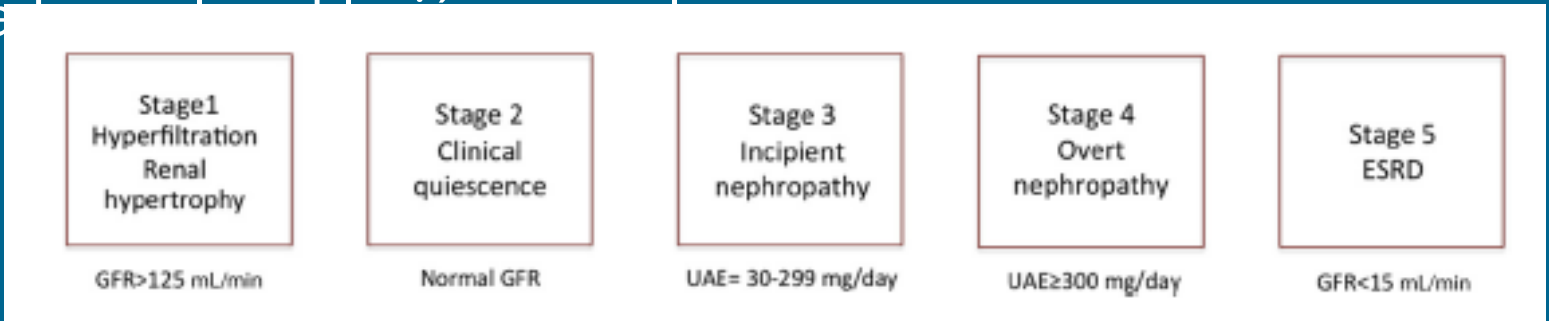
Introducción

- ERCT:
    - 33% en DM1.
    - 10 - 20% de DM2.

- Nefropatía diabética (ND): Aumenta en 6 veces la mortalidad a 10 años compara



Introducción

*1982: “microalbuminuria” identificada como factor de riesgo y de mortalidad en DM.

*2017:

- El uso de de inhibidores del SRAA parece no ser útil para el tratamiento de estadíos iniciales de la ND.
- Esto motivó a nuevas estrategias de tratamiento.

Perkins BA, Ficociello LH, Roshan B, Warram JH, Krolewski AS. In patients with type 1 diabetes and new onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. Kidney Int 2010;77(1):57–64.

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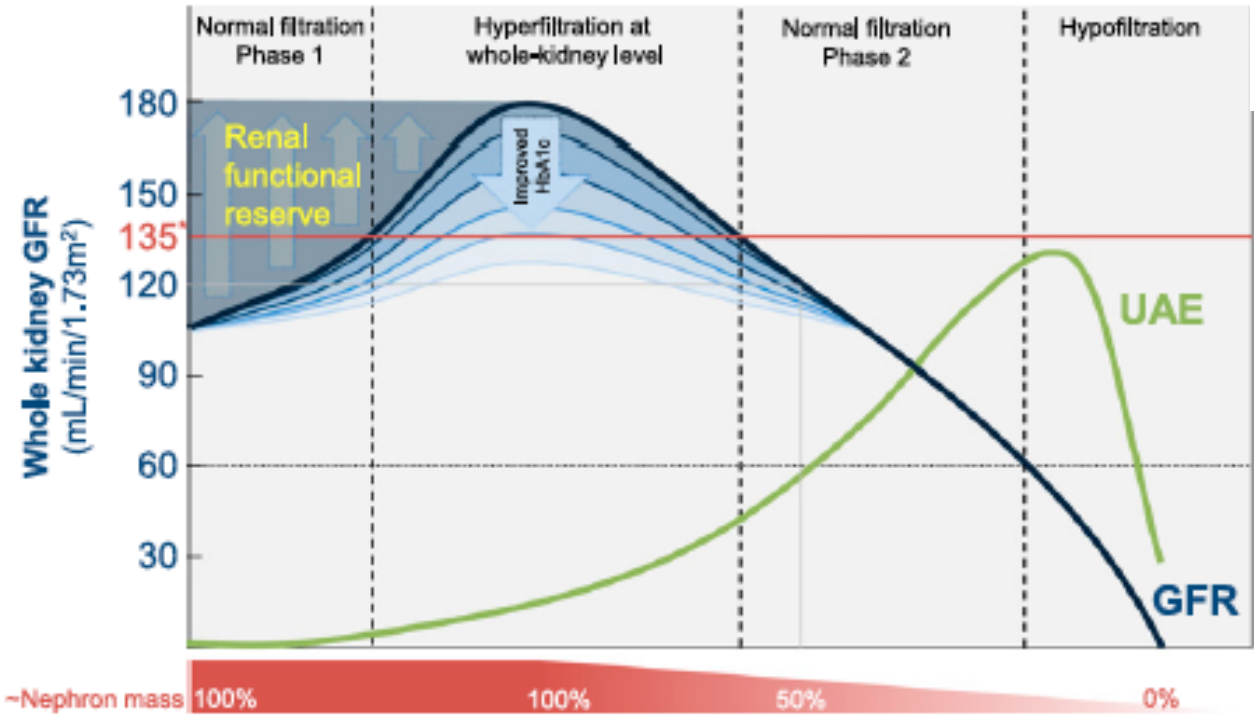

BRIEF REVIEW www.jasn.org

Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment

Lennart Tonneijck,* Marcel H.A. Muskiet,* Mark M. Smits,* Erik J. van Bommel,* Hiddo J.L. Heerspink,† Daniël H. van Raalte,* and Jaap A. Joles‡

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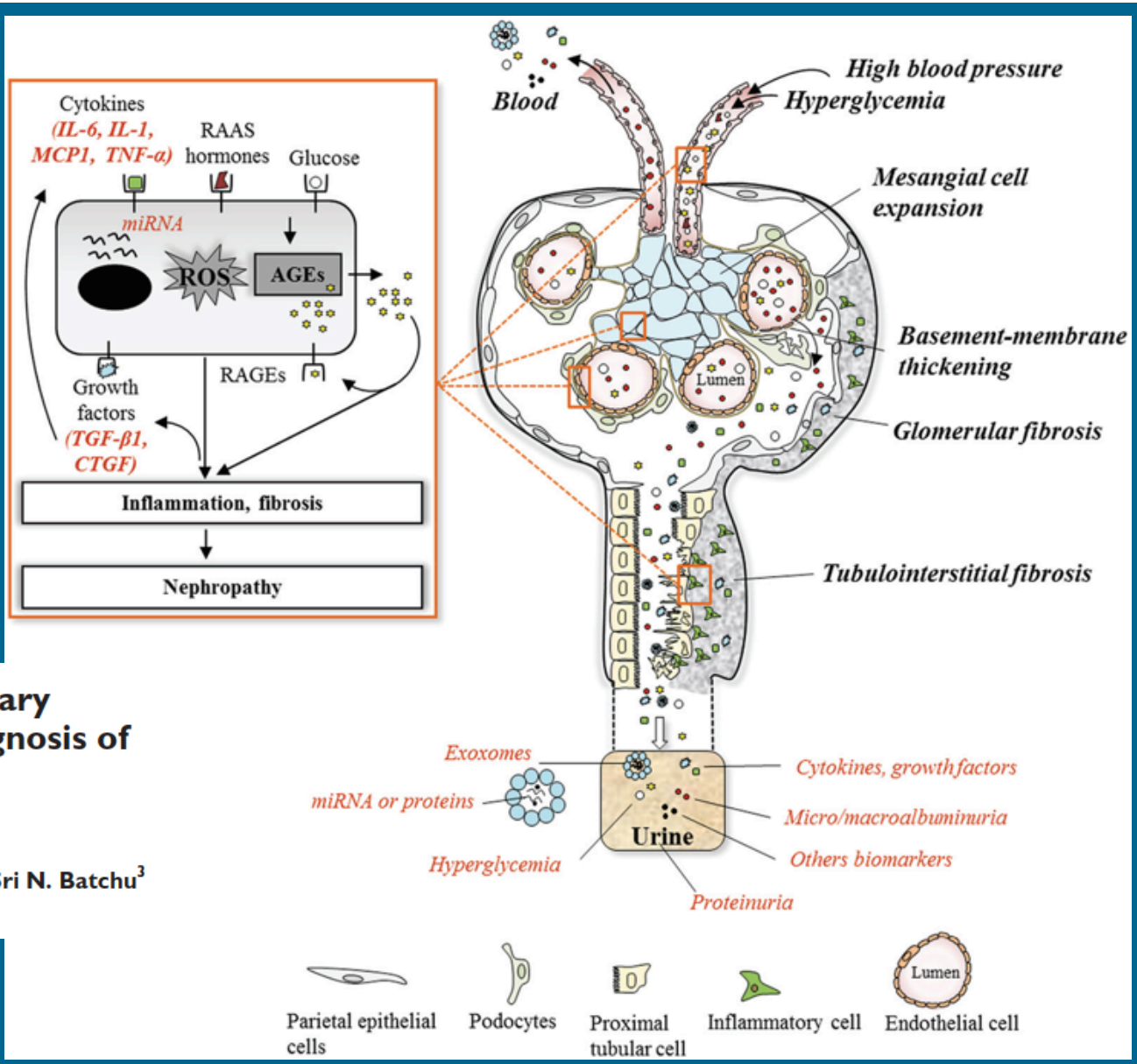

Potential Role of Serum and Urinary Biomarkers in Diagnosis and Prognosis of Diabetic Nephropathy

Carole G. Campion[1], Oraly Sanchez-Ferras[2], and Sri N. Batchu[3]

Factores Hemodinámicos

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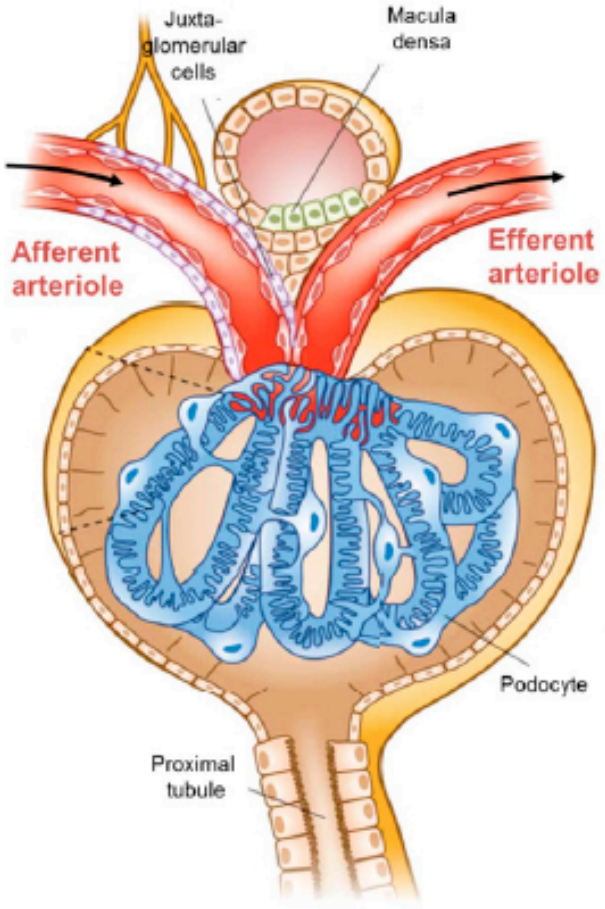
ı, The Netherlands; Netherlands; and rlands

Factors causing a net reduction of afferent arteriolar resistance
Vascular factors
Nitric oxide bioavailability
COX-2 prostanoids
Kalikrein-kinins
Atrial natiuretic peptide
Angiotensin(1-7)
Hyperinsulinemia *per se*
Tubular signals
Inhibition of tubuloglomerular feedback (macula densa signals)



Factors causing a net increase of efferent arteriolar resistance
Vascular factors
Angiotensin-II
Thromboxane A2
Endothelin-1 (ETA receptor)
Reactive oxygen species

Fisiopatología

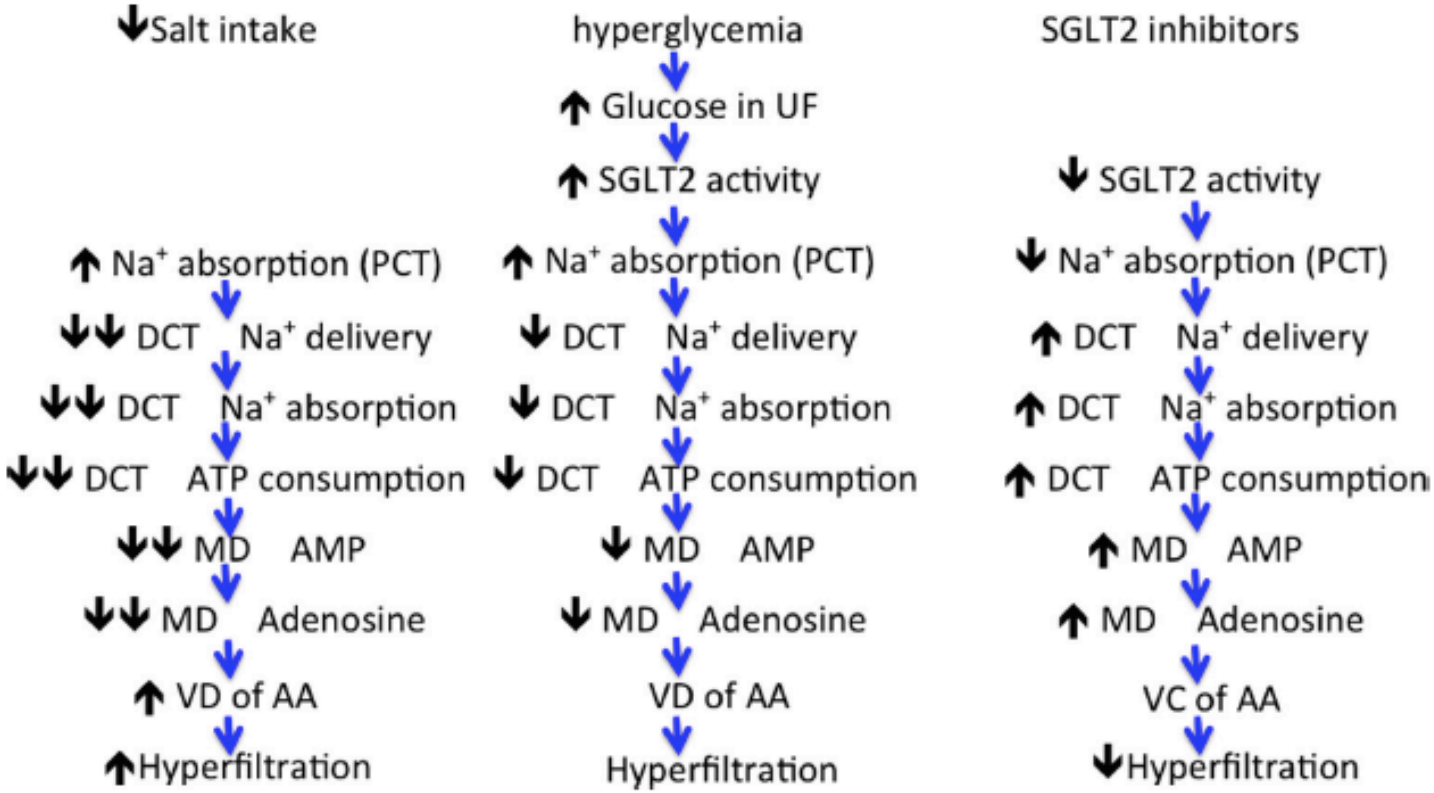


Fig. 2. Tubuloglomerular feedback:impact of low salt intake and SGLT2 inhibitors. UF = glomerular ultrafiltrate; SGLT = sodium glucose transporter; PCT = proximal convoluted tubules; DCT = distal convoluted tubule; MD = macula densa; AMP = adenosine monophosphate; VD = vasodilation; AA = afferent arteriole.

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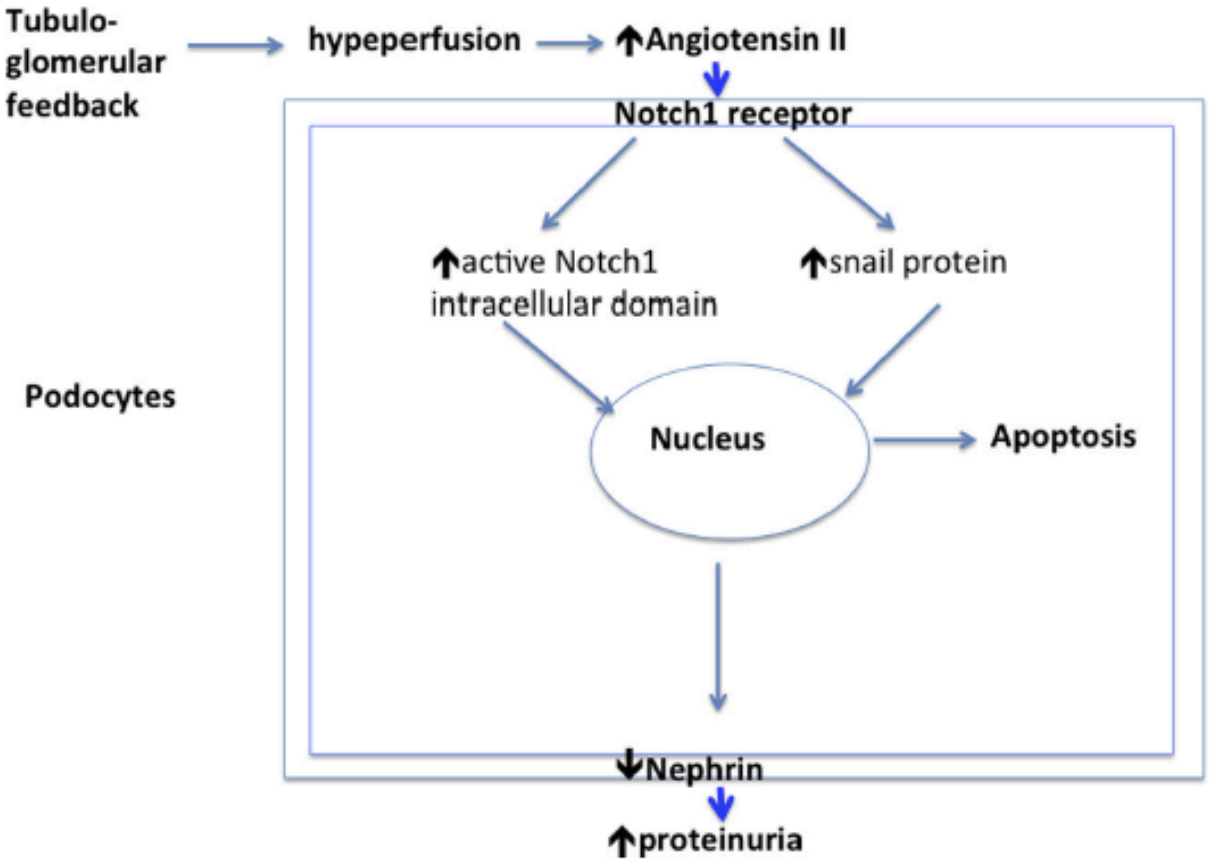

Fig. 5. Mechanism of podocyte injury and proteinuria induced by angiotensin II.

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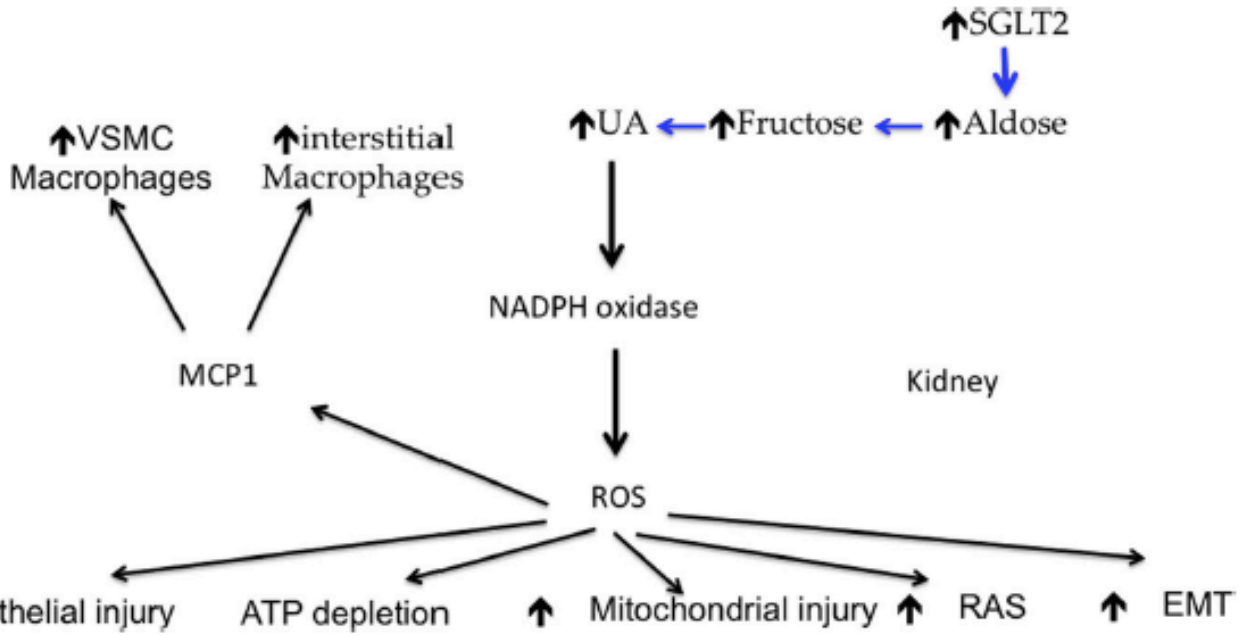

Fig. 3. Different pathogenic mechanisms of kidney injury possibly induced by uric acid. UA = acid; ROS = reactive oxygen species; MCP1 = Maacrophage chemo-attractant protein-1; RAS = renin angiotensin system; EMT = epithelium mesenchyme transition VSMC = vascular smooth muscle cells.

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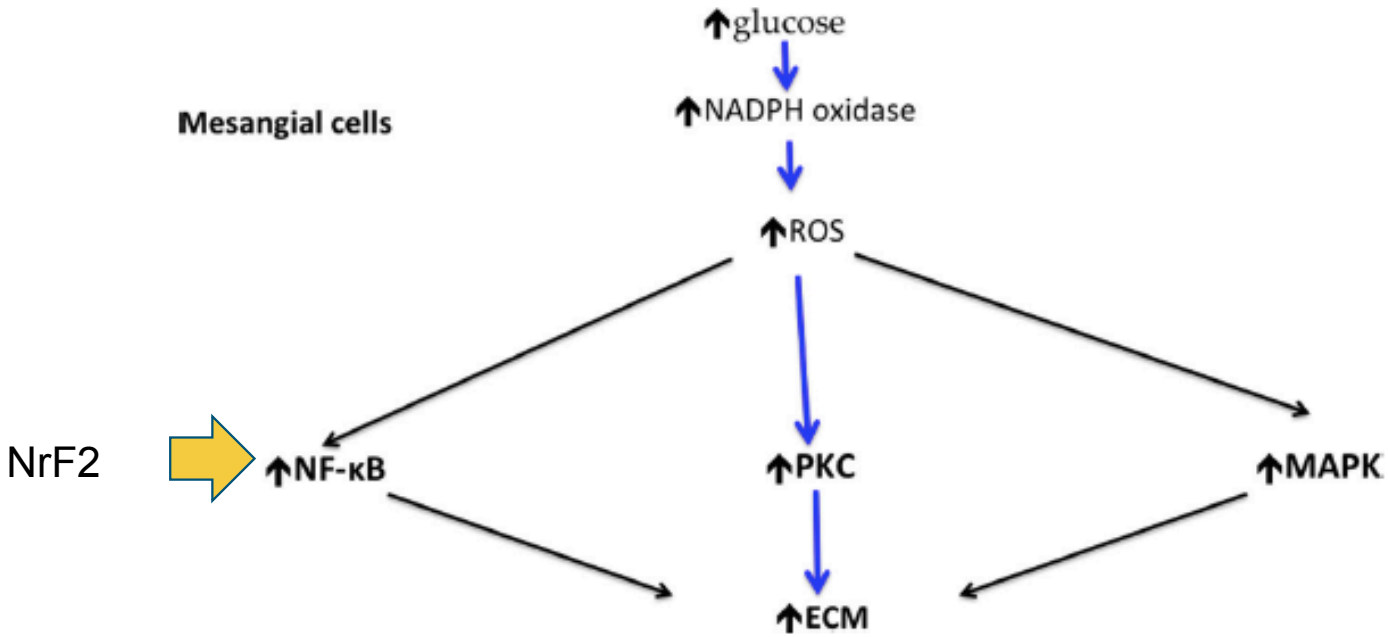

Fig. 4. Hyperglycemia induced mesangial expansion. NADp = Nicotinamide adenine dinucleotide phosphate; ROS = reactive oxygen species; NF-kB = nuclear factor-kB; PKC = protein kinase C; MAPK = mitogen-activated protein kinase; ECM = extracellular matrix.

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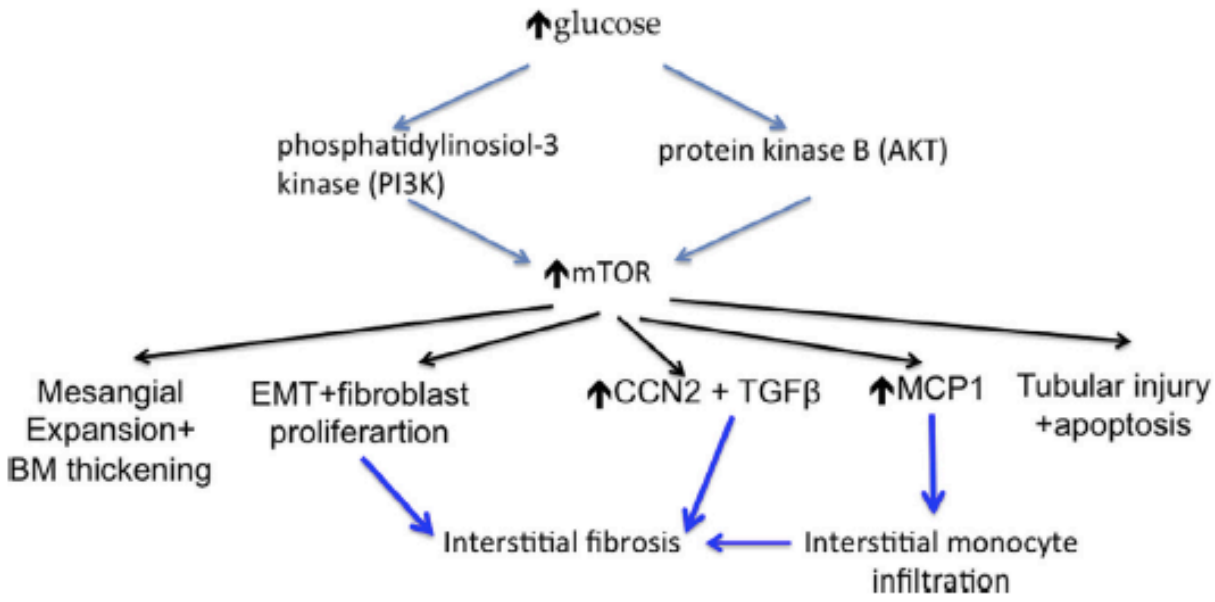


Fig. 6. Consequences of mTOR activation induced by hyperglycemia. mTOR = mammalian target of rapamycin; BM = basement membrane; EMT = epithelium mesenchyme transition tissue growth factor; TGFβ = transforming growth factorβ; MCP1 = macrophage chemoattractant protein.

Fisiopatología

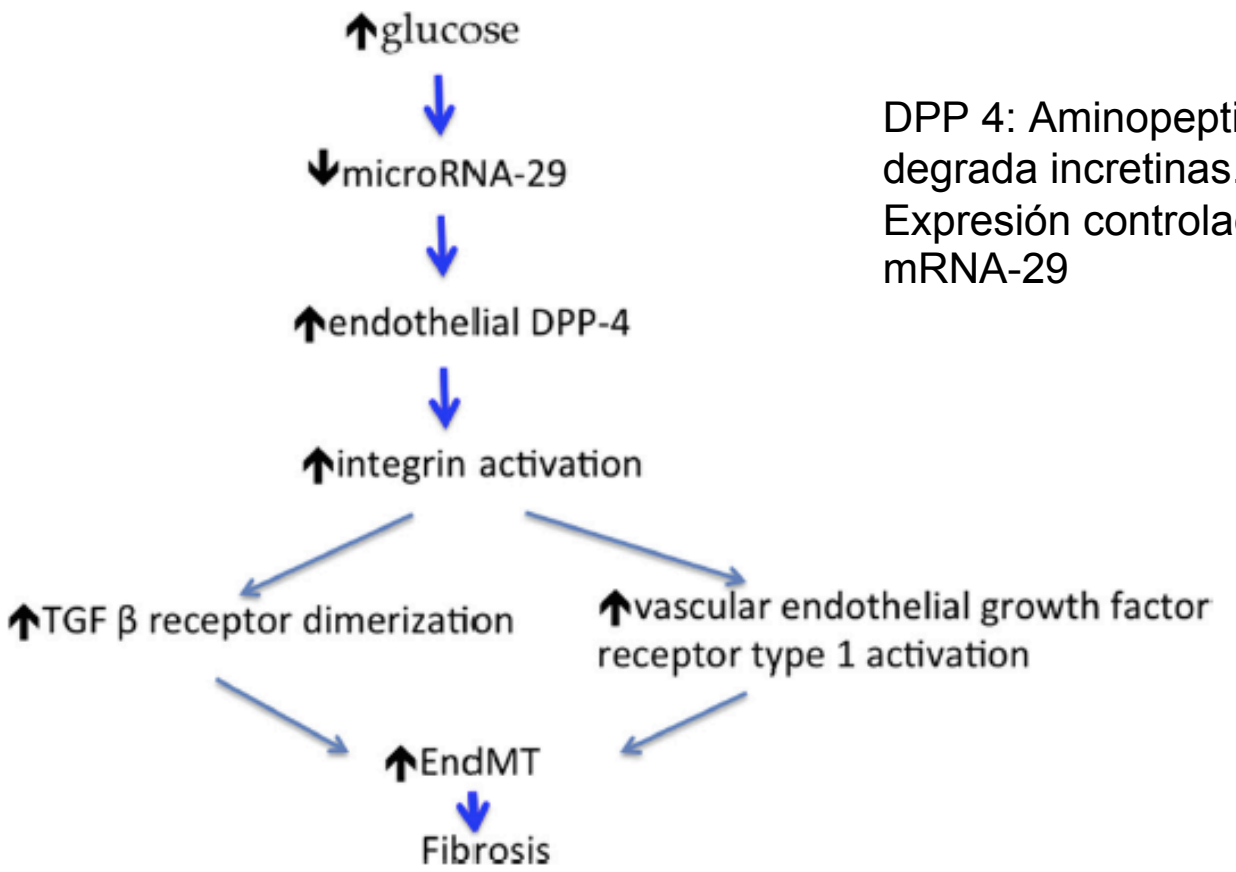


Fig. 8. DPP-4 mediated renel fibrosis. DPP4 = dipeptyl peptidase-4; TGFβ = transforming growth factorβ; EndMT = endothelial-mesenchymal transition.

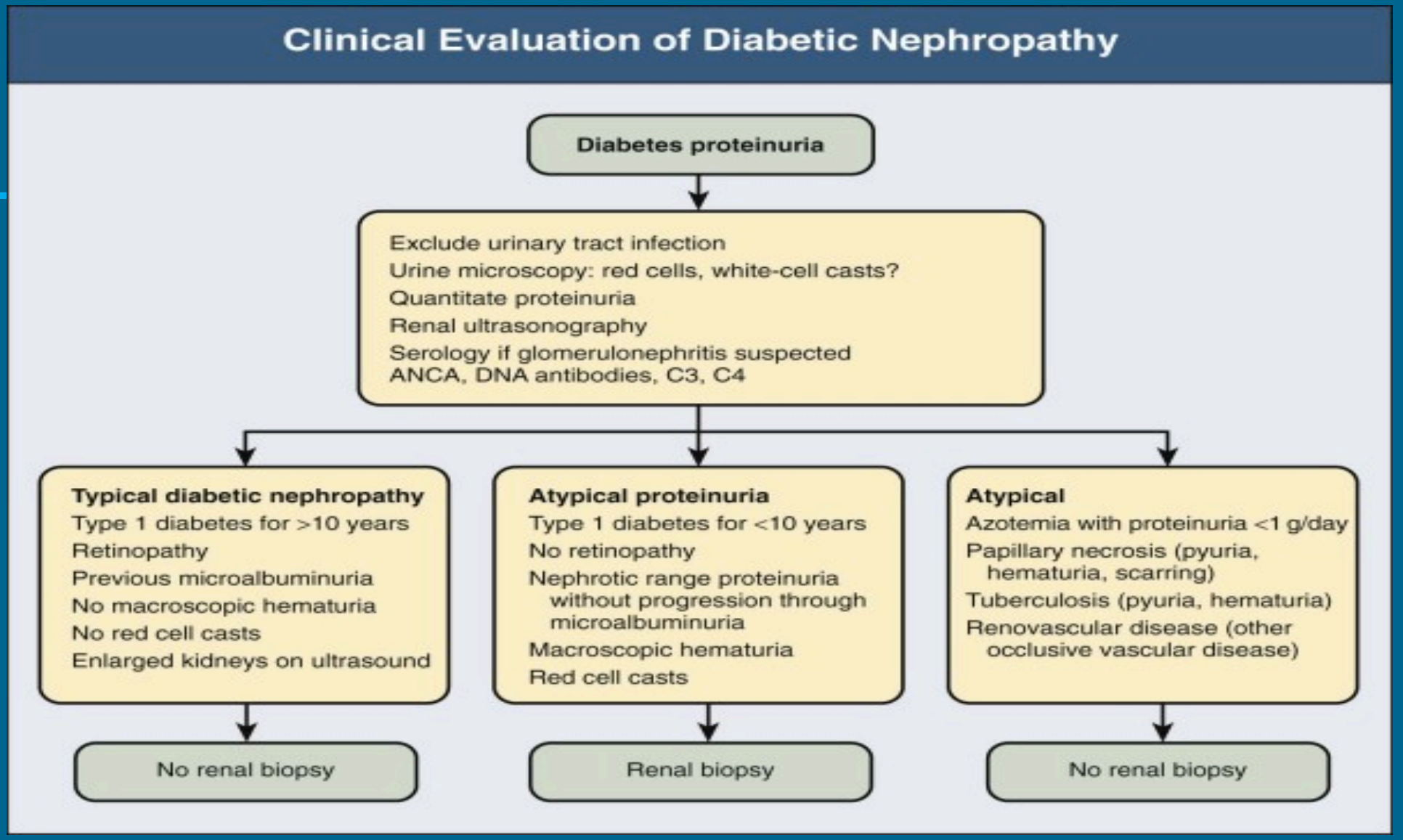
DPP 4: Aminopeptidasa que degrada incretinas.
Expresión controlada por el mRNA-29


Hiperfiltración
Inflamación
Fibrosis

Diagnóstico

- Albuminuria/ proteinuria
- Creatinina/ estimación VFG
- TA
- Fondo de ojo
- Biopsia renal

Urinary Albumin Excretion Rate		
	UAER	
Condition	24 hr (mg/day)	Overnight (µg/min)
Normoalbuminuria	>30	>20
Microalbuminuria	30–300	20–200
Overt nephropathy	>300	>200


Clinical Evaluation of Diabetic Nephropathy
Diabetes proteinuria
Exclude urinary tract infection
Urine microscopy: red cells, white-cell casts?
Quantitate proteinuria
Renal ultrasonography
Serology if glomerulonephritis suspected
ANCA, DNA antibodies, C3, C4
Typical diabetic nephropathy
Type 1 diabetes for >10 years
Retinopathy
Previous microalbuminuria
No macroscopic hematuria
No red cell casts
Enlarged kidneys on ultrasound
Atypical proteinuria
Type 1 diabetes for <10 years
No retinopathy
Nephrotic range proteinuria without progression through microalbuminuria
Macroscopic hematuria
Red cell casts
Atypical
Azotemia with proteinuria <1 g/day
Papillary necrosis (pyuria, hematuria, scarring)
Tuberculosis (pyuria, hematuria)
Renovascular disease (other occlusive vascular disease)
No renal biopsy
Renal biopsy
No renal biopsy

Biomarcadores

Table 2. Biomarkers of Diabetic Nephropathy Pathophysiology.

Class	Biomarkers	Clinical importance	Method of detection	Ref.
Oxidative stress	Pentosidine	Predictor of progression; influenced by glycemic levels and renal function; biomarker of microvascular complications and diabetic cardiovascular risk.	Serum/urine	77,78
	8-OHdG	Predictor of advanced stage; related to the severity of DN, associated with macroalbuminuria.	Urine	79,80
	Uric acid	Predictor of progression; associated with various stages of DN, onset and progression; *potential target for therapeutic intervention in diabetes.*	Serum	81,82
Fibrosis	TGF-β1	Predictor of advanced stage DN; positively correlates with micro- and macroalbuminuria	Serum/urine	31
	CTGF	Predictor of ESRD; correlates with the rate of decline in GFR.	Serum/urine	83,84
	VEGF	Predictor of progression; increased during the earlier stage of DN and shown to significantly correlate with urinary albumin excretion.	Serum/urine	85,86
Glomerular damage	Transferrin	Predictor of early stage; increased before development of microalbuminuria.	Urine	87
	Type IV collagen	Predictor of advanced stage of DN; associated with a faster decline in eGFR.	Urine	88,89
	Cystatin C	Predictor of early stage DN; raised early in DN and pre-DN; increased in patients with microalbuminuria without any	Serum/urine	90,91

Biomarcadores

Tubular damage	L-FABP	Predictor of early stage and progression of DN; increased from the microalbuminuric stage; elevated in patients with reduced eGFR.	Urine	92,93
	NGAL	Predictor of early stage and progression of DN; found in diabetic patients without early signs of glomerular damage (normoalbuminuric).	Urine	94,95
	KIM-1	Predictor of early stage DN; increased even before the onset of albuminuria and proteinuria.	Serum/urine	96,97
	ACE2	Biomarker of increased metabolism of Ang II in DN; its downregulation or excretion in urine predicts tubular injury and reduced renal function.	Serum/urine	98,99
	Angiotensinogen	Predictor of early and development of kidney injury; levels correlated with albuminuria, biomarker of the intrarenal RAAS.	Urine	100,101
	NAG	Predictor of early stage DN; associated with normoalbuminuric and microalbuminuric stages; increased in parallel with the severity of disease.	Urine	102,103
	α1-microglobulin	Predictor of early stage DN; directly correlates with albuminuria and severity of the disease.	Urine	104,105
	FGF23	Predictor of DN progression to ESRD; associated with macroalbuminuria and risk of mortality	Serum	106,107

Biomarcadores

Inflammation	TNF-α;TNFR1/2	Predictor of DN progression to ESRD and GFR loss; associated with the presence and severity of microalbuminuric stage.	Serum/urine	108,109
	MCP-1	Predictor of progressive renal disease; correlated significantly with albuminuria levels; accelerate nephropathy by increasing inflammation and fibrosis; *potential for therapeutic target for treating DN.*	Urine	110,111
	IL-18, IL-1, IL-6, IL-8	Predictor of DN progression; strongly associated with future risk of early progressive renal decline.	Serum/urine	18,112-114

Biomarcadores

-Micro ARNs

-ARN no codificantes.

-Exosomas urinarios.

-Micropartículas.

Tratamiento

- Control de TA:
    - Usar IECA / ARA 2 si hay albuminuria.
        - Disminuye Pº intraglomerular.
        - Menor producción de IL.
        - Estimula la producción de genes Klotho.
    - Objetivo: ??
- Control de glucemia:
    - UKPDS: Adecuado control metabólico disminuyó hasta 33% RR de progresión de

Tratamiento

- Metformina:
  - Activación del AMPK lleva a inhibición del mTOR.
  - Inhibe apoptosis del podocito.
- Tiazolidinedionas:
  - pioglitazona: protege podocito por disminución de efecto inflamatorio local.
- Agonitstas de GLP-1: sin evidencia al momento.
- Inhibidores DDP4: Linagliptina
- Inhibidores de SGLT2: El futuro?

Tratamiento

- Estatinas: para todos. No influye en la ND.
- Cese del hábito tabáquico.
- Dieta:
  - Ingesta de Na < 5- 6 gr/día
  - Fuerte asociación entre ingesta baja en Na y evolución de ND en DBT II.
  - La “paradoja de la sal” y la DBT I.
- Tratar la hiperuricemia: Impacto en evolución de ND.

Tratamiento

Table 2
Potential therapeutic modalities to prevent or withhold progression of DN.

Drug class	On-target action	Off-target actions	Remarks	Ref.
Ruboxistaurin	PKC↓	UAE ±, TGF-β±		[79]
Sulodexide		UAE ±		[80]
Atrasentan	Endothelin receptor antagonist	UAE↓	Serious side effects postponed approval	[81]
Aldose reductase inhibitors	IC sorbitol↓, IC fructose ↓	UAE↓	No adequate RCTs	[82]
Nrf2 activator	ROS↓	NF-κB↓, EMT↓		
Curcumin	ROS↓	UAE↓, inflam. ↓	No long term trials	[83]
Resveratrol	ROS↓	EMT↓	No clinical trials	[84]
Bardoxolone	ROS↓	GFR↑	UAE↑, BP↑, HF↑, mortality↑, nausea, wt loss, muscle spasm	[85,86]
Empaticap Pegol	MCP1↓	UAE↓	I.V administration	[89]
CCX140-B	CCR2 antagonist	UAE↓, GFR±	Oral administration	[90]
Exogenous klotho	EMT↓, TGF-β↓	Fibrosis↓		[91–93]
Low dose IL-17A	MCP1↓	UAE↓, kidney size↓, mes. matrix↓, IF↓, urine IP10↓, TNFα↓, IL-6↓, and S ureai	No clinical trials	[94]

THANK YOU !