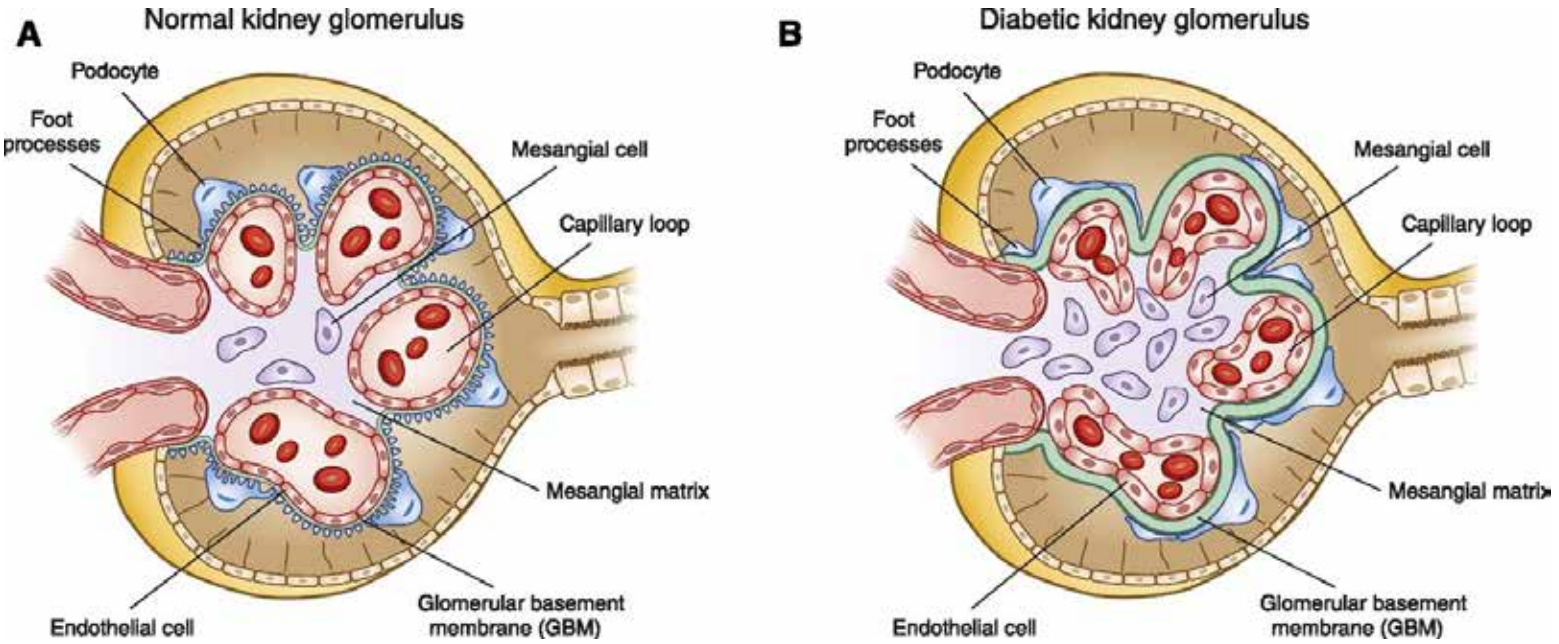
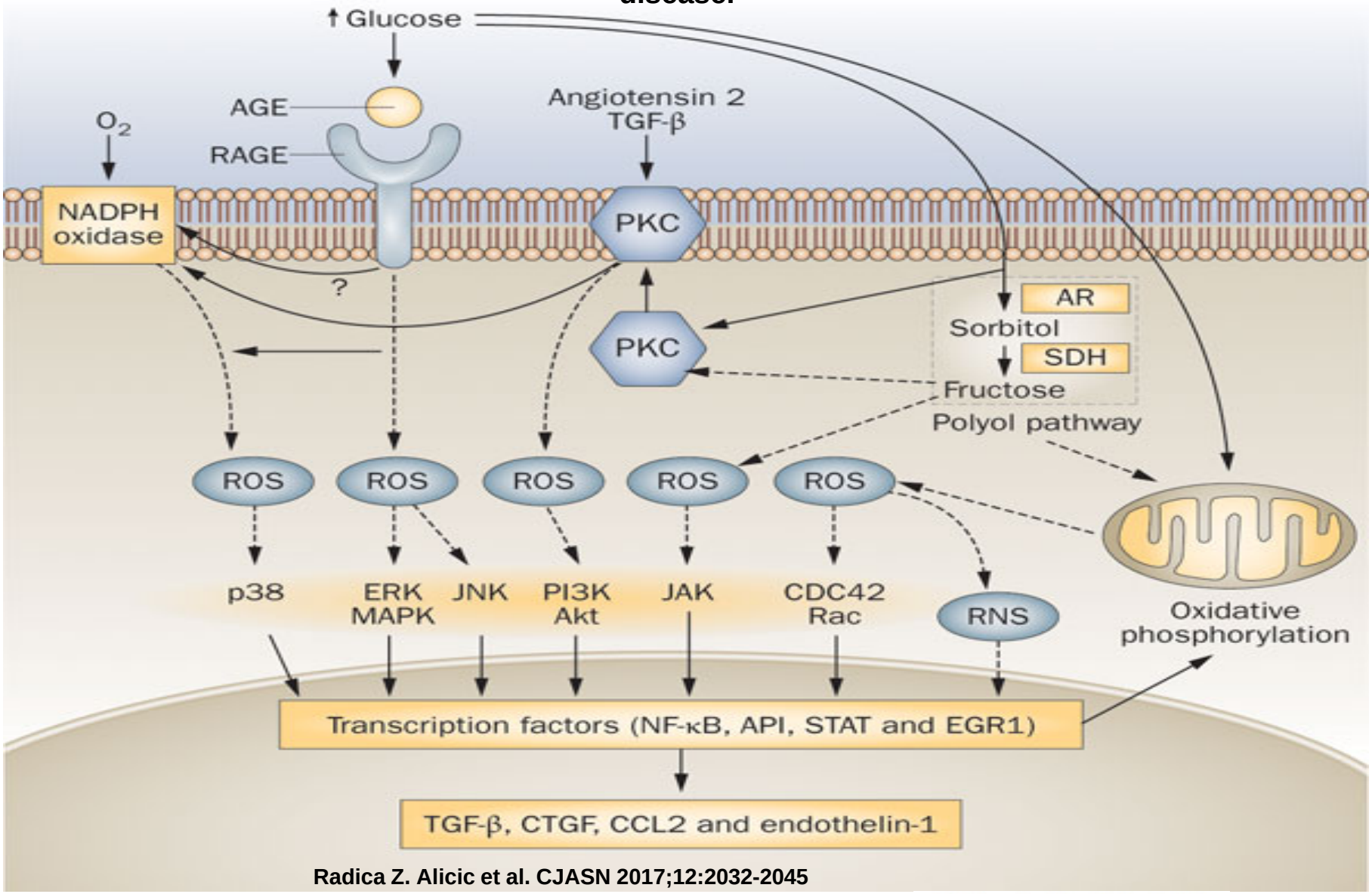


Ο Νεφρός στο Διαβήτη: Θύμα αλλά και Εργαλείο Θεραπείας

Μάριος Θ. Θεοδωρίδης - Νεφρολόγος, Διευθυντής ΕΣΥ

Παν. Νεφρολογική Κλινική Π.Γ.Ν. Αλεξανδρούπολης

Different pathways and networks involved in the initiation and progression of diabetic kidney disease.



Radica Z. Alicic et al. CJASN 2017;12:2032-2045

CJASN

AJKD
In Translation

Am J Kidney Dis. 2011;58(4):637-646

Podocytopathy in Diabetes: A Metabolic and Endocrine Disorder

Ana Diez-Sampedro, PhD,[1] Oliver Lenz, MD,[2] and Alessia Fornoni, MD, PhD[2,3]

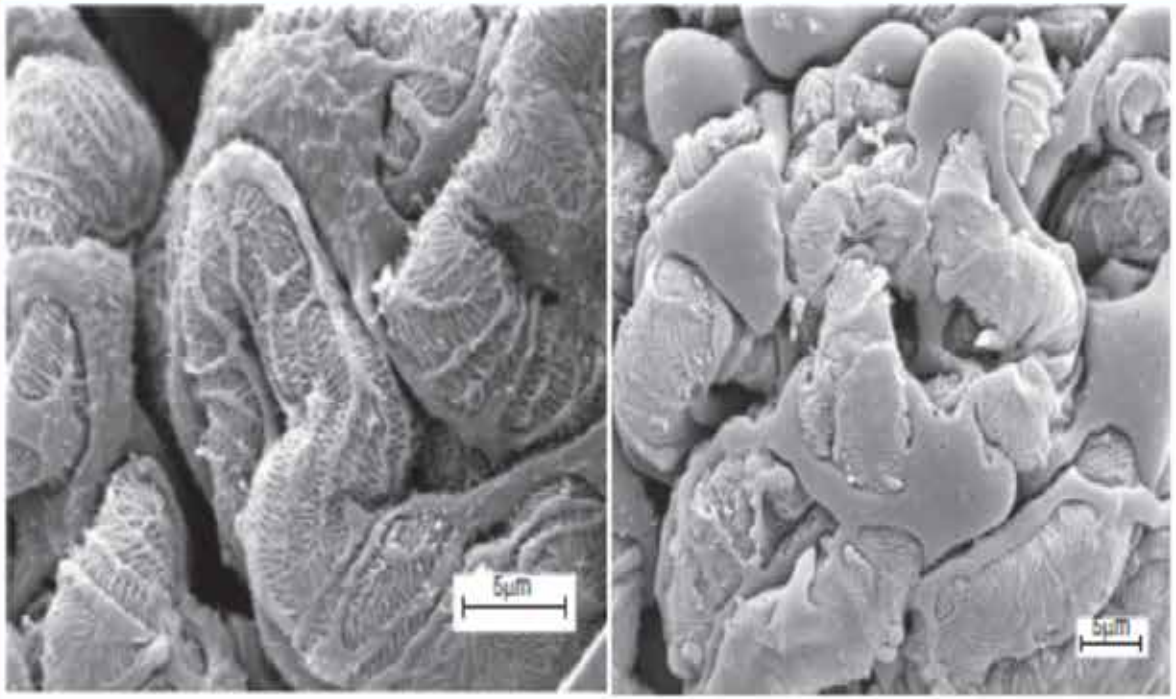


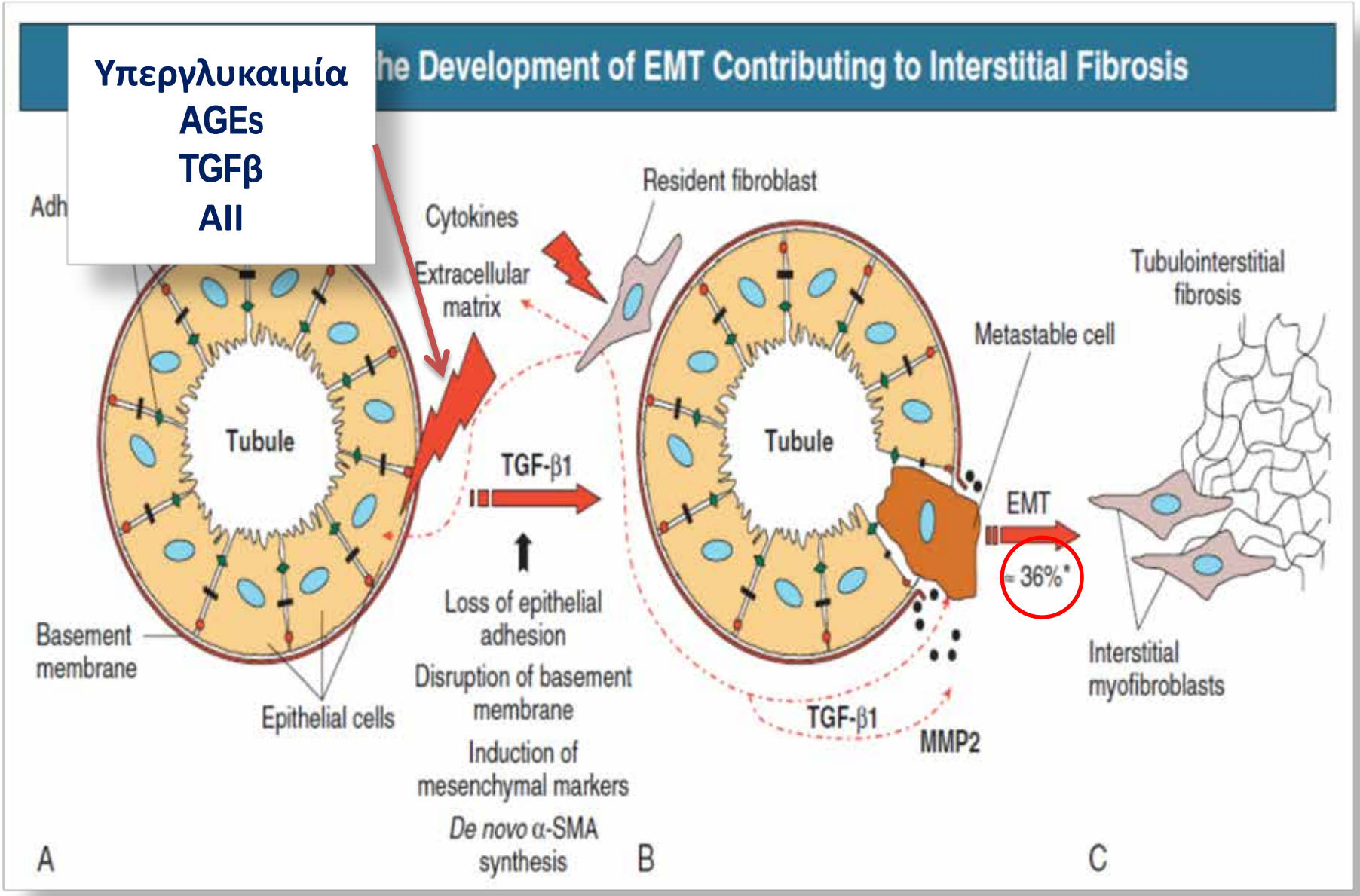
Figure 29.17 Electron micrograph of the external surface of glomerular tufts from rats after removal of Bowman's capsule by freeze-fracture. *Left,* A normal rat kidney with podocyte cell body; the primary processes and terminal foot processes resting on the glomerular capillary basement membrane are clearly seen. *Right,* The decrease in the density of foot processes and the denuded glomerular capillary basement membrane are apparent. *(From reference 59)*

cyclin-dependent kinase inhibitor 1B; p38, p38 mitogen-activated protein kinase; PI3K, phosphinositide 3-kinase; (P)RR, (pro)renin receptor; TGFβ, transforming growth factor β.

⇧Actin re-arrangement
⇧ Effacement
⇧ Apoptosis

Adiponectin

Διαμεσοσωληναριακή ίνωση & Σωληναριακή ατροφία



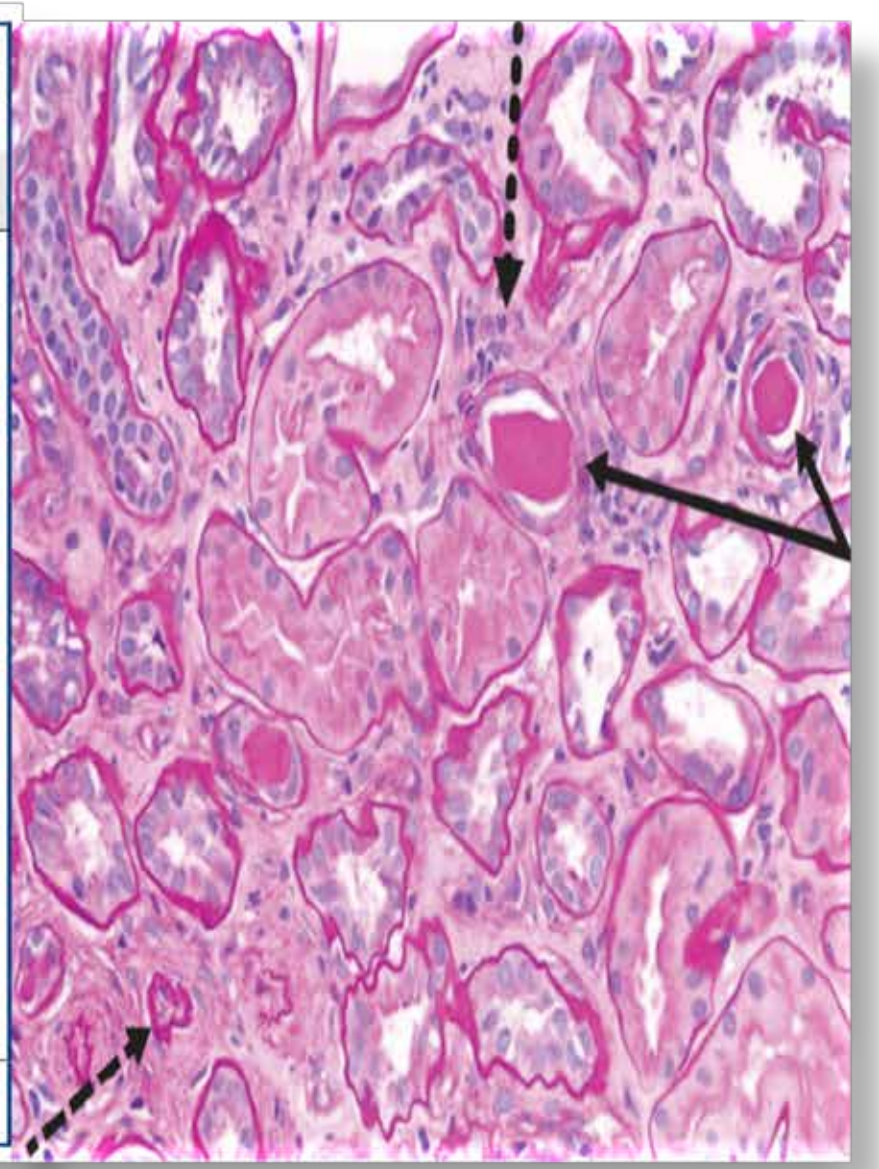
Loffler I.Diabetes and Kidney Disease. New York: Wiley-Blackwell; 2013

Παθολογική Ανατομική ΔΝΝ

Table 3. International classification of interstitial and vascular lesions in diabetic kidney disease

Type of Lesion and Criteria	Score
IFTA, %	
Absent	0
<25	1
25–50	2
>50	3
Interstitial inflammation	
Absent	0
Infiltration only in relation to IFTA	1
Infiltration in areas without IFTA	2
Vascular lesions arteriolar hyalinosis	
Absent	0
At least one area of arteriolar hyalinosis	1
More than one area of arteriolar hyalinosis	2
Presence of large vessels arteriosclerosis	
No intimal thickening	0
Intimal thickening less than thickness of media	1
Intimal thickening greater that thickness of media	2

IFTA, interstitial fibrosis and tubular atrophy.



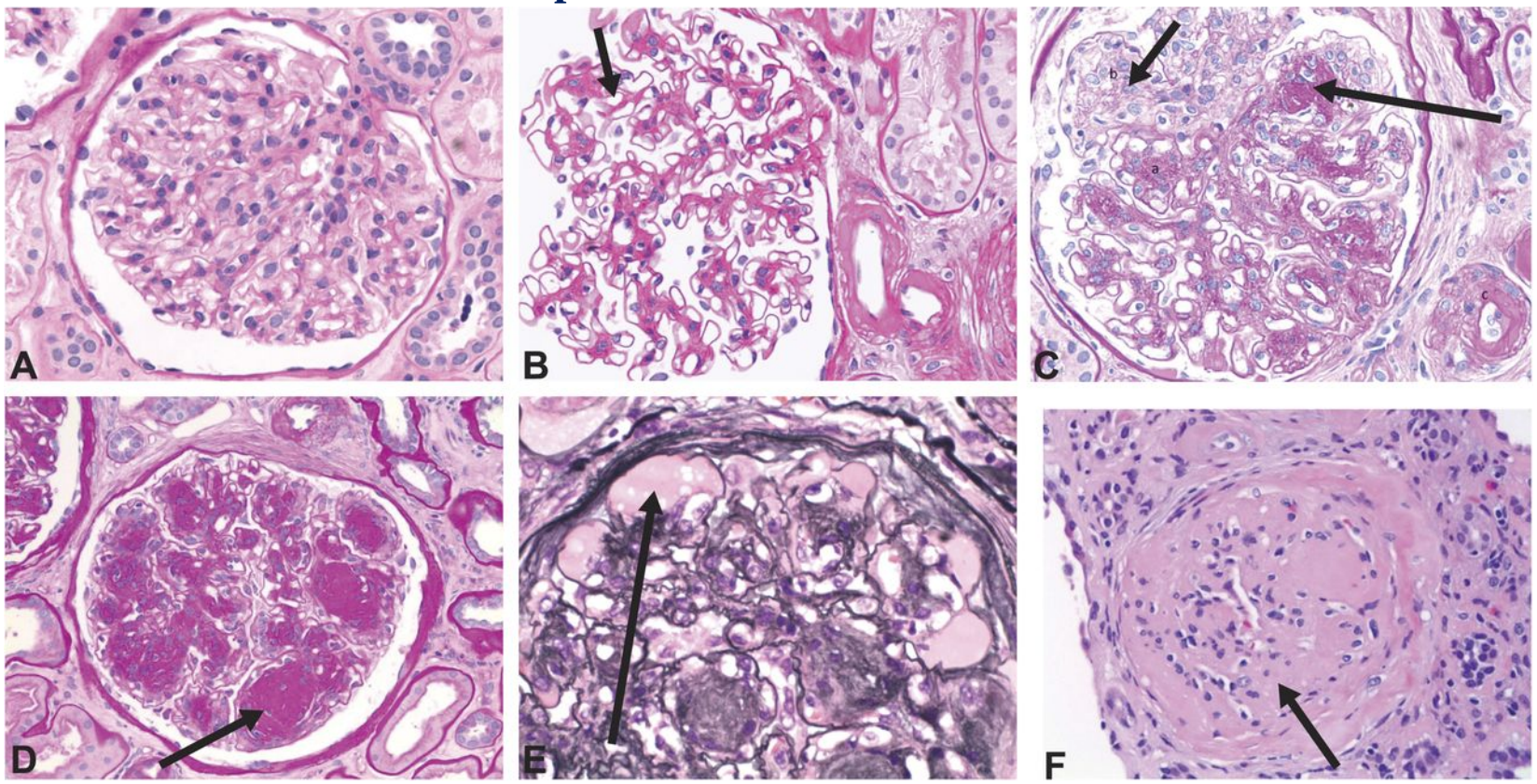
Alicic RZ, Clin J Am Soc Nephrol. 2017 Dec 7;12(12):2032-2045.

ΔΝΝ : Σπειραματικές βλάβες

Normal glomerulus

Diffuse mesangial expansion

Prominent mesangial expansion / early nodularity



Kimmelstiel–Wilson nodules

Dilation of capillaries forming microaneurysms

Obsolescent glomerulus

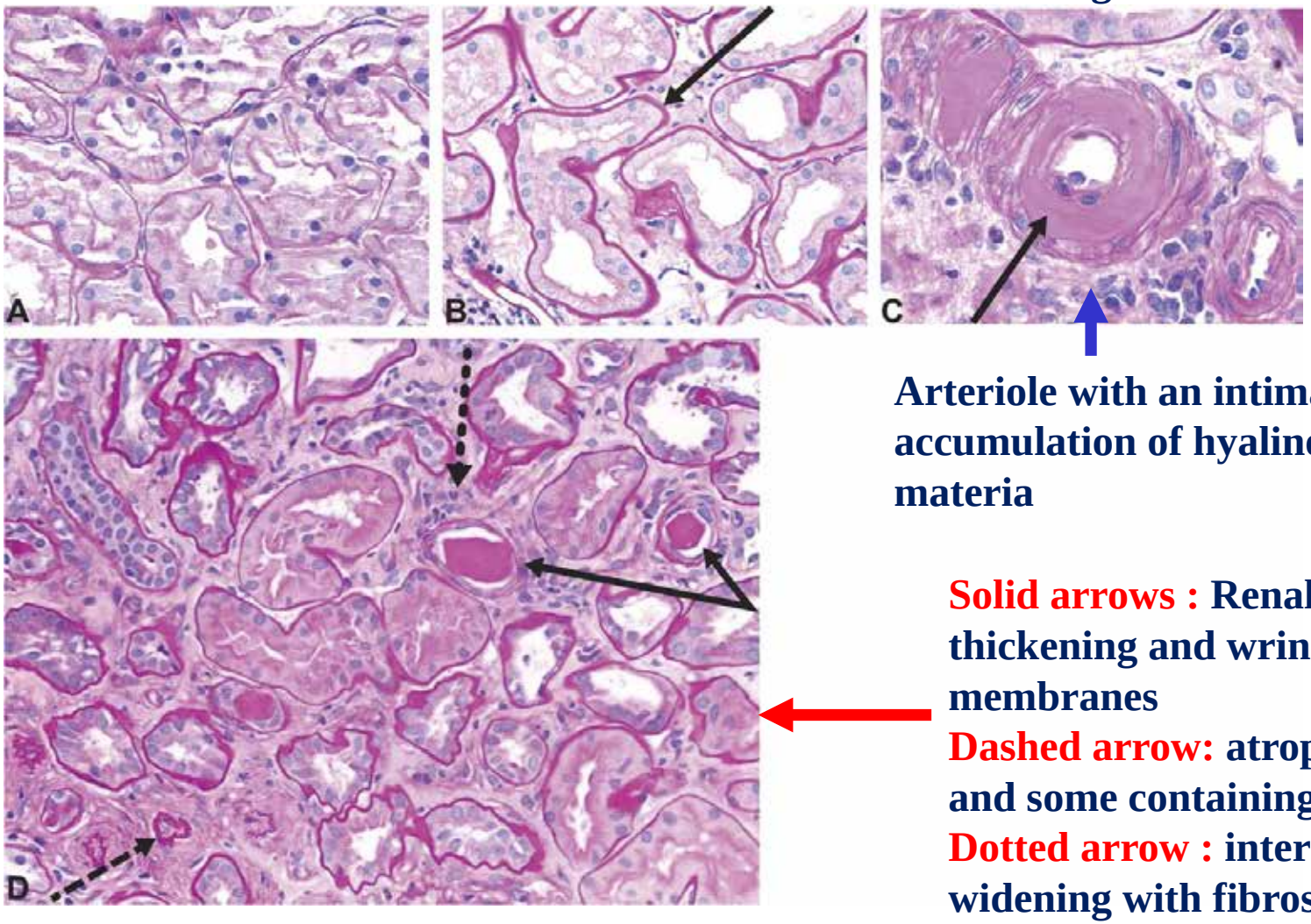
Radica Z. Alicic et al. CJASN 2017;12:2032-2045

CJASN

ΔΝΝ : Διαμεσοσωληναριακές βλάβες & Υαλίνωση των αρτηριδίων

Normal renal cortex

Thickened tubular basement membranes and interstitial widening



Arteriole with an intimal accumulation of hyaline materia

Solid arrows : Renal tubules with thickening and wrinkled basement membranes

Dashed arrow: atrophic tubules and some containing casts

Dotted arrow : interstitial widening with fibrosis

Radica Z. Alicic et al. CJASN 2017;12:2032-2045

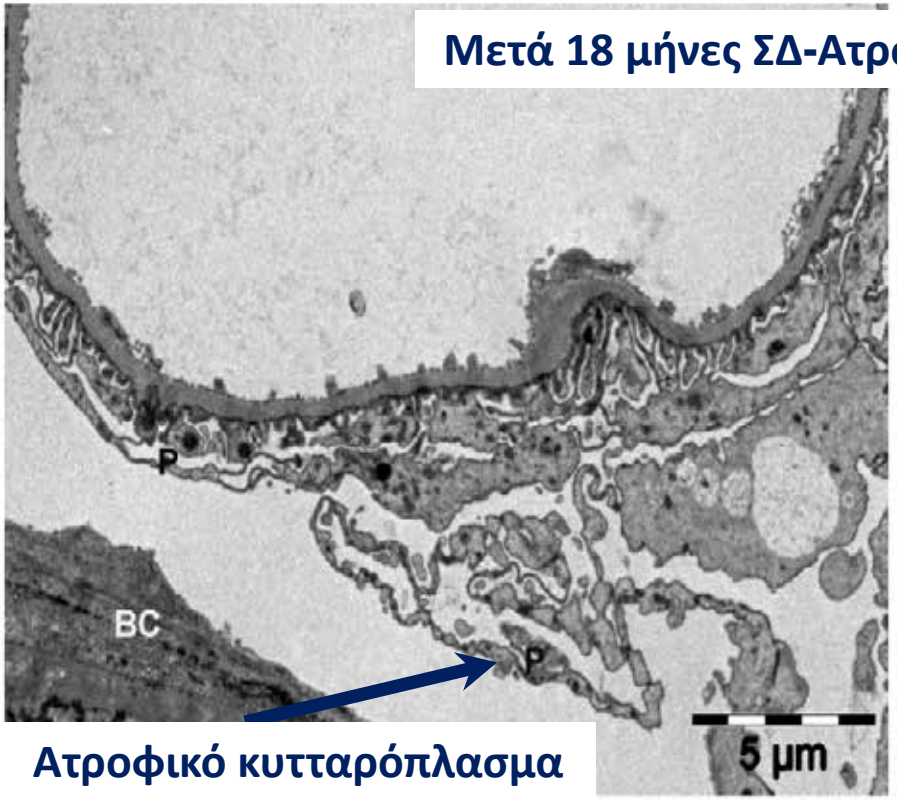
CJASN

Nanostructural features of diabetic podocytopathy

E. MANDACHE, M. PENESCU

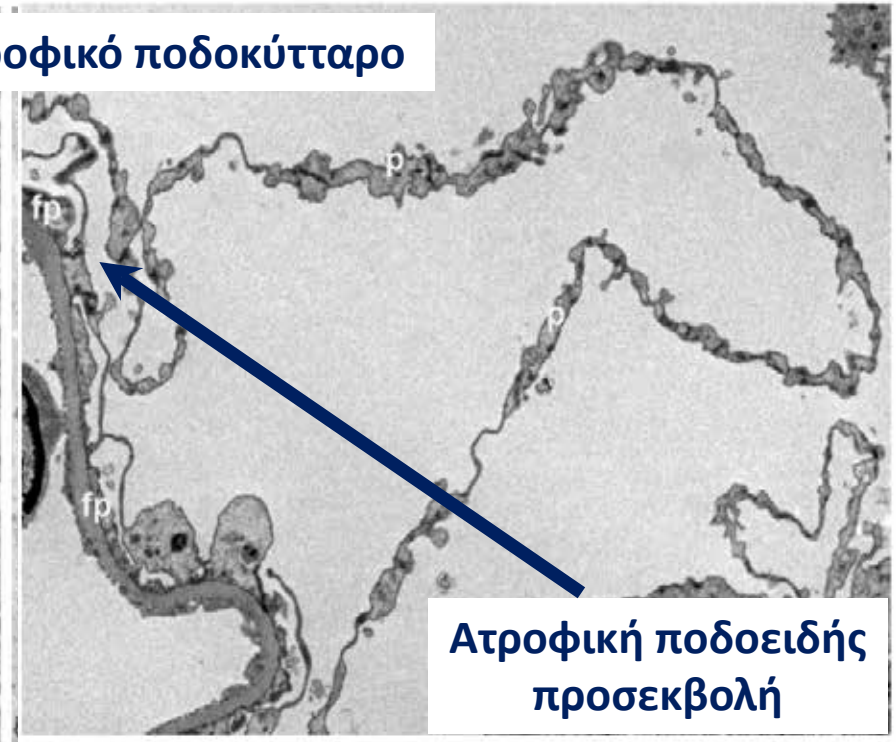
Departments of Nephropathology and Nephrology,
"Carol Davila" Clinical Hospital for Nephrology, Bucharest

Μετά 18 μήνες ΣΔ-Ατροφικό ποδοκύτταρο



Ατροφικό κυτταρόπλασμα

Figure 7 – *Atrophic podocyte after 18 months of open hyperglycemia. Thin cytoplasmic processes (P) and normal foot processes. Bowman capsule (B).*

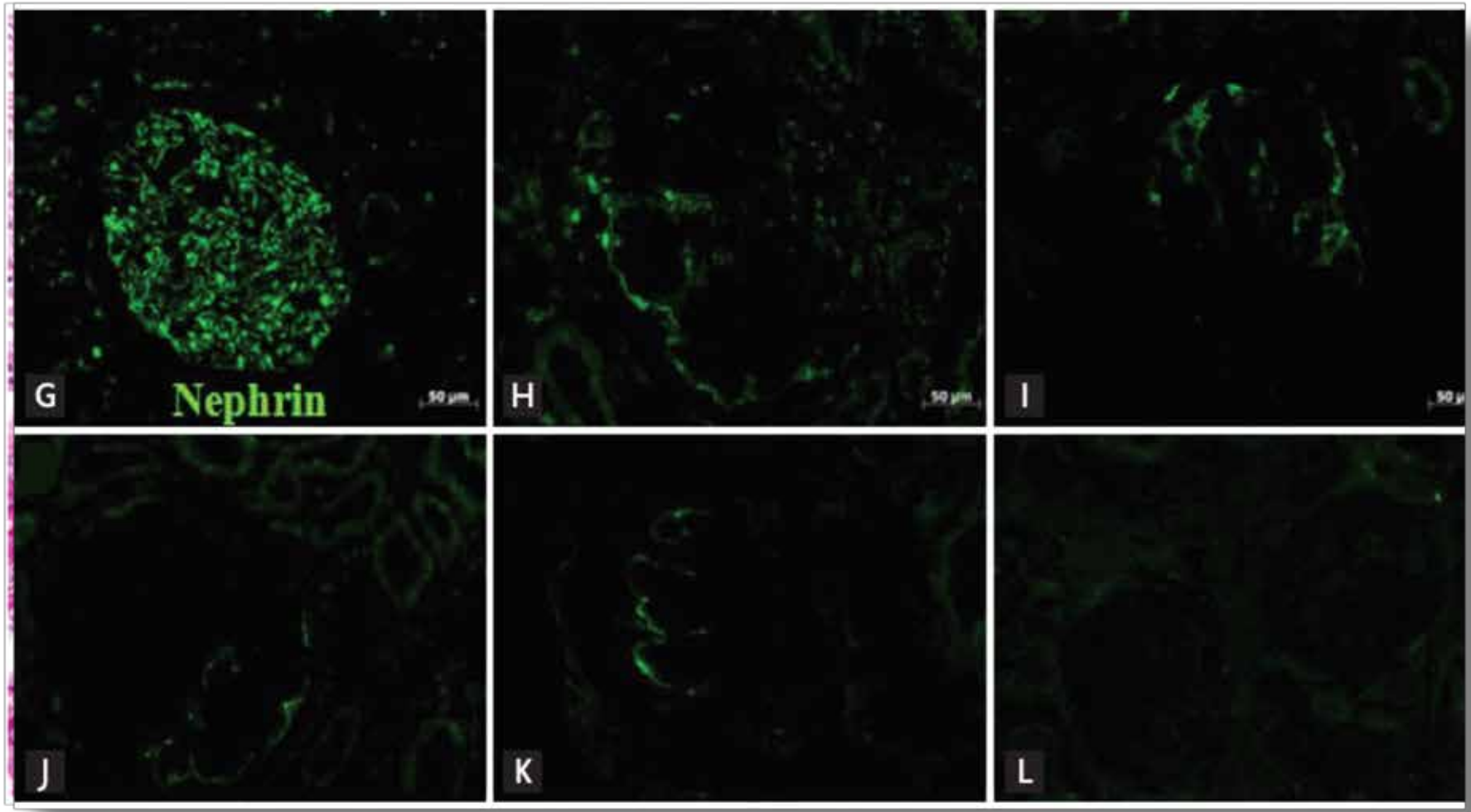


Ατροφική ποδοειδής προσεκβολή

Figure 9 – *Atrophic podocyte after 18 months of open hyperglycemia. Effaced foot processes (fp). Very slender primary podocyte processes (p). Podocyte body (P).*

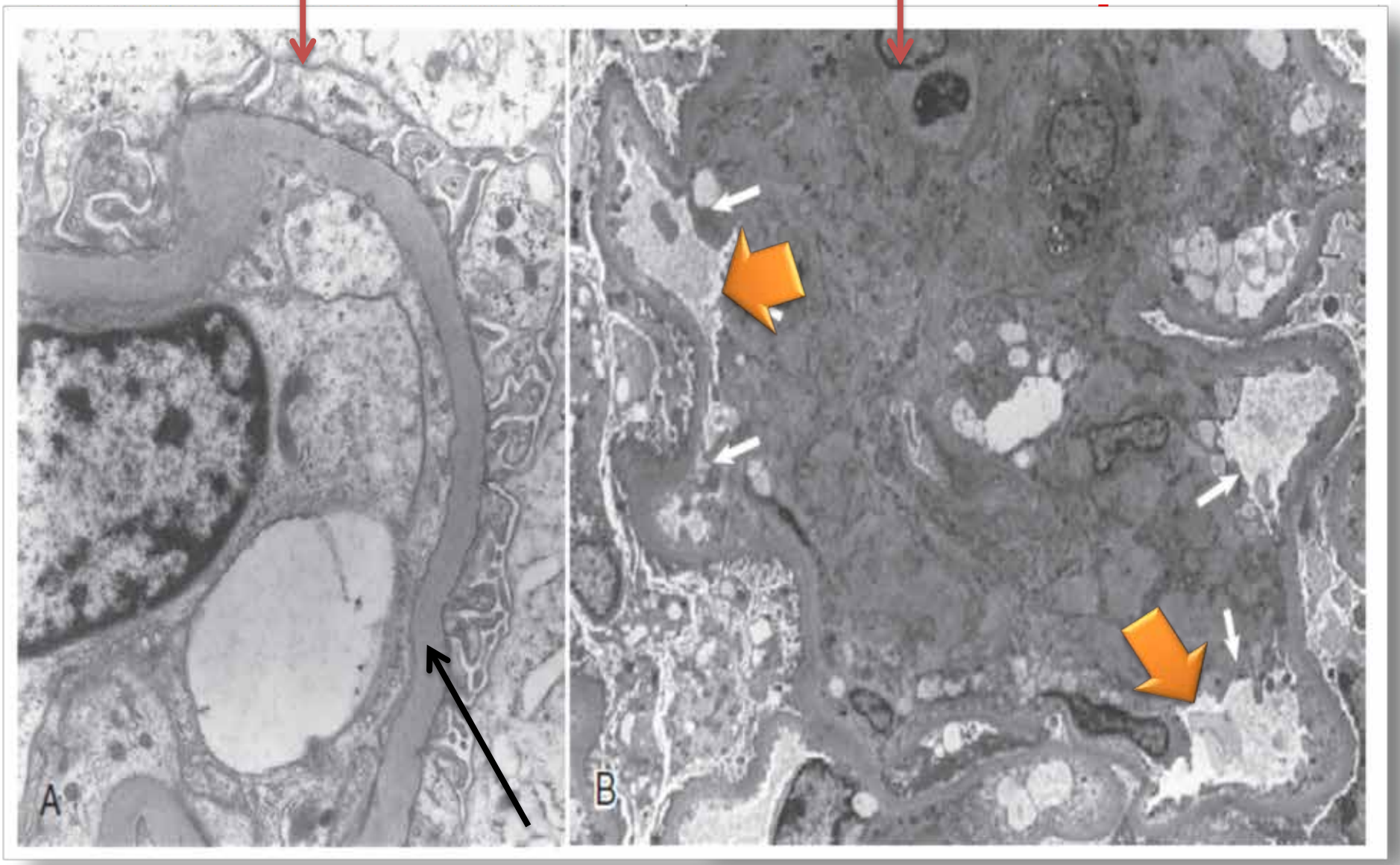
New therapeutic agents in diabetic nephropathy

Yaeni Kim and Cheol Whee Park



The Korean Journal of Internal Medicine Vol. 32, No. 1, January 2017

Πάχυνση BM & υπερπλασία του μεσαγγείου



ΔΝΝ : Υπερπλασία του Μεσαγγείου

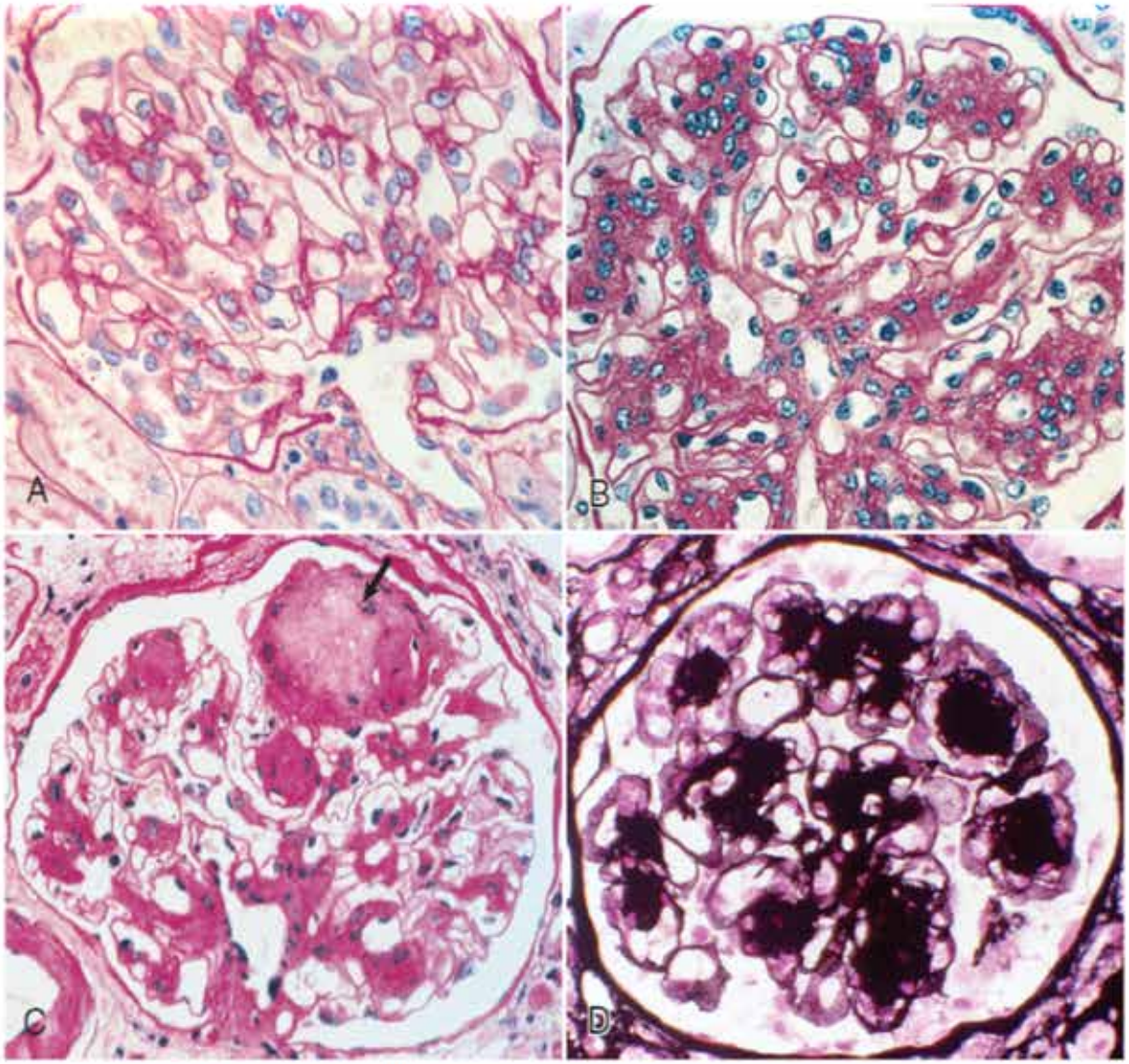


Figure 30-16 **Light microscopy of structural changes in diabetic nephropathy (DN). A,** Normal glomerulus. **B,** Diffuse glomerular lesion: widespread mesangial expansion. **C,** Nodular lesion as well as mesangial expansion: there is a typical Kimmelstiel-Wilson nodule at the top of the glomerulus *(arrow)*. (**A, B,** and **C,** Periodic acid–Schiff reaction). **D,** Nodular lesion: methenamine silver staining shows the marked nodular expansion of mesangial matrix.

Kidney International, Vol. 40 (1991), pp. 107–114

Global glomerular sclerosis and glomerular arteriolar hyalinosis in insulin dependent diabetes

RALPH D. HARRIS, MICHAEL W. STEFFES, RUDOLF W. BILOUS, DAVID E.R. SUTHERLAND, and S. MICHAEL MAUER

lesions of global glomerular sclerosis and arteriolar hyalinosis in 43 (29 females) IDDM

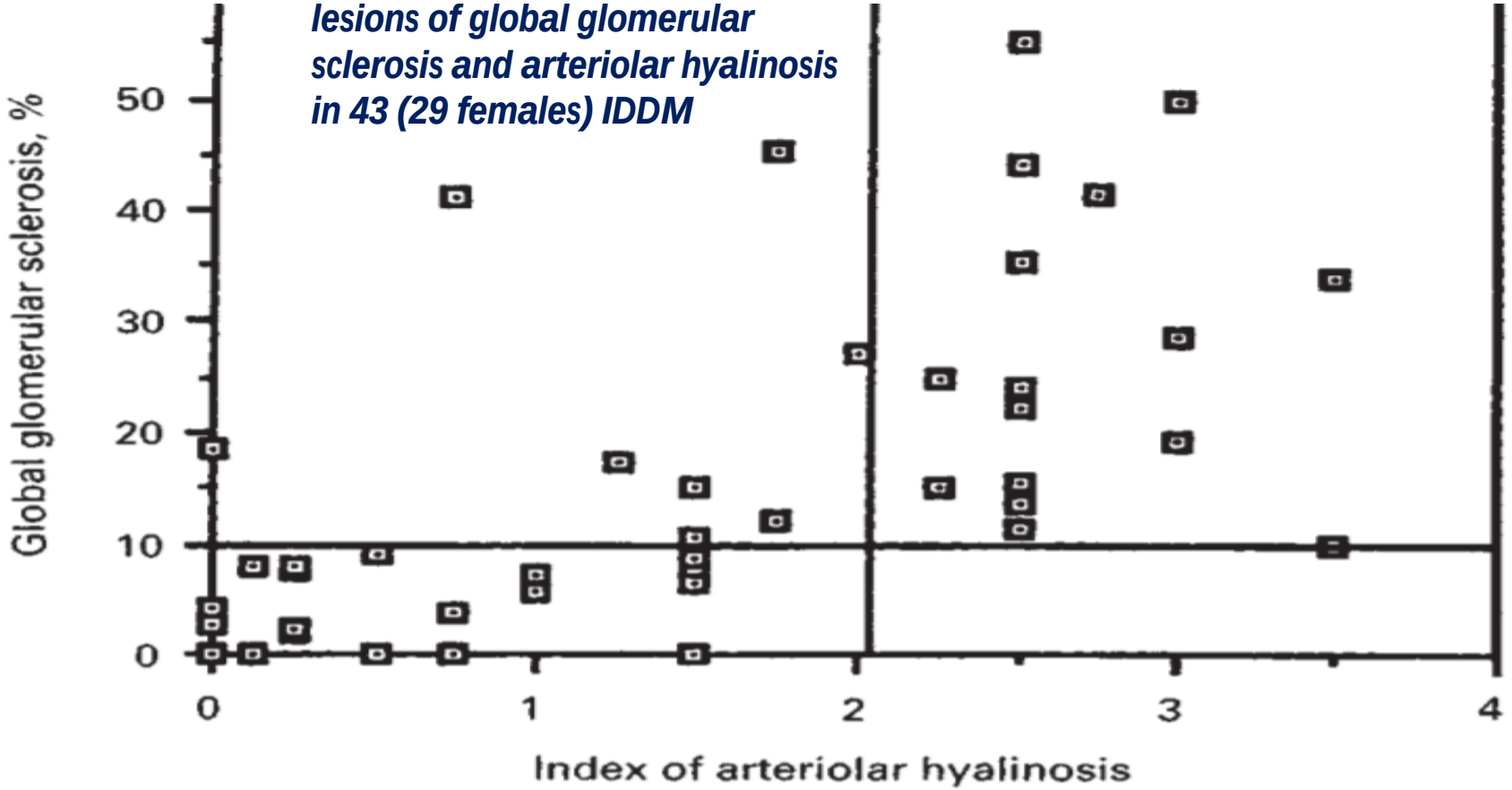


Fig. 3. *Relationship of global glomerular sclerosis and index of arteriolar hyalinosis* ($r = +0.66$, $P < 0.0005$).

Glomerulotubular Junction Abnormalities Are Associated with Proteinuria in Type 1 Diabetes

Behzad Najafian,*† John T. Crosson,† Youngki Kim,* and Michael Mauer*

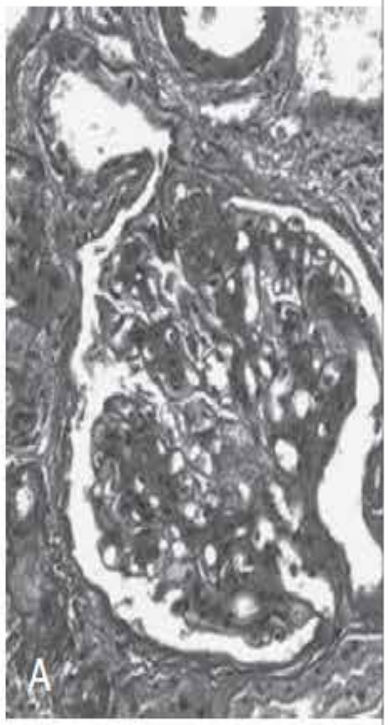


FIGURE 38-5 Glomerulotubula
to a long atrophic tubule (LAT). (
lus (AG). (From Najafian B, Cros
Nephrol 17:S53-S60, 2006.)

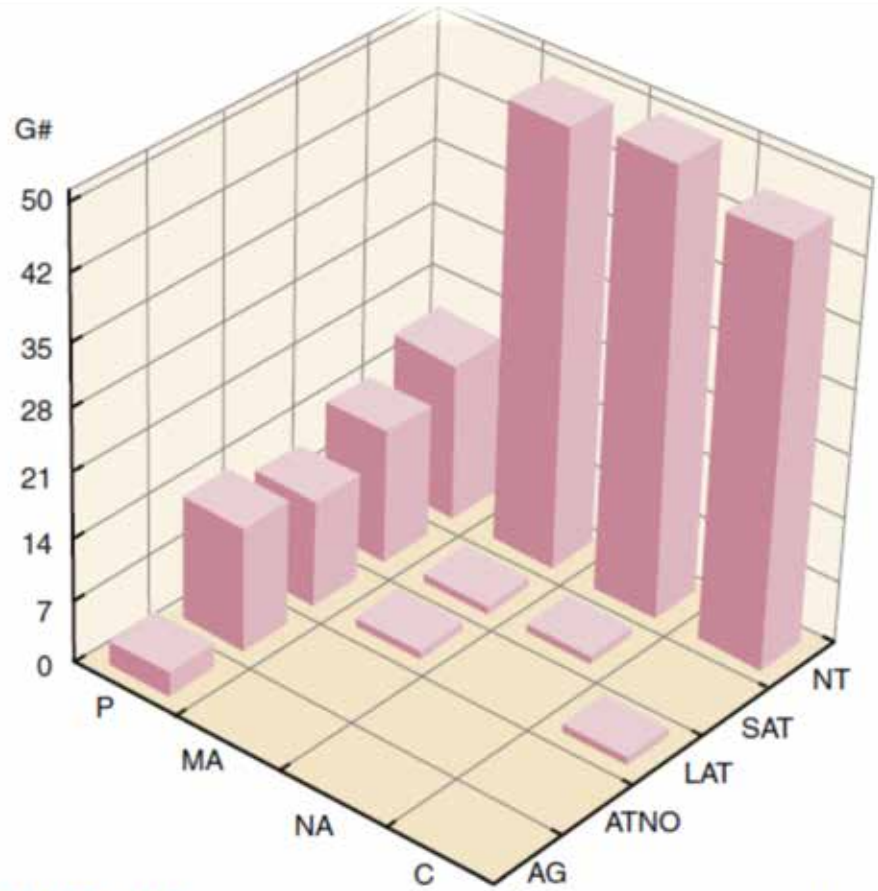
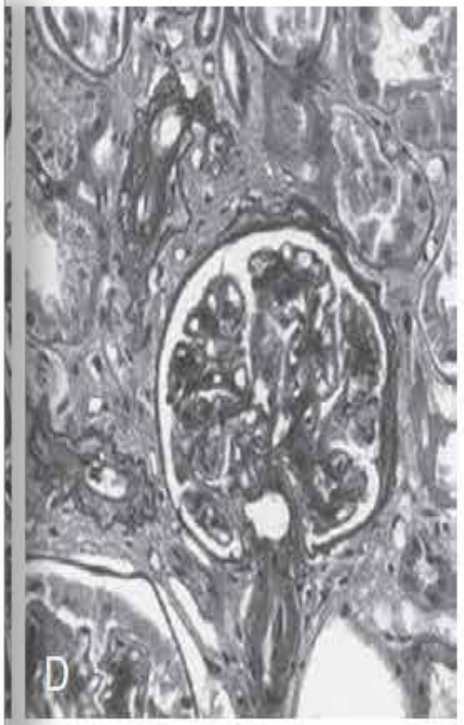


FIGURE 38-6 Frequency of glomerulotubular junction abnormalities (GTJA) in normoalbuminuric (NA), microalbuminuric (MA), and proteinuric (P) patients and control subjects (C). G#, Number of glomeruli; NT, normal tubules. (From Najafian B, Crosson JT, Kim Y, et al: Glomerulotubular junction abnormalities are associated with proteinuria in type 1 diabetes, *J Am Soc Nephrol* 17:S53-S60, 2006.)



c tubule (SAT). **B,** Glomerulus attached
) and a tip lesion. **D,** Atubular glomeru-
proteinuria in type 1 diabetes, *J Am Soc*

Renal biopsies from ***s, 6 proteinuric pts, & 5 control subjects wer***

J Am Soc Nephrol 17: S53–S60, 2006

Εξιδρωματικές βλάβες ΔΝΝ

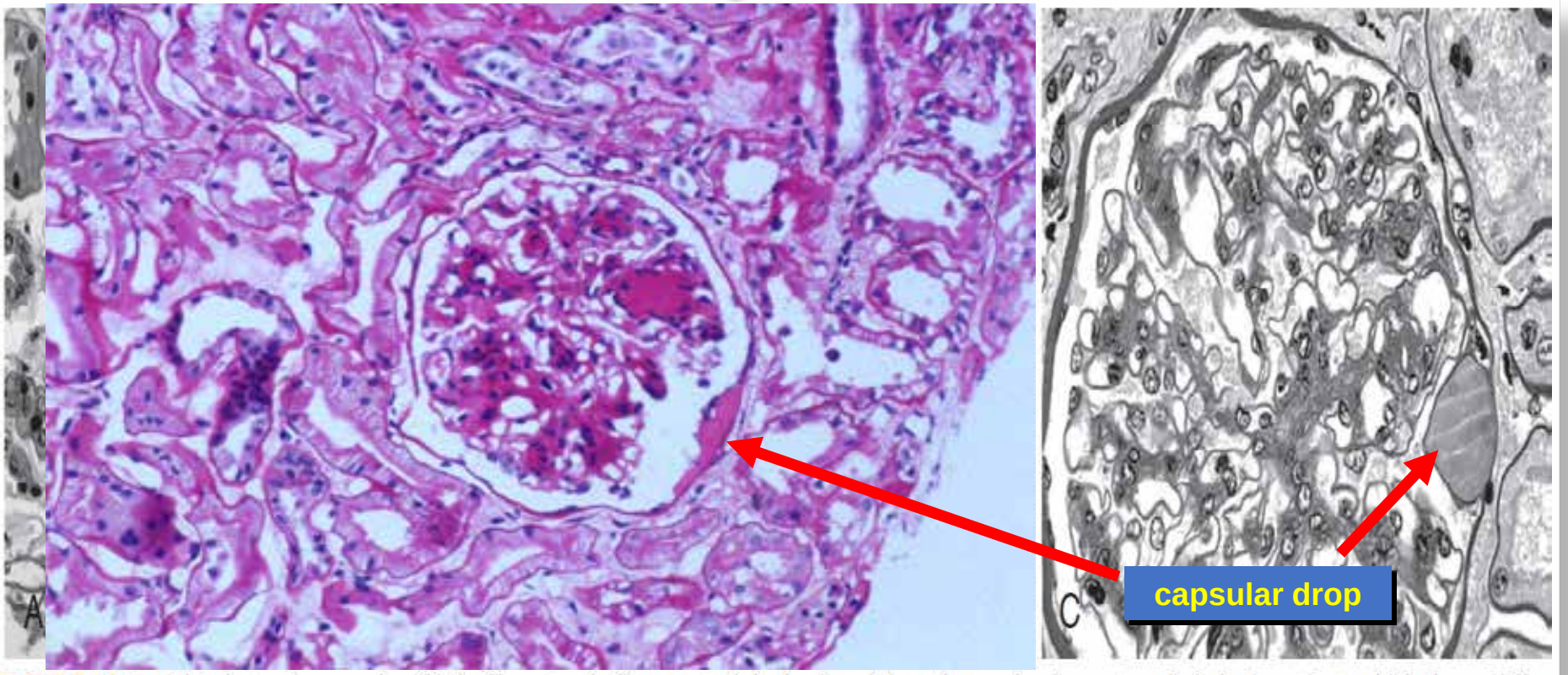
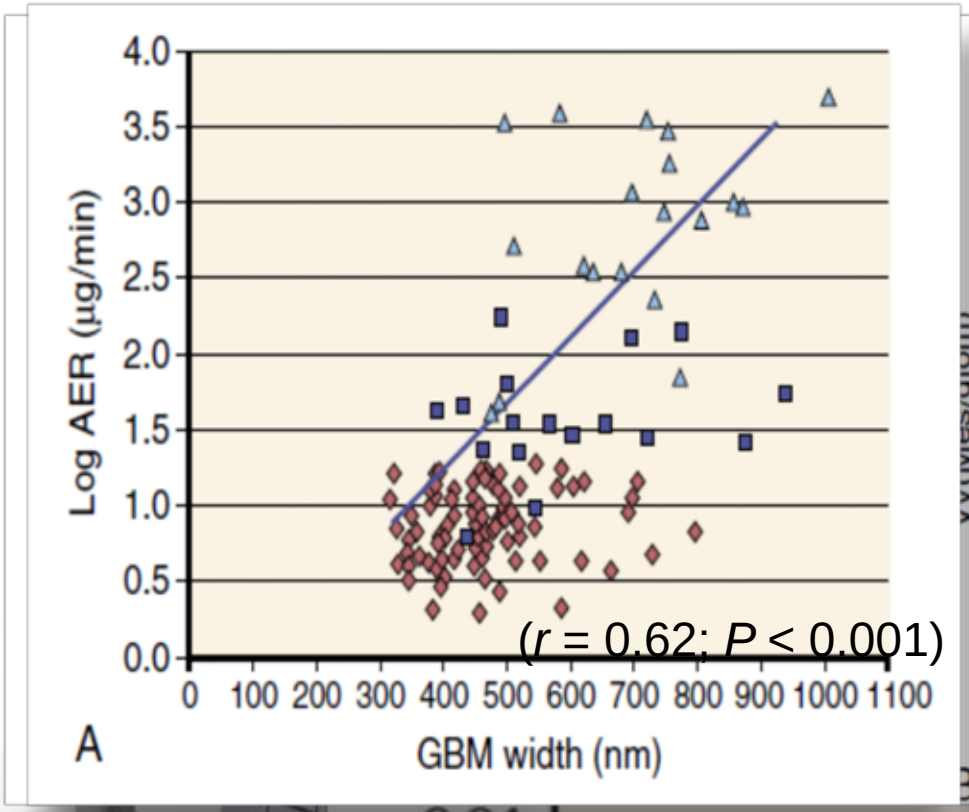
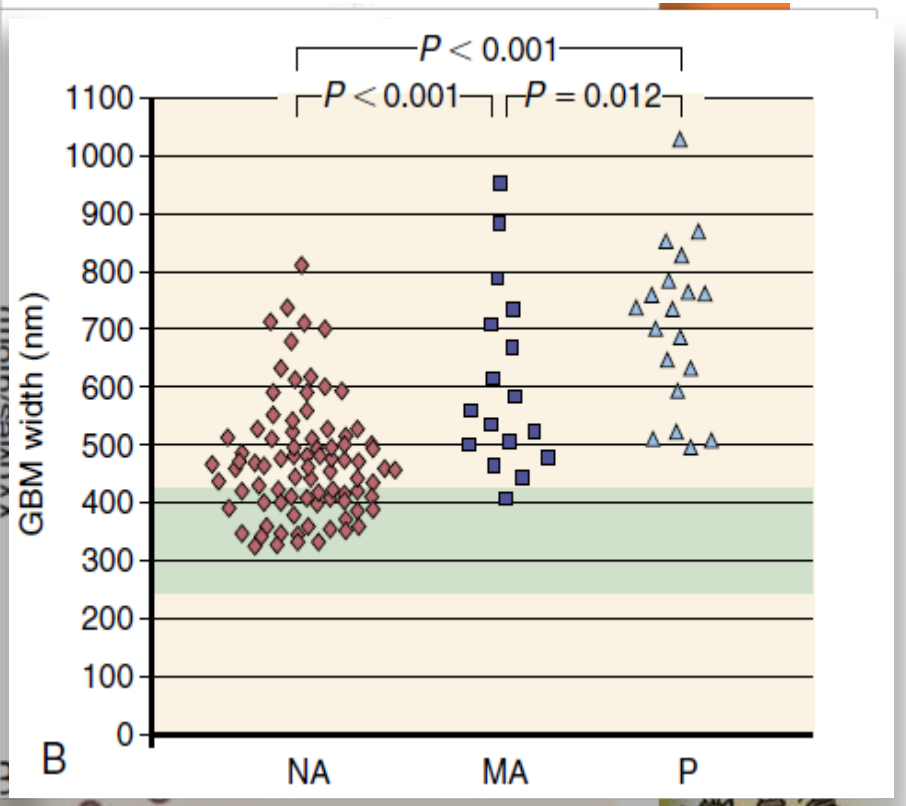


FIGURE 38-3 Light photomicrographs of (A) afferent and efferent arteriolar hyalinosis in a glomerulus from a type 1 diabetic patient, which shows diffus and nodular mesangial expansion (periodic acid–Schiff [PAS] stain); (B) glomerular arteriole showing almost complete replacement of the smooth muscl wall by hyaline material and luminal narrowing (PAS stain); and (C) glomerulus with minimal mesangial expansion and a capsular drop at the 3 o'cloc position.

Østerby R, Diabetologia. 2002;45(4):542-549

Correlation between glomerular basement membrane (GBM) width and albumin excretion rate (AER)





123 patients with type 1 diabetes (88 normoalbuminuric(NA), 17 microalbuminuric (MA), and 19 proteinuric (P)). The shaded area represents the mean ± 2 standard deviation units in a group of 76 age-matched normal control subjects

FIGURE 38-10 Relationship of mesangial fractional volume (% Total Mesangium) and filtration surface density [Sv(Peripheral Capillary/Surface)] in type 1 diabetic patients.

Caramori ML, Diabetes 51[2]:506-513, 2002

Is Podocyte Injury Relevant in Diabetic Nephropathy?

Studies in Patients With Type 2 Diabetes

Michele Dalla Vestra, Alessandra Masiero, Anna Maria Roiter, Alois Saller, Gaetano Crepaldi, and Paola Fioretto

DIABETES, VOL. 52, APRIL 2003

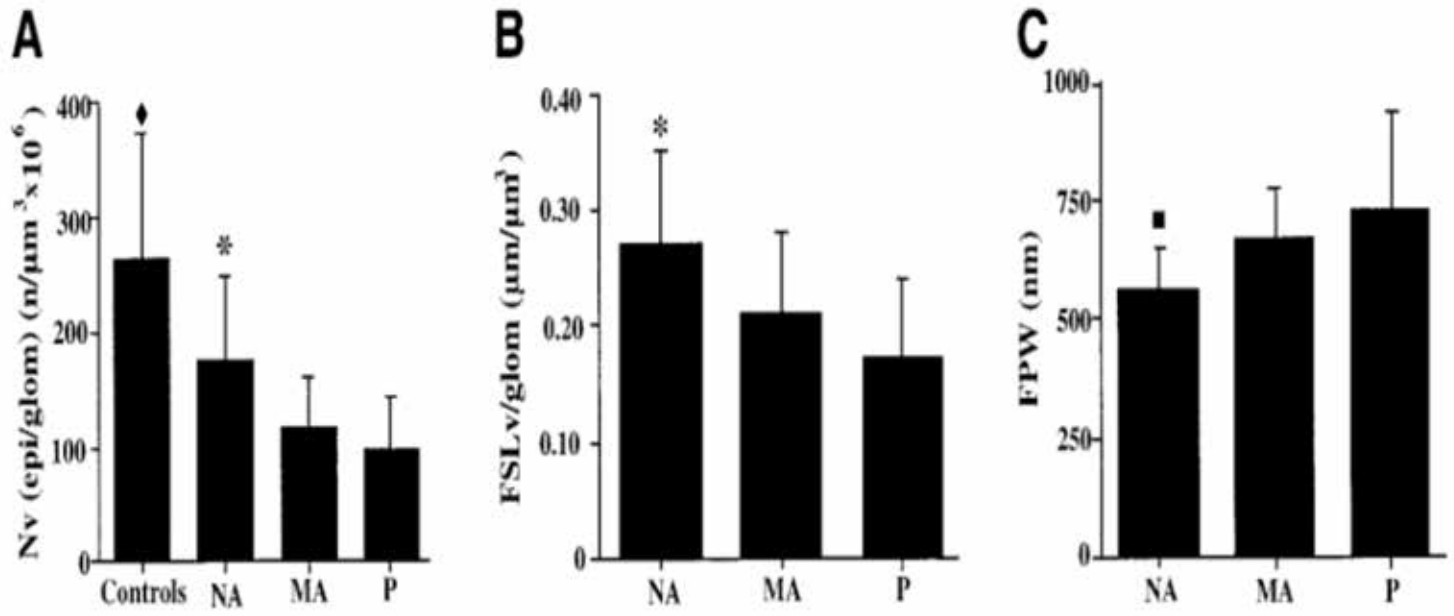


FIG. 1. Podocyte morphometric parameters. Bars represent mean ± 1 SD. *A*: Numerical density of podocytes per glomerulus [Nv(epi/glom)] in patients with type 2 diabetes and normal control subjects. ♦$P < 0.0001$, control vs. all type 2 diabetic subjects; *$P < 0.01$, NA vs. MA and P. *B*: Filtration slit length density per glomerulus (FSLv/glom) in patients with type 2 diabetes. *$P < 0.01$, NA vs. MA and P. *C*: FPW in patients with type 2 diabetes. ■ $P < 0.05$, NA vs. MA and $P < 0.005$, NA vs. P.

Table 4. Clinical features of patients with different glomerular and interstitial lesions

	Class IIa		P-value	Class IIb + III		P-value
	IFTA < 25% (n = 76)	IFTA ≥ 25% (n = 11)		IFTA < 25% (n = 106)	IFTA ≥ 25% (n = 94)	
Age (years)	47.9 ± 9.0	52.2 ± 7.4	0.133	50.0 ± 8.9	52.3 ± 9.1	0.078
Duration of diabetes (m)	57.0 ± 54.0	43.1 ± 40.4	0.416	119.3 ± 73.7	116.9 ± 66.0	0.806
BMI (kg/m^2)	27.2 ± 3.8	26.2 ± 1.3	0.120	24.5 ± 3.2	24.7 ± 3.6	0.715
SBP (mmHg)	134 ± 15	135 ± 8	0.945	141 ± 19	146 ± 19	0.084
DBP (mmHg)	84 ± 9	85 ± 5	0.816	82 ± 9	86 ± 11	0.007
MAP (mmHg)	101 ± 10	101 ± 5	0.765	102 ± 10	106 ± 12	0.010
History of hypertension	76.3	100.0	0.070	77.4	90.4	0.013
24-h proteinuria (g/day)	0.93 ± 1.10	1.64 ± 1.24	0.052	2.67 ± 2.74	3.54 ± 2.86	0.030
Serum creatinine (mg/dL)	0.95 ± 0.38	1.55 ± 0.78	0.029	1.07 ± 0.39	1.65 ± 0.58	<0.001
e-GFR(mL/min/1.73 m^2)	94.8 ± 28.6	59.3 ± 23.7	<0.001	79.8 ± 25.8	49.4 ± 21.5	<0.001
Serum albumin (g/L)	44.1 ± 5.2	42.4 ± 4.2	0.299	35.8 ± 6.3	34.3 ± 5.8	0.070
Cholesterol (mmol/L)	4.54 ± 1.57	4.13 ± 1.20	0.424	5.31 ± 1.60	5.46 ± 1.55	0.508
Triglyceride (mmol/L)	2.14 ± 1.05	2.22 ± 1.34	0.831	1.82 ± 0.90	1.90 ± 1.08	0.555
FBS (mmol/L)	6.54 ± 1.62	6.30 ± 1.53	0.648	7.14 ± 2.82	6.39 ± 1.99	0.029
HbA1c (%)	7.19 ± 1.57	7.04 ± 0.87	0.796	7.37 ± 1.49	6.71 ± 1.49	0.026

Table 2. Associations between pathologic parameters and renal outcomes

	Rate of renal survival				Survival from doubling of creatinine			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Glomerular lesions	2.99 (2.32–3.87)	<0.001	1.49 (1.10–2.02)	0.011	2.55 (2.05–3.16)	<0.001	1.38 (1.05–1.80)	0.021
IFTA	3.93 (3.01–5.12)	<0.001	1.51 (1.05–2.17)	0.028	2.98 (2.37–3.74)	<0.001	1.45 (1.03–2.03)	0.031
Interstitial inflammation	6.71 (4.27–10.53)	<0.001	1.31 (0.76–2.28)	0.332	5.21 (3.51–7.73)	<0.001	1.49 (0.90–2.45)	0.120
Arteriolar hyalinosis	7.95 (0.64–99.48)	0.108			5.07 (0.90–28.5)	0.066		
Arteriosclerosis	1.28 (0.96–1.70)	0.090			1.20 (0.93–1.56)	0.163		

IFTA, interstitial fibrosis and tubular atrophy; HR, hazard ratio; CI, confidence interval.

[a]Adjusting for baseline log-proteinuria, MAP and eGFR.

The NEW ENGLAND JOURNAL of MEDICINE

Reversal of Lesions of Diabetic Nephropathy after Pancreas Transplantation

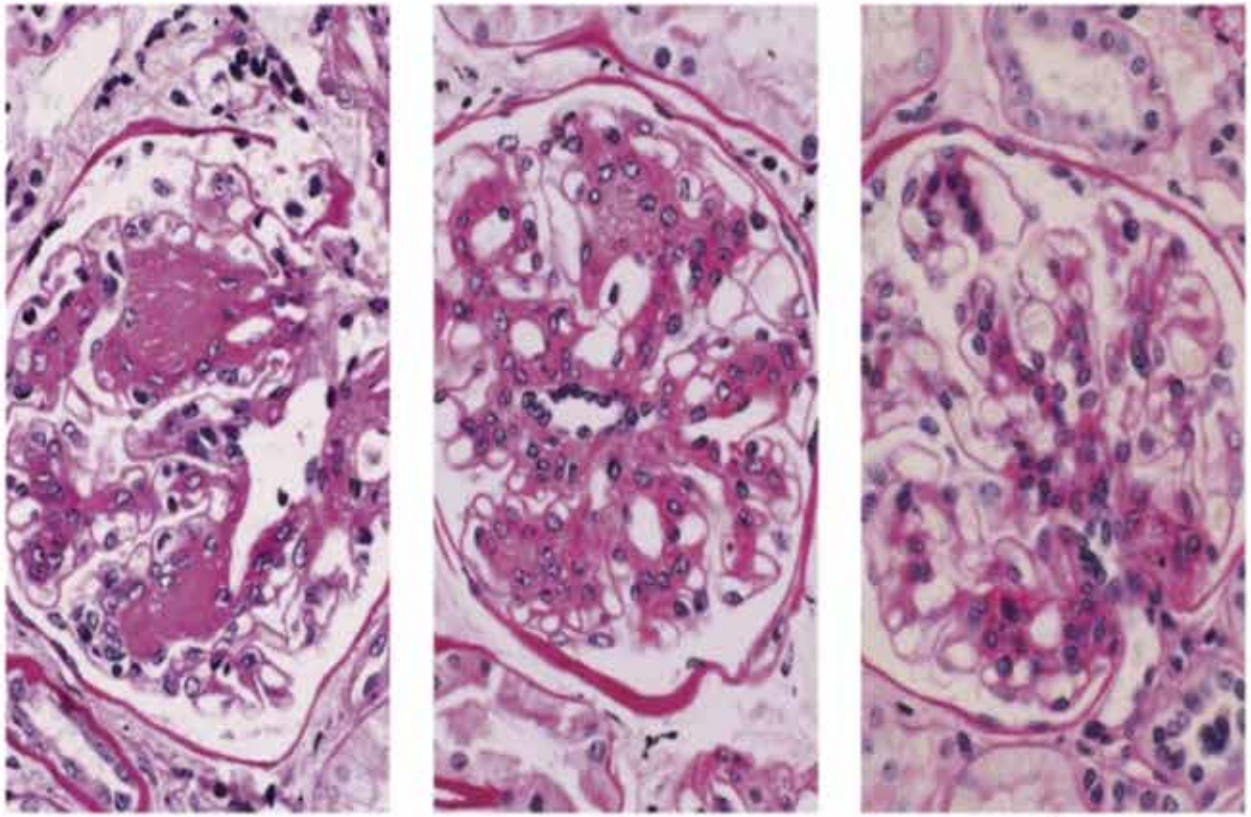


Figure 2. Photomicrographs of Renal-Biopsy Specimens Obtained before and after Pancreas Transplantation from a 33-Year-Old Woman with Type 1 Diabetes of 17 Years' Duration at the Time of Transplantation (Periodic Acid–Schiff, ×120).

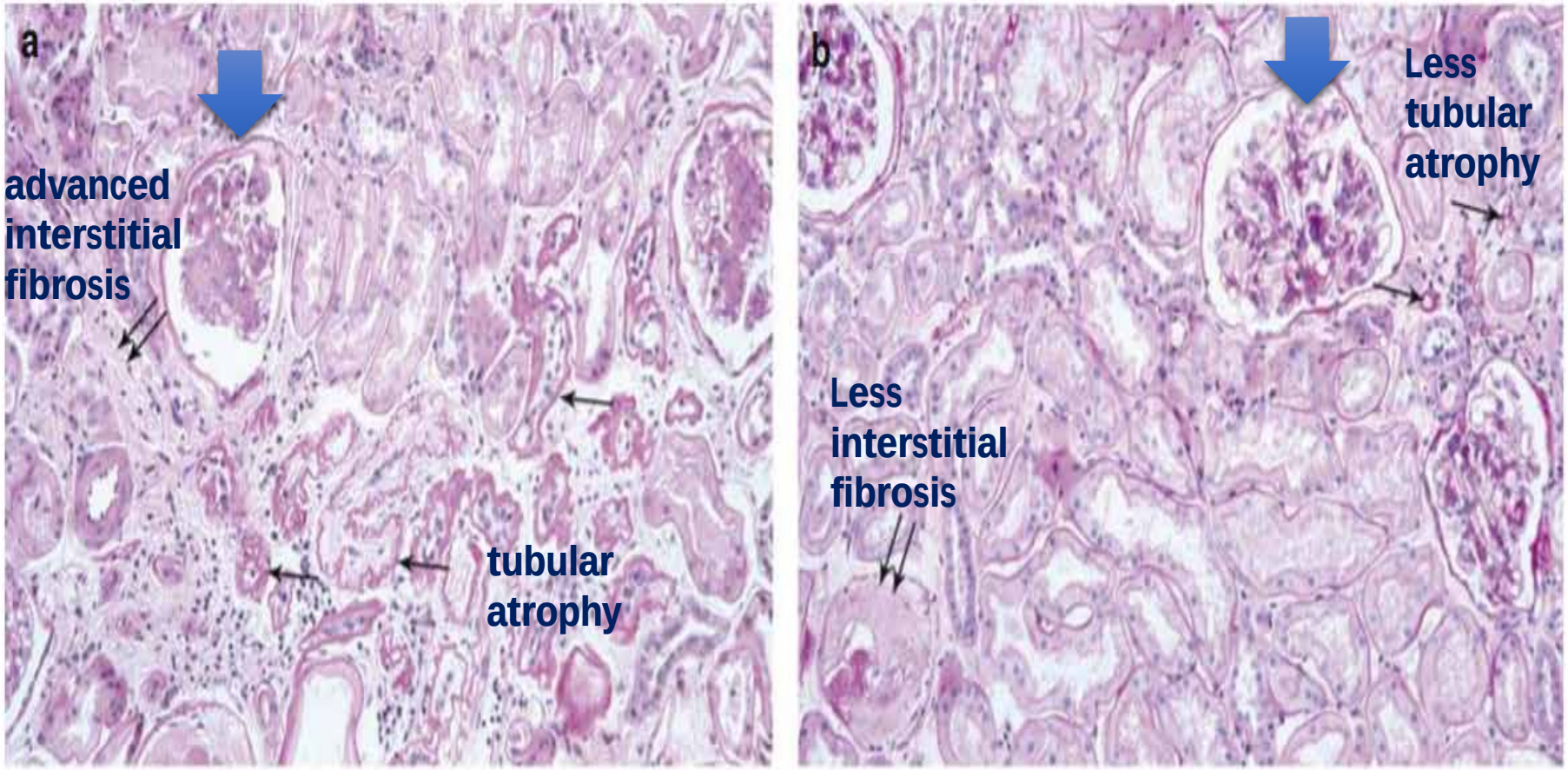
Panel A shows a typical glomerulus from the base-line biopsy specimen, which is characterized by diffuse and nodular (Kimmelstiel–Wilson) diabetic glomerulopathy. Mesangial-matrix expansion and the palisading of mesangial nuclei around the nodular lesions are evident. In Panel B, a typical glomerulus five years after transplantation shows the persistence of the diffuse and nodular lesions. Panel C shows a typical glomerulus 10 years after transplantation, with marked resolution of diffuse and nodular mesangial lesions and more open glomerular capillary lumina.

http://www.kidney-international.org original article

Remodeling of renal interstitial and tubular lesions in pancreas transplant recipients

P Fioretto[1], DER Sutherland[2], B Najafian[3] and M Mauer[3]

8 non-uremic type I DM patients at 5 and 10 years after PTA



5 and 10 years after PTA from the same patient

Ο ρόλος του νεφρού στο μεταβολισμό της γλυκόζης

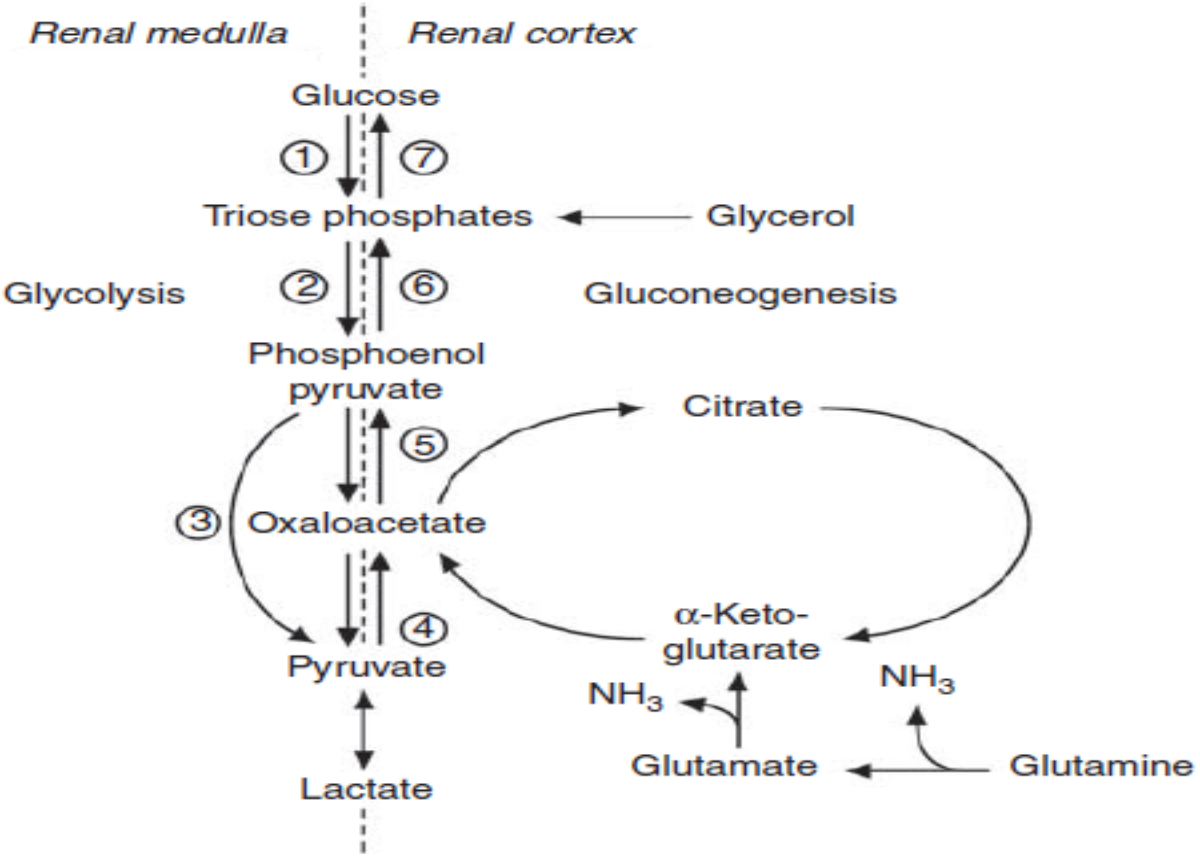


Figure 1 | Renal glycolysis and gluconeogenesis—pathway and enzyme localization. Glycolytic key enzymes (1) hexokinase, (2) phosphofructokinase, and (3) pyruvate kinase are predominantly localized in cells of the renal medulla. The key enzymes of gluconeogenesis, (4) pyruvate carboxylase, (5) phosphoenol pyruvate carboxykinase, (6) fructose-1,6-biphosphatase, and (7) glucose 6-phosphatase, are found mainly in renal cortical cells.[8] Copyright 1997, Springer-Verlag.

3. Επαναρρόφηση της γλυκόζης στους Νεφρώνες

- **Επαναφορά της γλυκόζης στη κυκλοφορία από το σπειραματικό διήθημα**
- **Απαιτείται η κατανάλωση ενέργειας στο ΕΣΑ**

υνθήκες

Gerich JE. *Diabet Med*. 2010;27:136-142.

http://www.kidney-international.org

Glucose handling by the kidney

Amanda Mather[1] and Carol Pollock[1]

[1]Department of Medicine, Kolling Institute of Medical Research, University of Sydney, Sydney, NSW, Australia

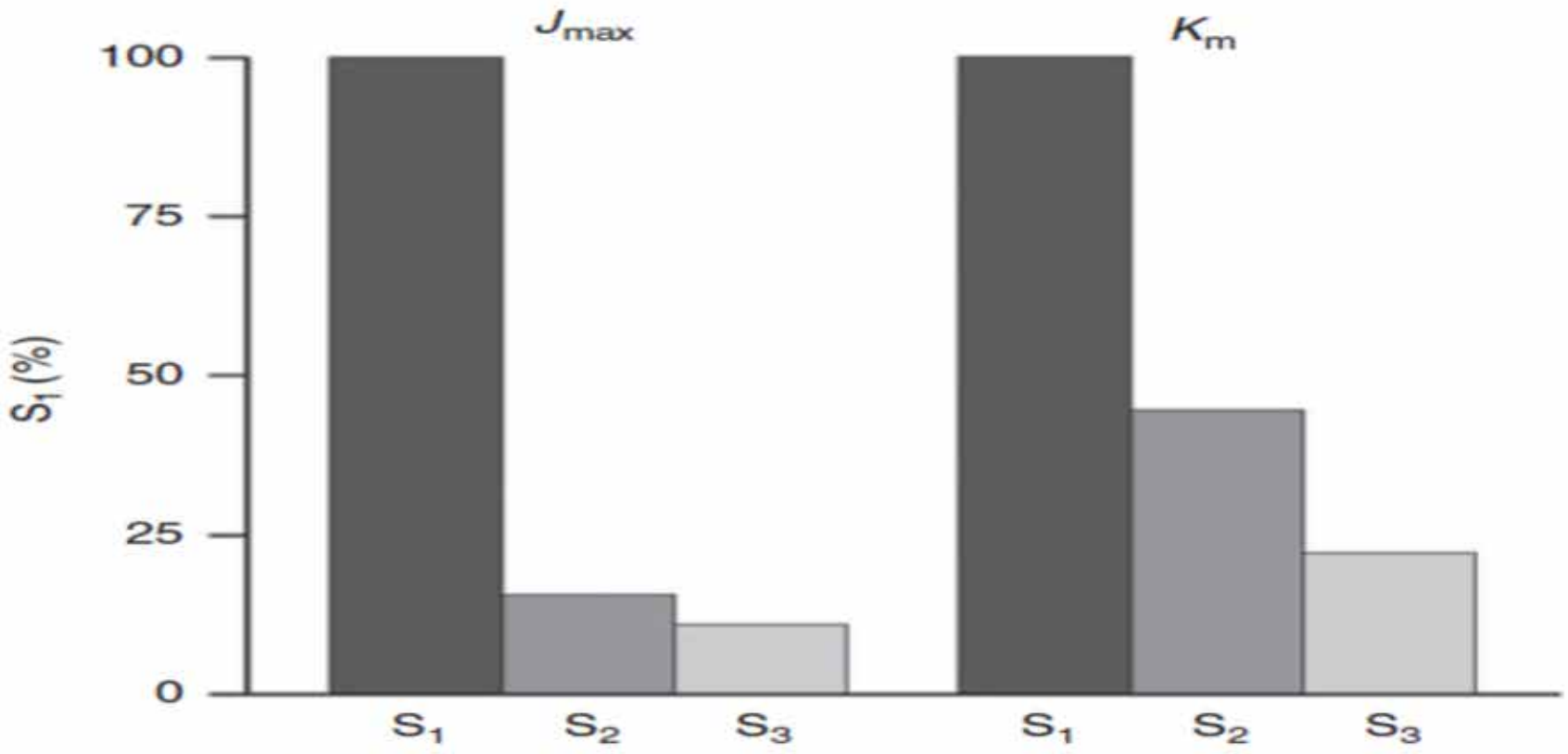
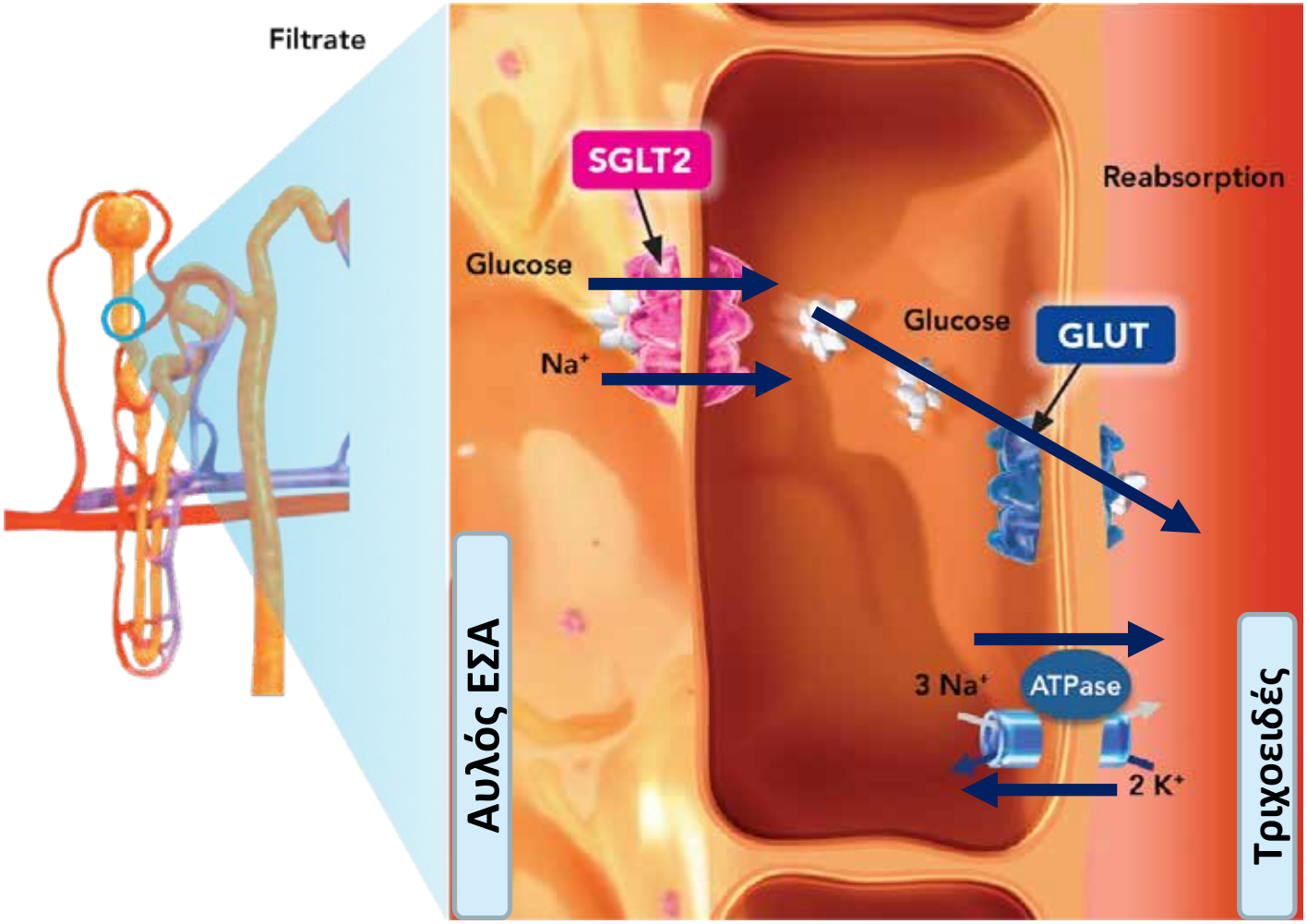


Figure 3 | Relative magnitude of glucose transport characteristics in different segments of the proximal tubule. J_{max}, maximal glucose transport rate; K_m, affinity constant for glucose.[18,21] Copyright 2007, Saunders, an imprint of Elsevier.

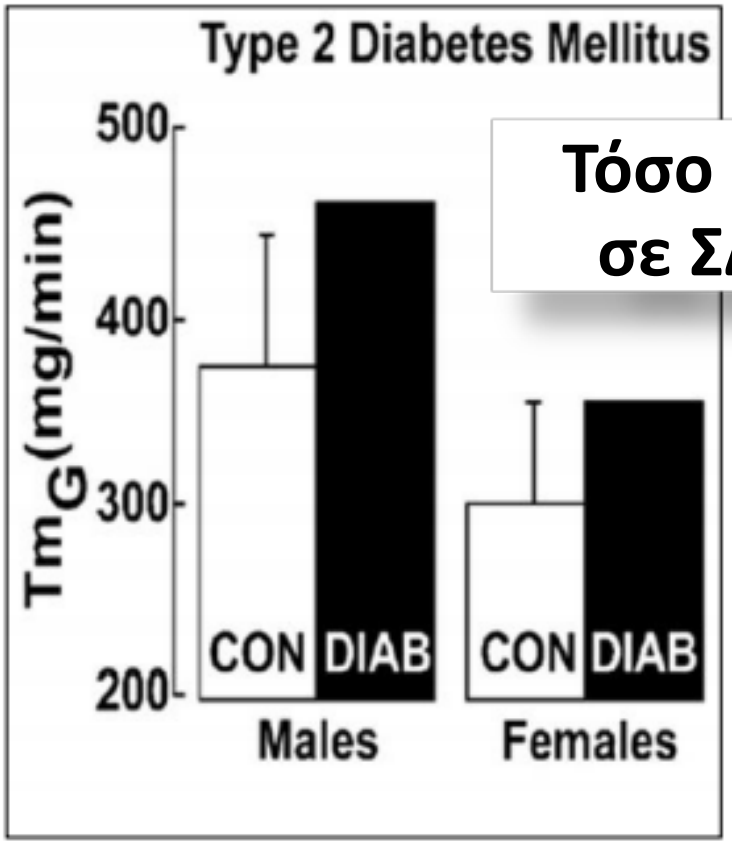
Πρωτεϊνικές δομές στη μεμβράνη ρυθμίζουν τη διακυτταρική μεταφορά της γλυκόζης



SGLT-2=sodium-glucose cotransporter-2; GLUT=facilitative glucose transporter; ATPase=adenosine-5'-triphosphotase.

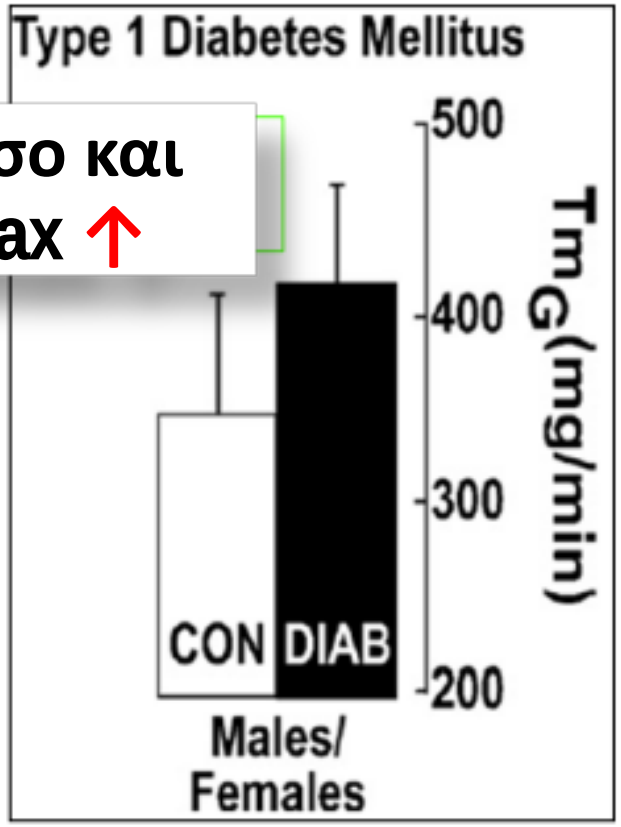
1. Zhao FQ et al. *Curr Genomics*. 2007;8:113-128.
2. Asano T et al. *Curr Med Chem*. 2004;11:2717-2724.

Η επίδραση της υπεργλυκαιμίας στην νεφρική ουδό (Tm) επαναρρόφησης της γλυκόζης σε ΣΔΤ1 και ΣΔΤ2



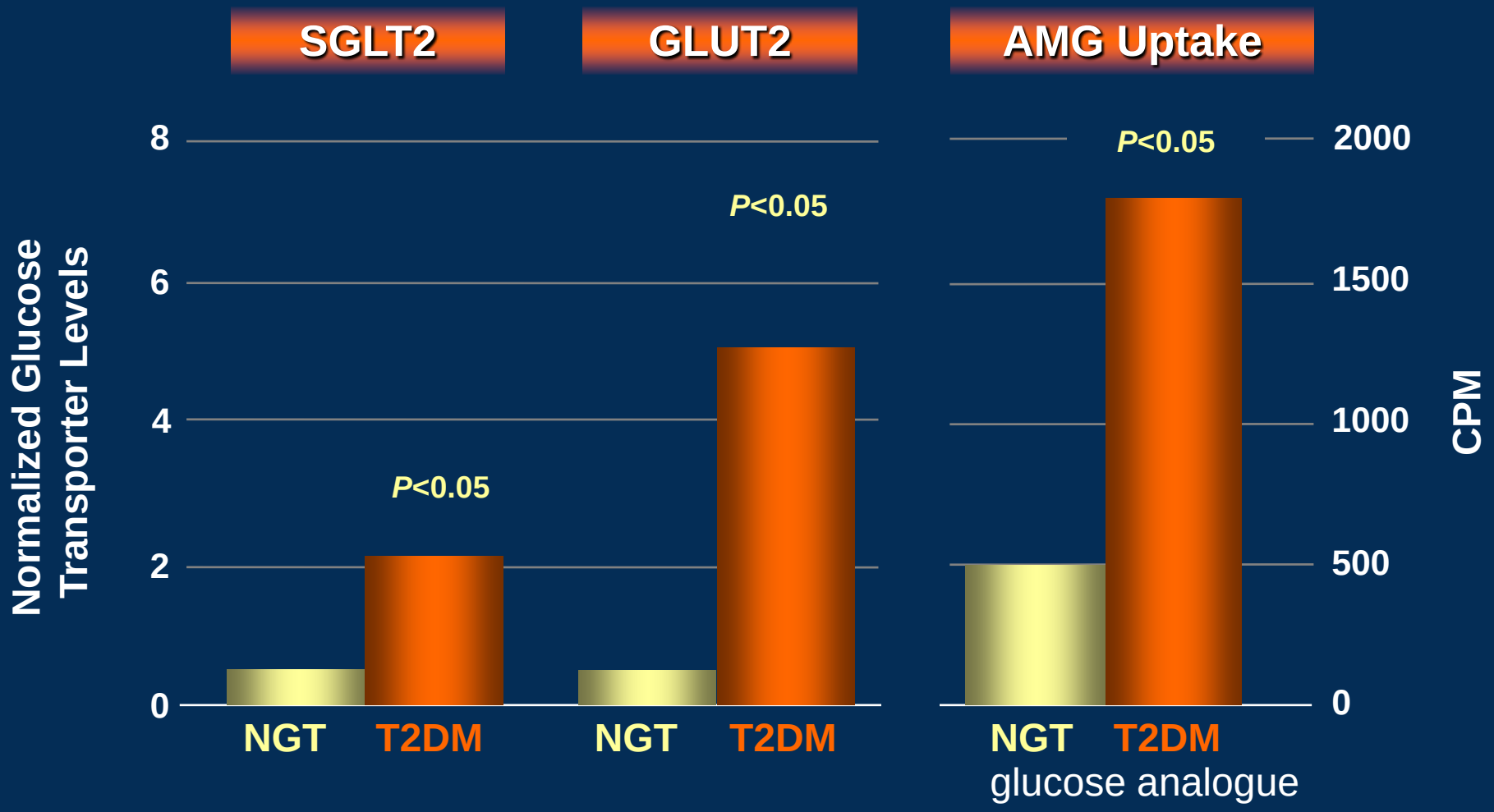
Faber SJ,
J Clin Invest 1951;30:125–129

Τόσο σε ΣΔΤ1 όσο και σε ΣΔΤ2 το Tmax ↑



Mogensen CE ,
Scand J Clin Lab Invest 1971;28:183–193

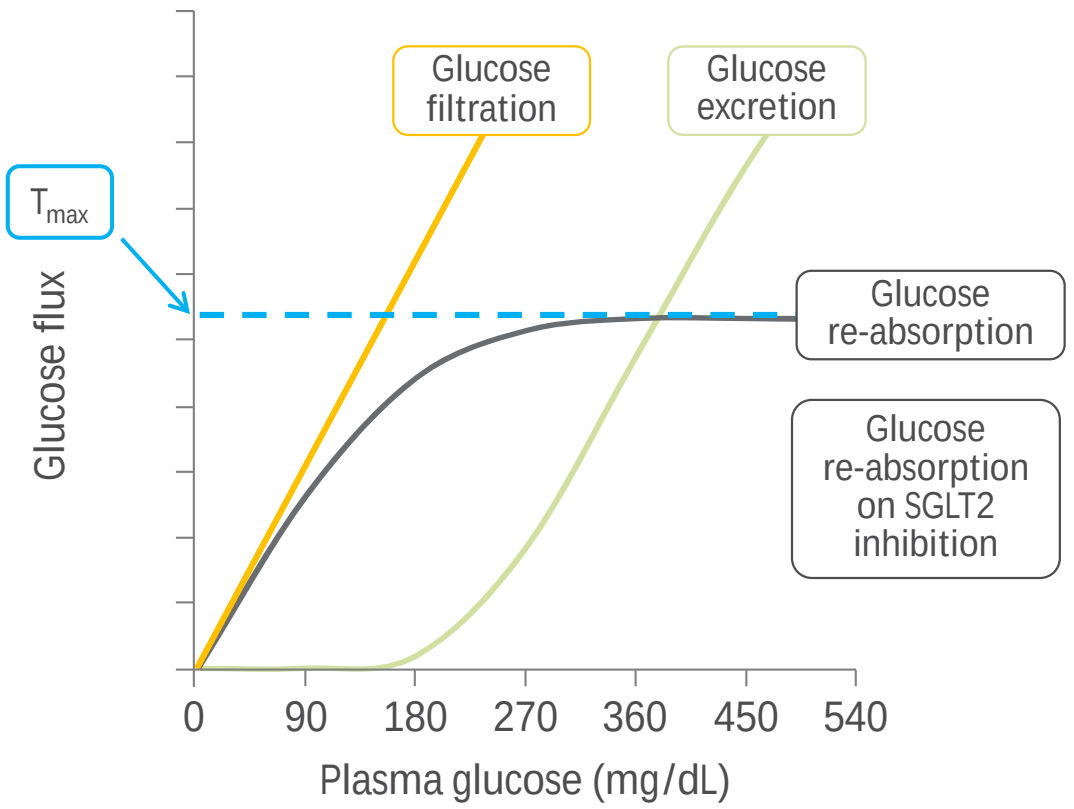
Αυξημένη έκφραση και δραστηριότητα των πρωτεϊνών μεταφοράς της γλυκόζης στο ΣΔΤ2



AMG=methyl-a-D-[U^{14}C]-glucopyranoside; CPM=counts per minute.

Rahmoune H, et al. *Diabetes.* 2005;54:3427-3434.

Renal glucose re-absorption and excretion



Η επαναρρόφηση της γλυκόζης αυξάνεται στο ΣΔΤ2...

...ελαττώνοντας την αποβαλλόμενη ποσότητα γλυκόζης για το αντίστοιχο επίπεδο στο αίμα

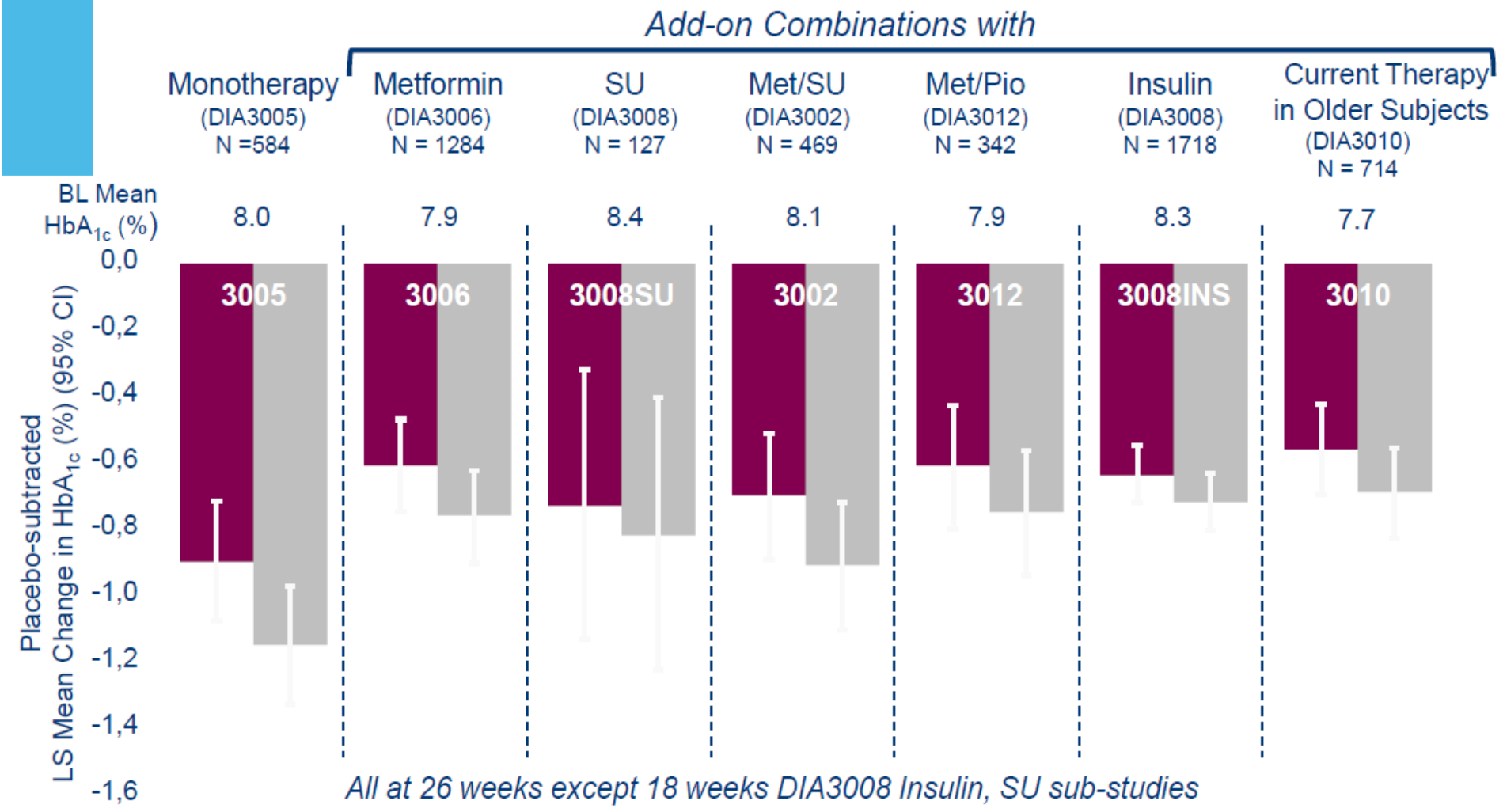
Οι SGLT2inh μειώνουν την ποσότητα της γλυκόζης η οποία δύναται να απορροφηθεί δηλ. μείωση του T_{max}

Αύξηση στην αποβολή της γλυκόζης

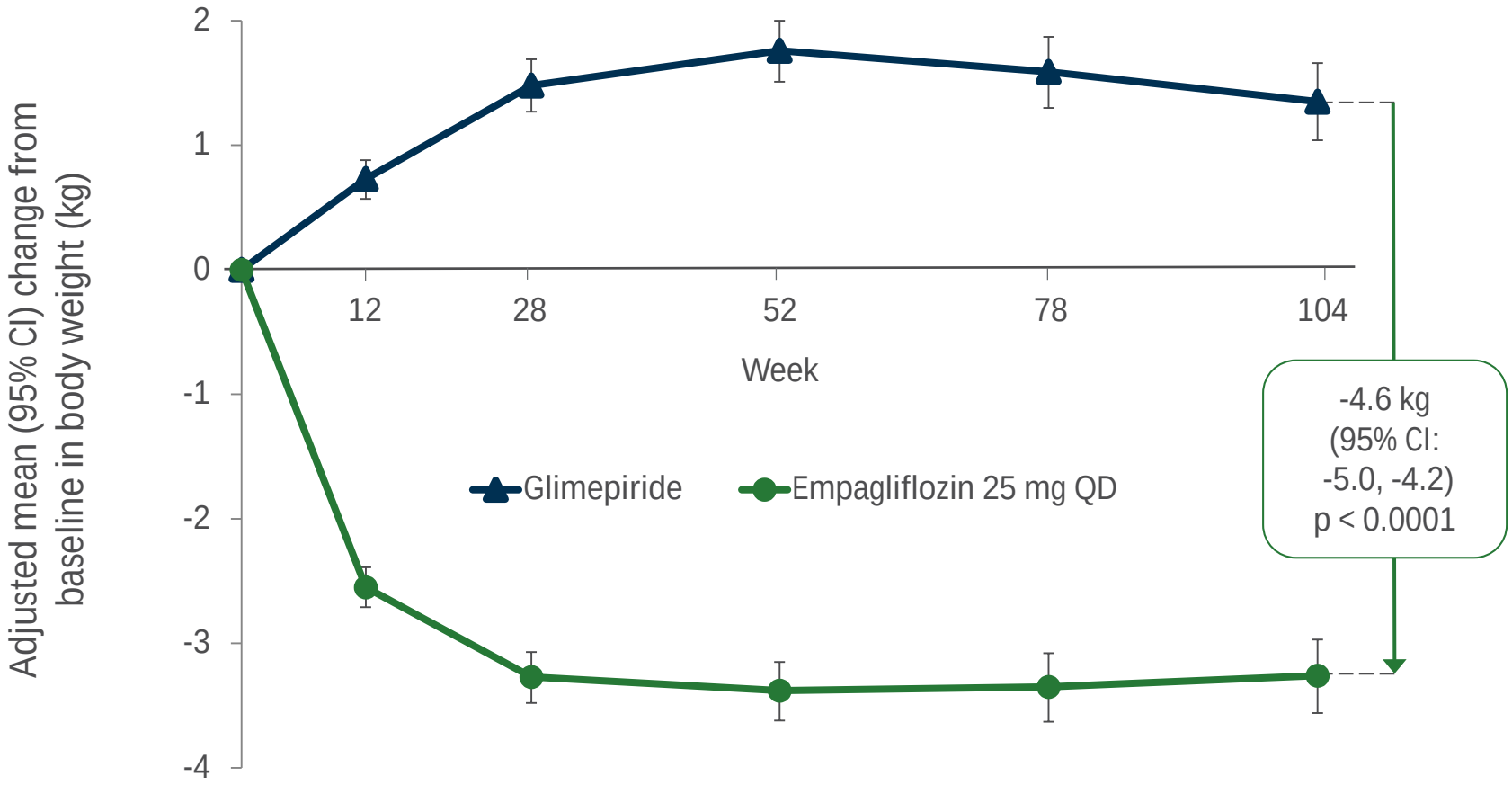
SGLT2, sodium glucose cotransporter 2; T2D, Type 2 Diabetes; T_{max}, transport maximum.

Nair S, Wilding JPH. *J Clin Endocrinol Metab*. 2010;95:34–42.

SGLT2 decreases HbA1c on top of other diabetic medications



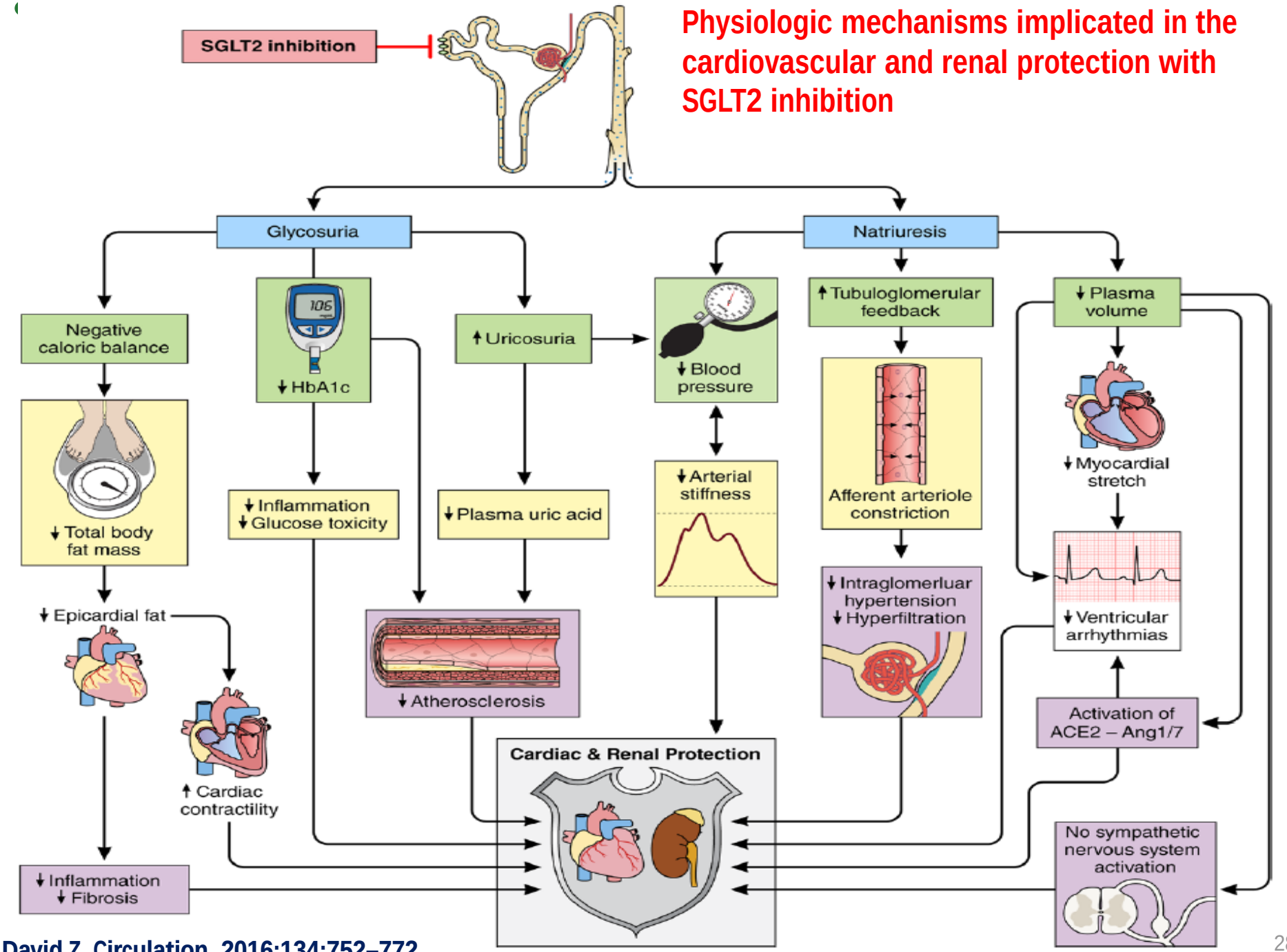
104-week study with empagliflozin H2H versus glimepiride
Change in body weight over time



Analysed patients						
Glimepiride	745	743	703	610	526	462
Empagliflozin	739	737	706	643	595	555

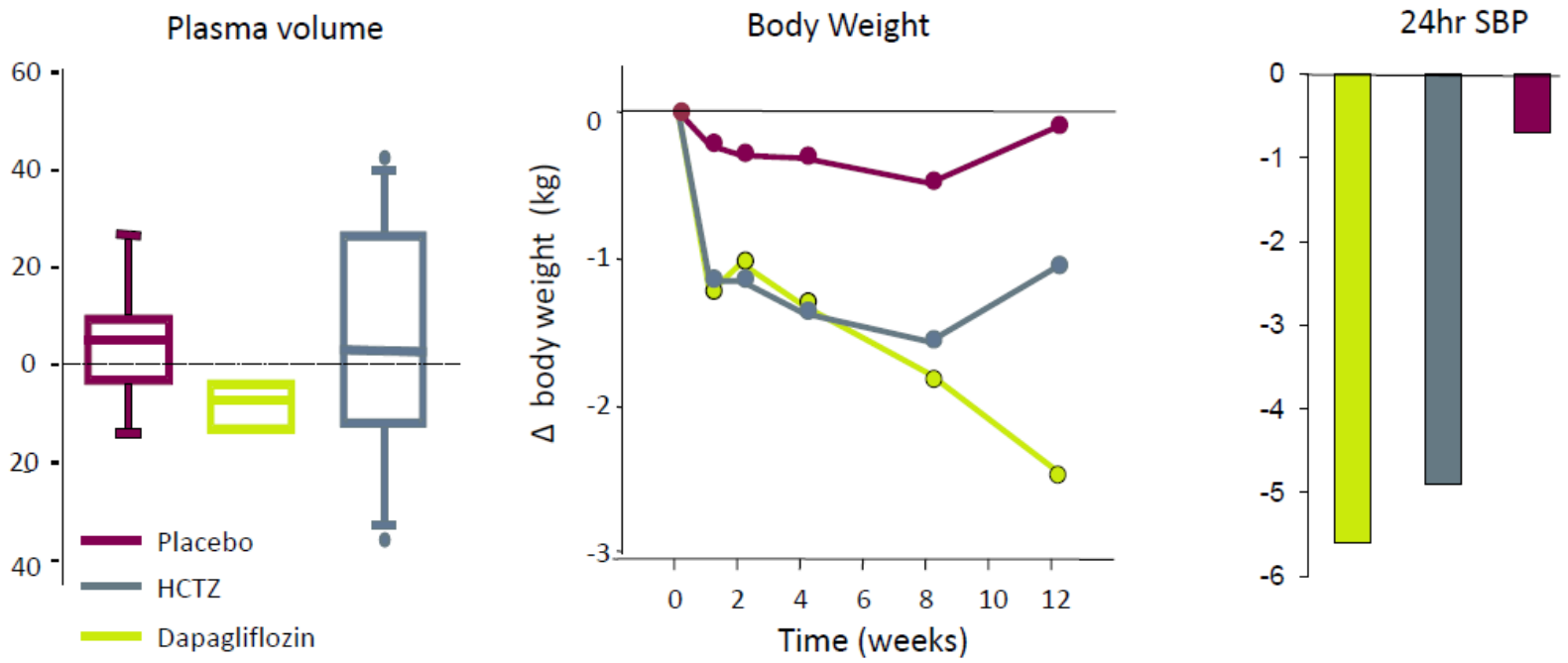
CI, confidence interval; H2H, head-to-head; QD, once daily; SE, standard error.
MMRM. FAS (OC).
Ridderstråle M, et al. *Lancet Diabetes Endocrinol.* 2014;2:691–700.

Physiologic mechanisms implicated in the cardiovascular and renal protection with SGLT2 inhibition



David Z .Circulation. 2016;134:752–772.

Dapagliflozin diuretic effects: lower plasma volume, body weight, and 24-hr blood pressure



- Dapagliflozin reduces plasma volume compared to placebo or HCTZ as measured by ^{51}Cr Albumin
- Reductions in body weight during the initial 4 weeks paralleled reductions in body weight during HCTZ

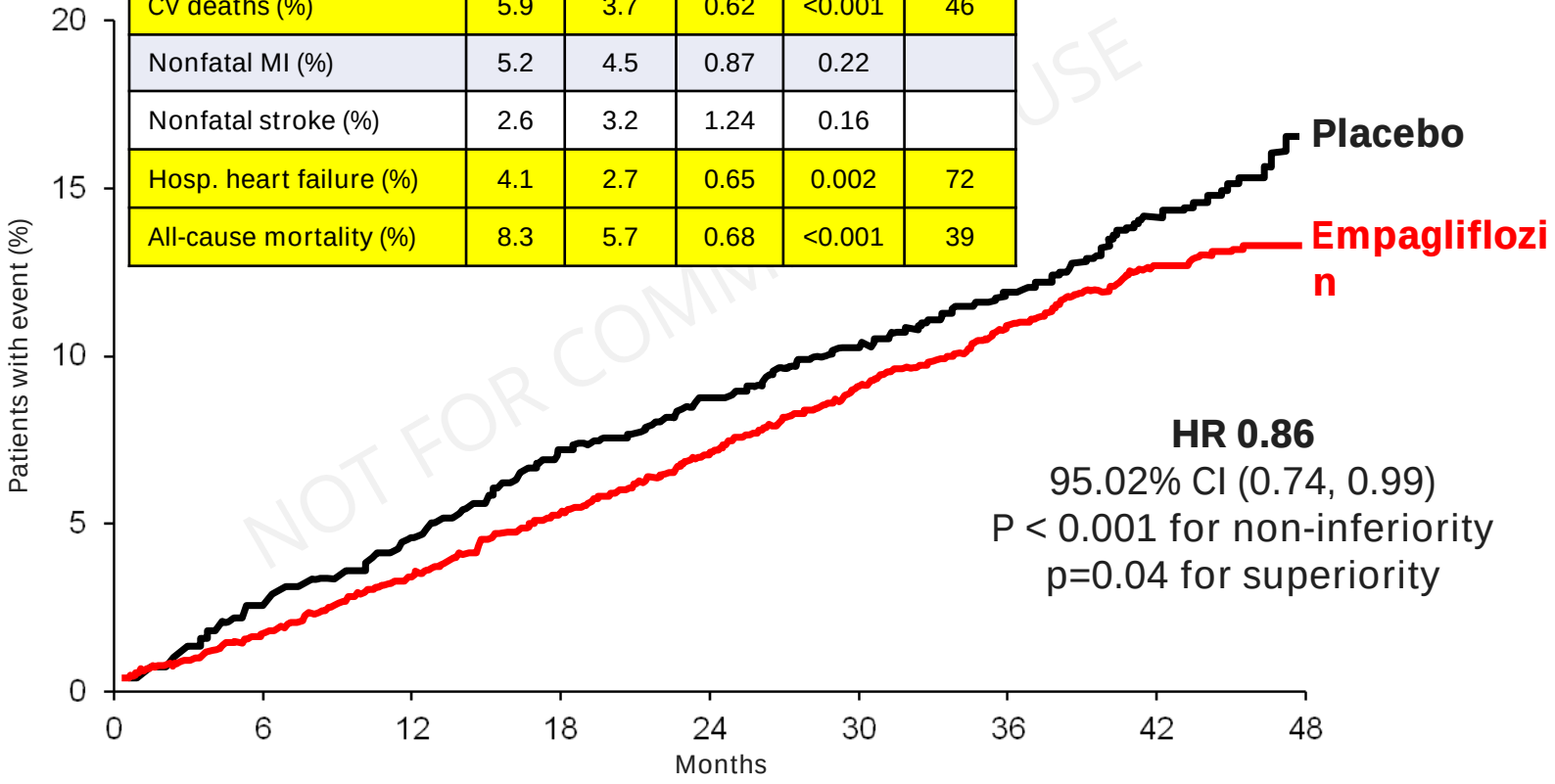
Abbreviations: HCTZ, hydrochlorothiazide, SBP, systolic blood pressure

*Heerspink et al. Diabetes Obesity Metabolism 2013;*15(9):853-62

Empagliflozin reduced CV events

CV death, non-fatal MI, or non-fatal stroke

	PBO	EMPA	HR	P	NNT3
CV death, MI, stroke (%)	12.1	10.5	0.86	0.04	63
CV deaths (%)	5.9	3.7	0.62	<0.001	46
Nonfatal MI (%)	5.2	4.5	0.87	0.22	
Nonfatal stroke (%)	2.6	3.2	1.24	0.16	
Hosp. heart failure (%)	4.1	2.7	0.65	0.002	72
All-cause mortality (%)	8.3	5.7	0.68	<0.001	39

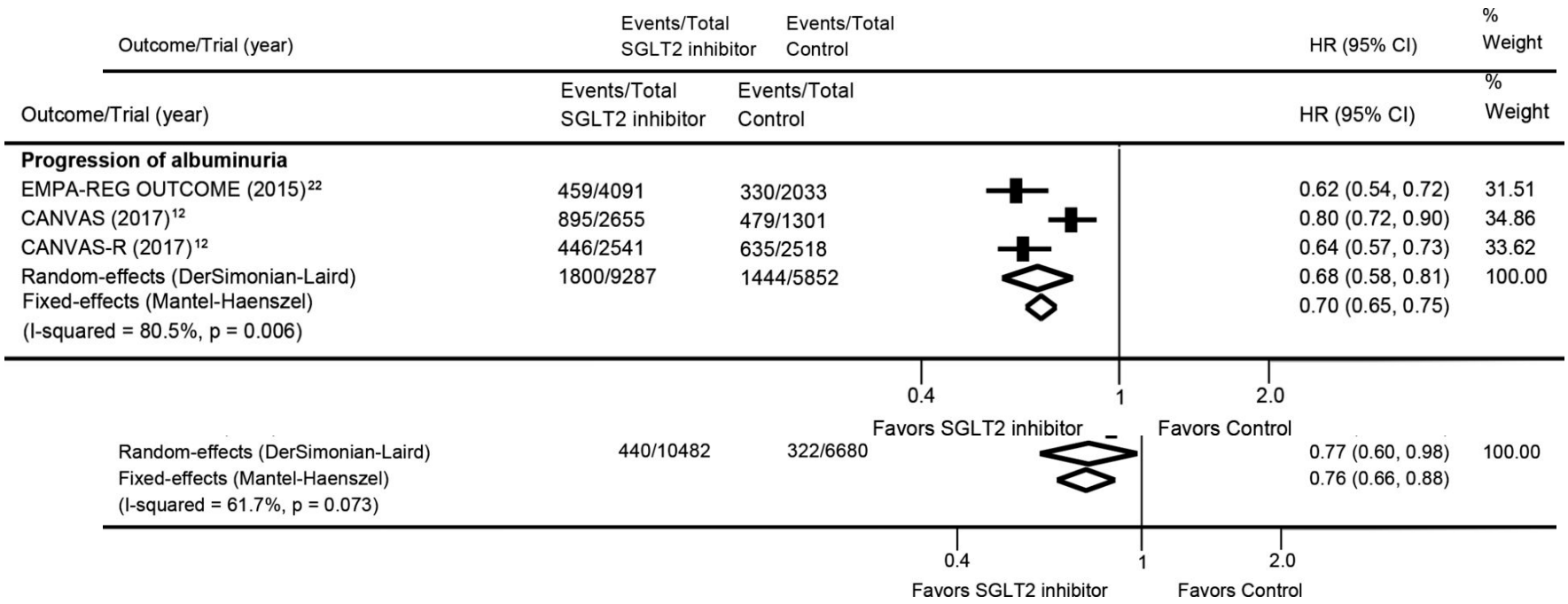


No. of patients

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Zinman B et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1504720

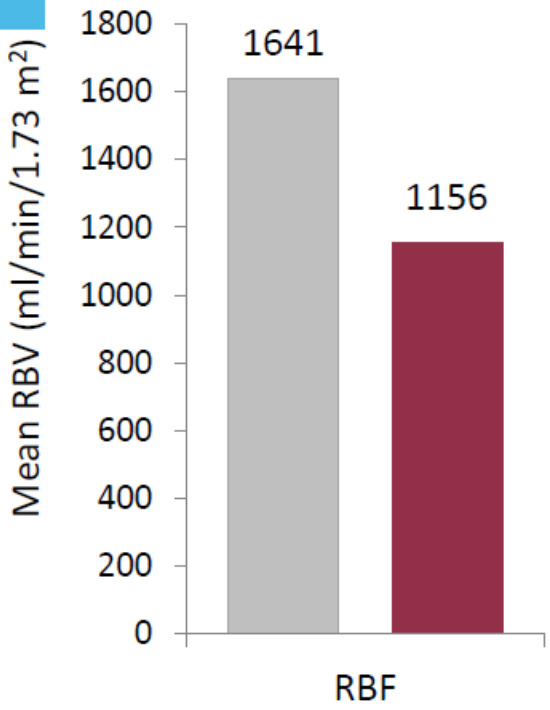
Effects of SGLT2 inhibitors on progression of albuminuria.
Effects of SGLT2 inhibitors on all-cause death (top) and cardiovascular death (bottom).

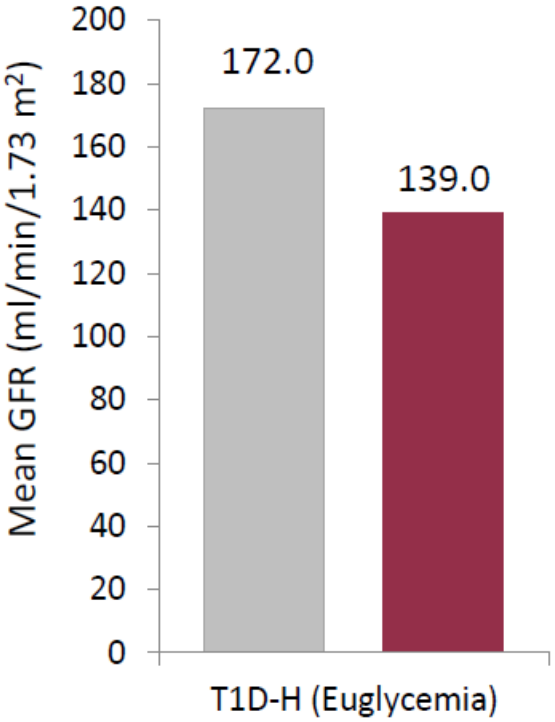


Xin-Lin Zhang et al. J Am Heart Assoc 2018;7:e007165

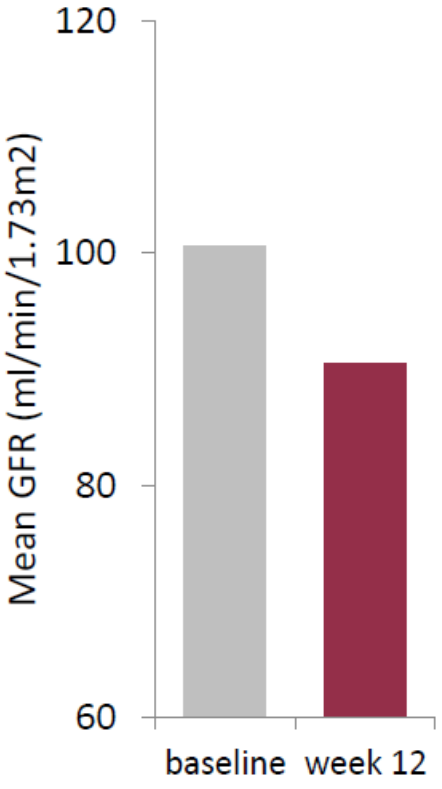
SGLT2 inhibitors decrease RPF and GFR

Type 1 diabetes





Type 2 diabetes

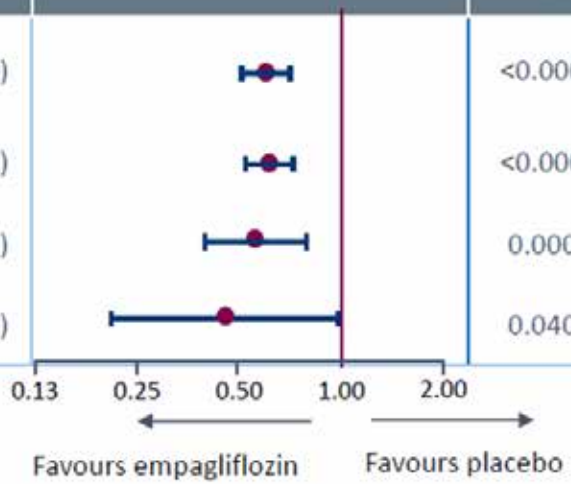


Cherney D et al. Circulation 2014:129;587-99

Heerspink et al. DOM 2013; 15:853-62

EMPAREG: Empagliflozin reduces renal risk

	N With Event/N Patients					
	Empagliflozin	Placebo	HR	(95% CI)		*P*-value
New onset/worsening of nephropathy	525/4124	388/2061	0.61	(0.53, 0.70)		<0.0001
New onset macroalbuminuria	459/4091	330/2033	0.62	(0.54, 0.72)		<0.0001
Doubling of serum-creatinine*	70/4645	60/2323	0.56	(0.39, 0.79)		0.0009
Initiation of renal replacement therapy	13/4687	14/2333	0.45	(0.21, 0.97)		0.0409



* Accompanied by estimated glomerular filtration rate (MDRD) ≤45 mL/min/1.73 m².

Wanner C et.al. N Engl J Med. 2016 Jul 28;375(4):323-34

Clin J Am Soc Nephrol. 2017 Dec 7;12(12):2032-2045. doi: 10.2215/CJN.11491116. Epub 2017 May 18.

Diabetic Kidney Disease: Challenges, Progress, and Possibilities.

Alicic RZ[1,2], Rooney MT[3], Tuttle KR[3,2,4,5,6].

Kidney outcomes in clinical trials of newer antihyperglycemic therapies

Name of the Study	Tested Intervention/Drugs	Study Population	Outcomes
SAVOR-TIMI ([84])	Saxagliptin (DPP-4 inhibitor)	DM2, HbA1c≥6.5%, high risk for CV events	Improvement in and/or less deterioration in ACR categories from baseline to end of trial (P=0.02, P<0.001, and P=0.05 for normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively); no changes in eGFR
CARMELINA ([85])	Linagliptin (DPP-4 inhibitor)	DM2, 6.5%≥HbA1c≤10%, albuminuria, macrovascular complications, eGFR>15 ml/min per 1.73 m^2	In progress, estimated completion in January of 2018
LEADER ([75])	Liraglutide (GLP-1 receptor agonist)	DM2, HbA1c>7%, eGFR<60 ml/min per 1.73 m^2, CV coexisting disease	Lower incidence of nephropathy (new-onset albuminuria, doubling of SCr and CrCl<45 ml/min per 1.73 m^2; need for RRT, death to renal causes [1.5 number of events per 100 patients per year versus 1.9 number of events per 100 patients per year; P=0.003])
AWARD-7, ([86])	Dulaglutide (GLP-1 receptor agonist)	DM2, 7.5%≥HbA1c≤10.5%, 15≥eGFR≤60 ml/min per 1.73 m^2	In progress, estimated completion in July of 2018
EMPA-REG OUTCOME ([78])	Empaglifozin (SGLT-2 inhibitor)	DM2, eGFR≥30 ml/min per 1.73 m^2, high CV risk	44% Relative risk reduction of doubling of SCr (1.5% versus 2.6%); 38% relative risk reduction of progression to macroalbuminuria (11.2% versus 16.2%); 55% relative risk reduction of initiation of RRT (0.3% versus 0.6%); slowing GFR decline (annual decrease 0.19±0.11 versus 1.67±0.13 ml/min per 1.73 m^2; P<0.001)
CREDENCE ([87])	Canaglifozin (SGLT-2 inhibitor)	DM2, 6.5%≥HbA1c≤12%, high CV risk, 300 mg/g≥UACR≤5000 mg/g, 30≥eGFR≤90 ml/min per 1.73 m^2	In progress, estimated completion in June of 2019

Alicic R, Clin J Am Soc Nephrol 13: ccc–ccc, 2017

Ευχαριστώ Πολύ !!