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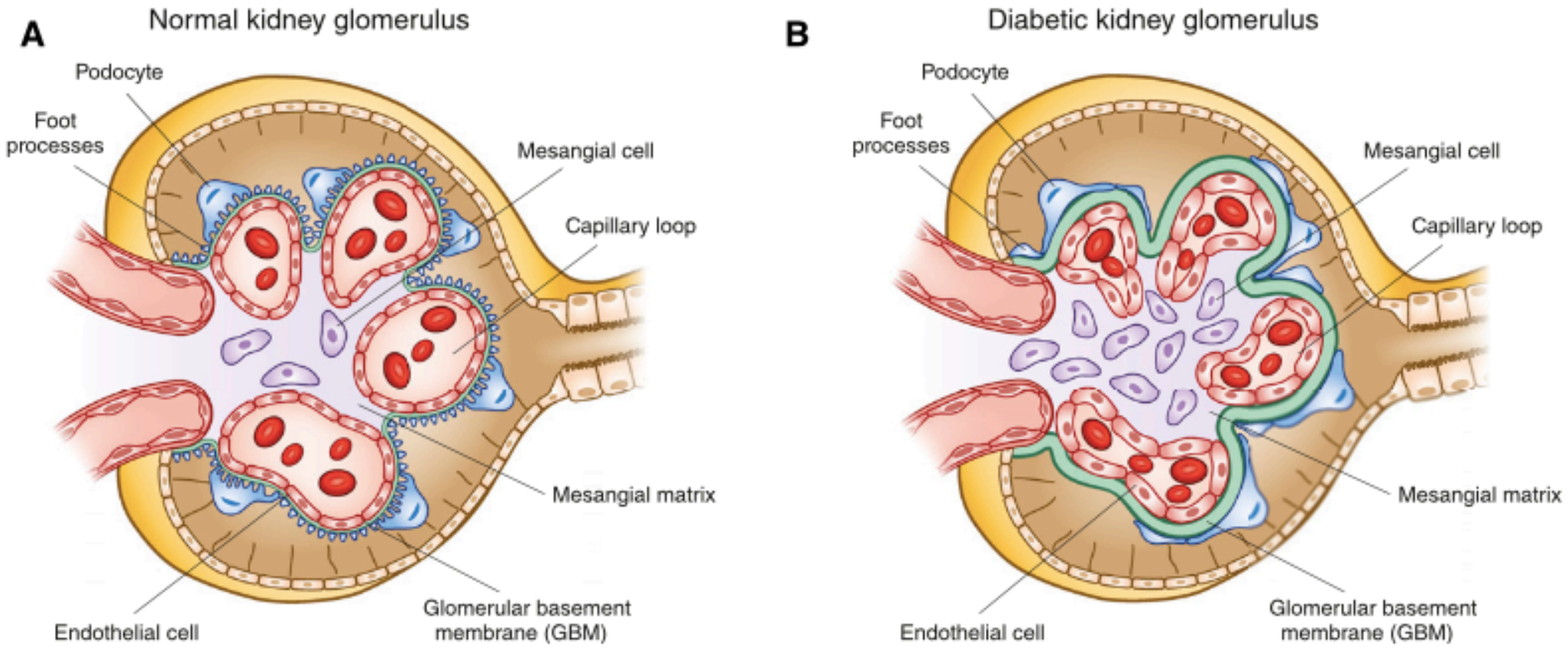
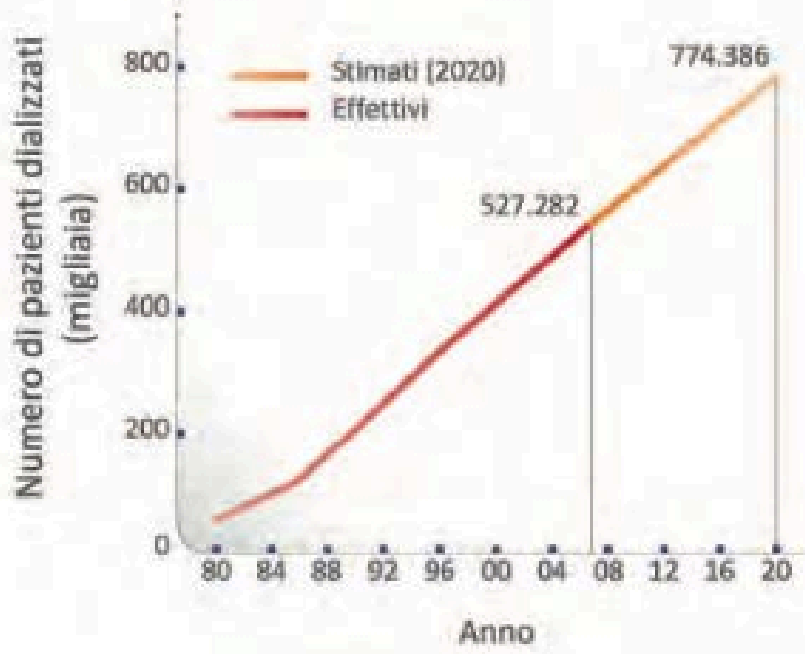


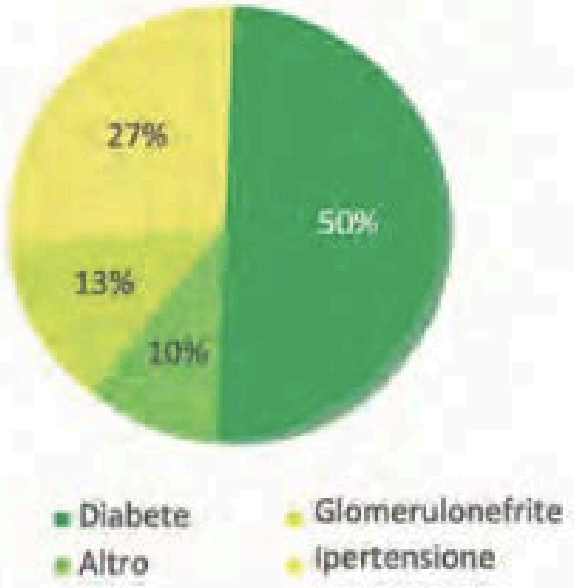
Figure 2. | Normal kidney morphology and structural changes in diabetes mellitus. Diabetic kidney disease induces structural changes, including thickening of the glomerular basement membrane, fusion of foot processes, loss of podocytes with denuding of the glomerular basement membrane, and mesangial matrix expansion.

Il diabete è la causa principale della patologia renale in stadio terminale

- **L'incidenza è in sensibile aumento**



} **Diagnosi primaria per i pazienti che iniziano la dialisi**



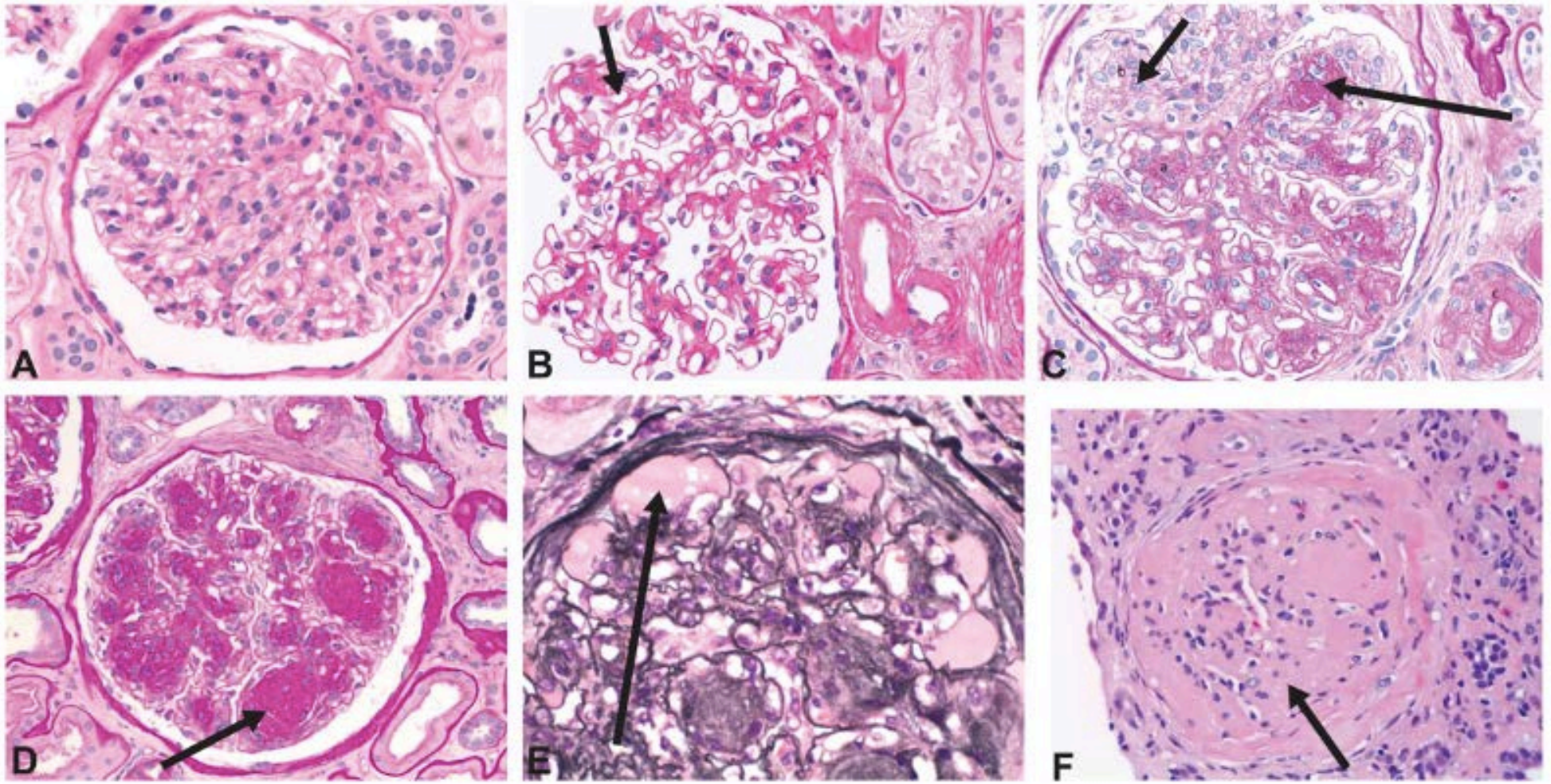
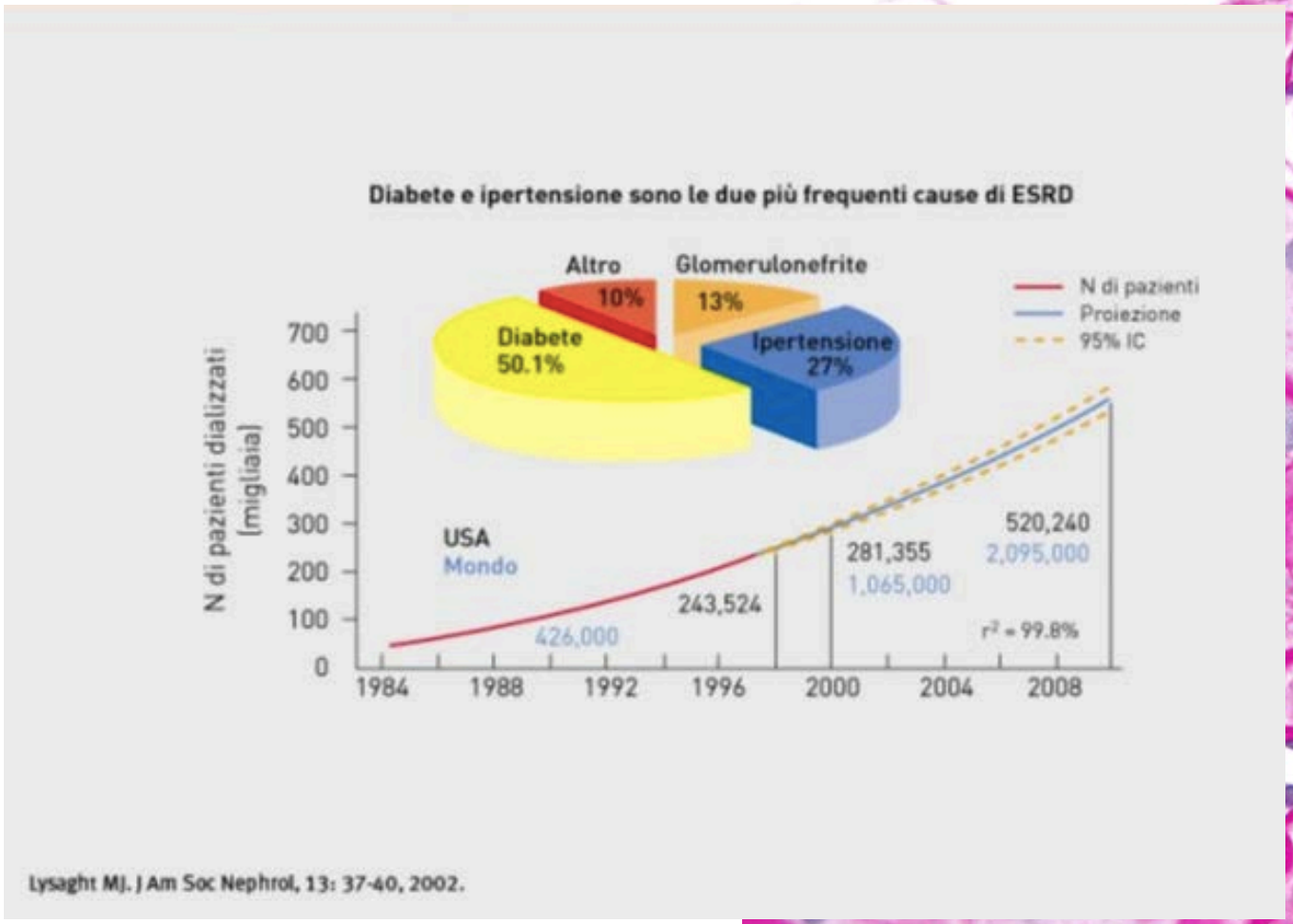
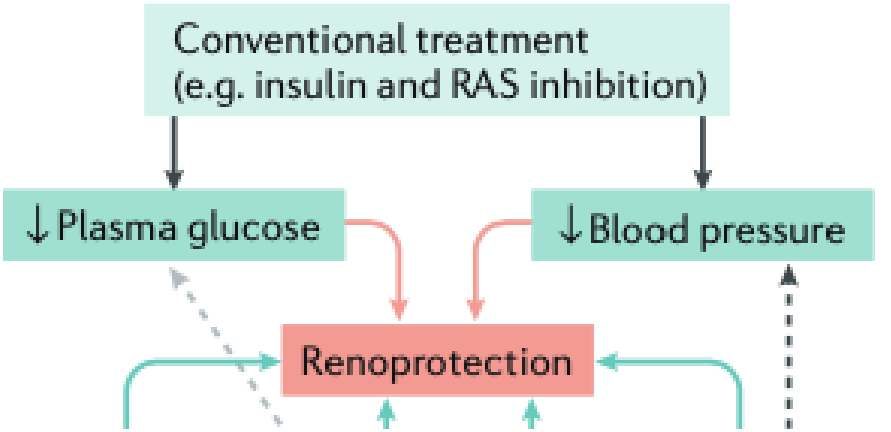
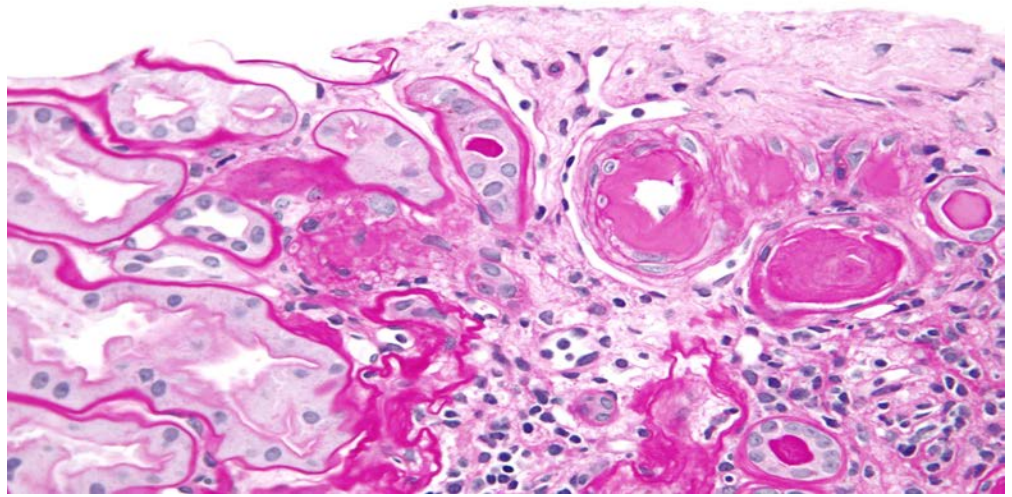


Figure 3. | **Diabetic glomerulopathy.** Changes in glomerular histology in diabetic glomerulopathy (A) Normal glomerulus. (B) Diffuse mesangial expansion with mesangial cell proliferation. (C) Prominent mesangial expansion with early nodularity and mesangiolysis. (D) Accumulatic mesangial matrix forming Kimmelstiel–Wilson nodules. (E) Dilation of capillaries forming microaneurysms, with subintimal hyaline (plasm insudation). (F) Obsolescent glomerulus. A–D and F were stained with period acid–Schiff stain, and E was stained with Jones stain. Orig magnification, ×400.


Diabete e ipertensione sono le due più frequenti cause di ESRD
Altro
10%
Glomerulonefrite
13%
Diabete
50.1%
Ipertensione
27%
N di pazienti
Proiezione
95% IC
N di pazienti dializzati (migliaia)
700
600
500
400
300
200
100
0
1984
1988
1992
1996
2000
2004
2008
USA
Mondo
426,000
243,524
281,355
1,065,000
520,240
2,095,000
r² = 99.8%
Lysaght MJ. J Am Soc Nephrol, 13: 37-40, 2002.


Conventional treatment
(e.g. insulin and RAS inhibition)
↓Plasma glucose
↓Blood pressure
Renoprotection



Le raccomandazioni (B) per la terapia dell'ipertensione nel diabete sono:

Approccio non farmacologico

↓ Se dopo 4-6 sett. PA ancora ≥ 130/80

ACE-I o AIIRA
o Calcio Antagonisti a lento rilascio (diabetici anziani con ipertensione sistolica isolata) o β-bloccanti cardioselettivi (se cardiopatia ischemica, tachiaritmia, ecc.)

↓ Se dopo 3 sett. PA ancora ≥ 130/80

Aggiungere un 2°farmaco di altra classe o sostituire
(ideale: ACE-I + Ca-Antag.)

↓ Se dopo 3 sett. PA ancora ≥ 130/80

Sostituire o aggiungere un 3° farmaco
(spesso un DIURETICO, specie in pazienti edematosi)

↓ Se dopo 3 sett. PA ancora ≥ 130/80

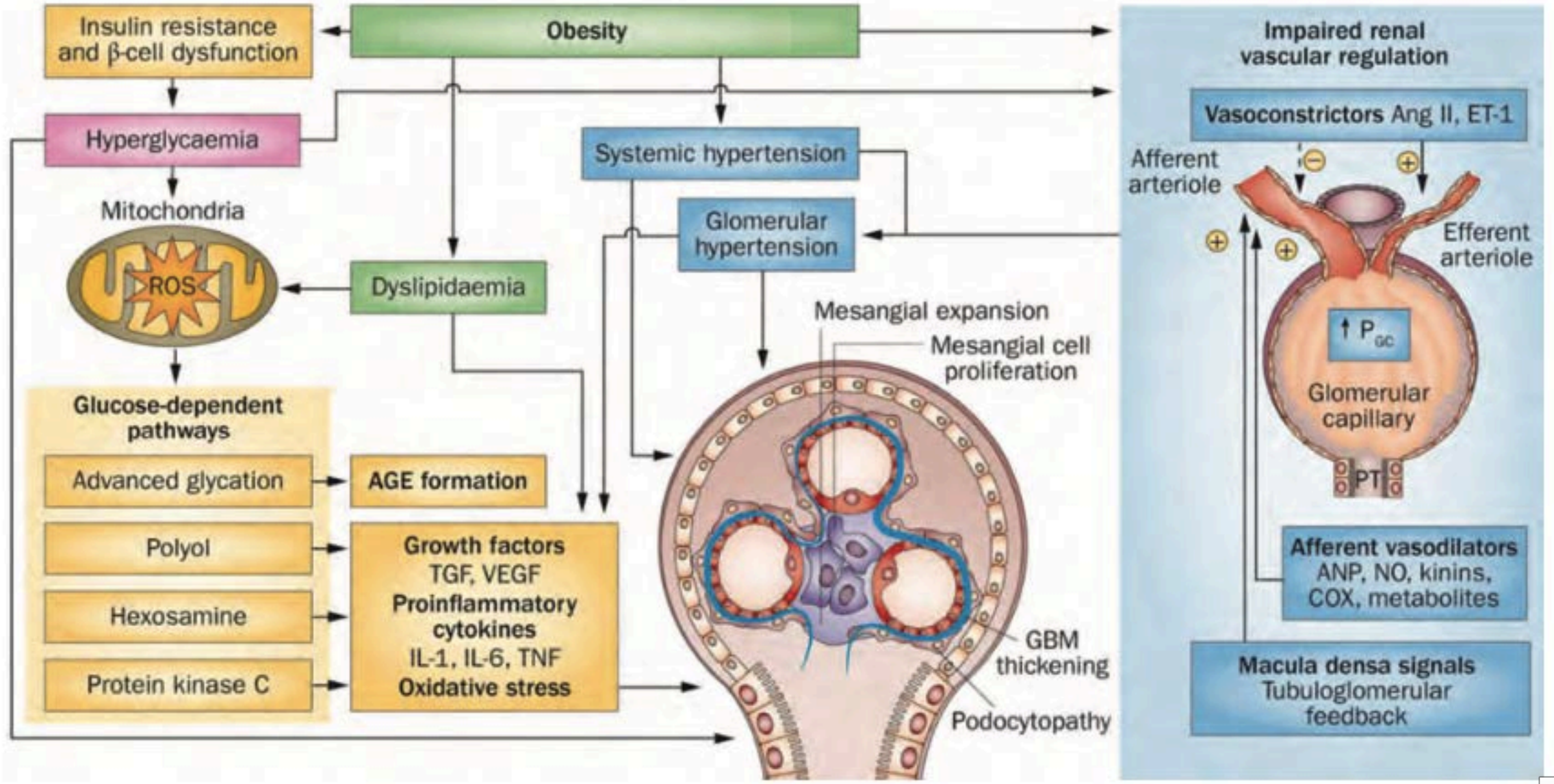
Aggiungere un 4° farmaco
(ideale: AIIRA + ACE-I)

↓ Se dopo 3 sett. PA ancora ≥ 130/80

Sostituire un farmaco con un altro

Polso ≥ 80 → **Inserire β-blocc. C. Selett. O α-β-bloccante**

Polso < 80 → **Inserire α1-Blocc.**


Insulin resistance and β-cell dysfunction
Obesity
Impaired renal vascular regulation
Hyperglycaemia
Systemic hypertension
Vasoconstrictors Ang II, ET-1
Afferent arteriole
Mitochondria
ROS
Glomerular hypertension
Efferent arteriole
Dyslipidaemia
Mesangial expansion
Mesangial cell proliferation
↑ P_{GC}
Glomerular capillary
PT
Glucose-dependent pathways
Advanced glycation
AGE formation
Polyol
Growth factors
TGF, VEGF
Proinflammatory cytokines
IL-1, IL-6, TNF
Oxidative stress
Hexosamine
Protein kinase C
Afferent vasodilators
ANP, NO, kinins, COX, metabolites
GBM thickening
Podocytopathy
Macula densa signals
Tubuloglomerular feedback

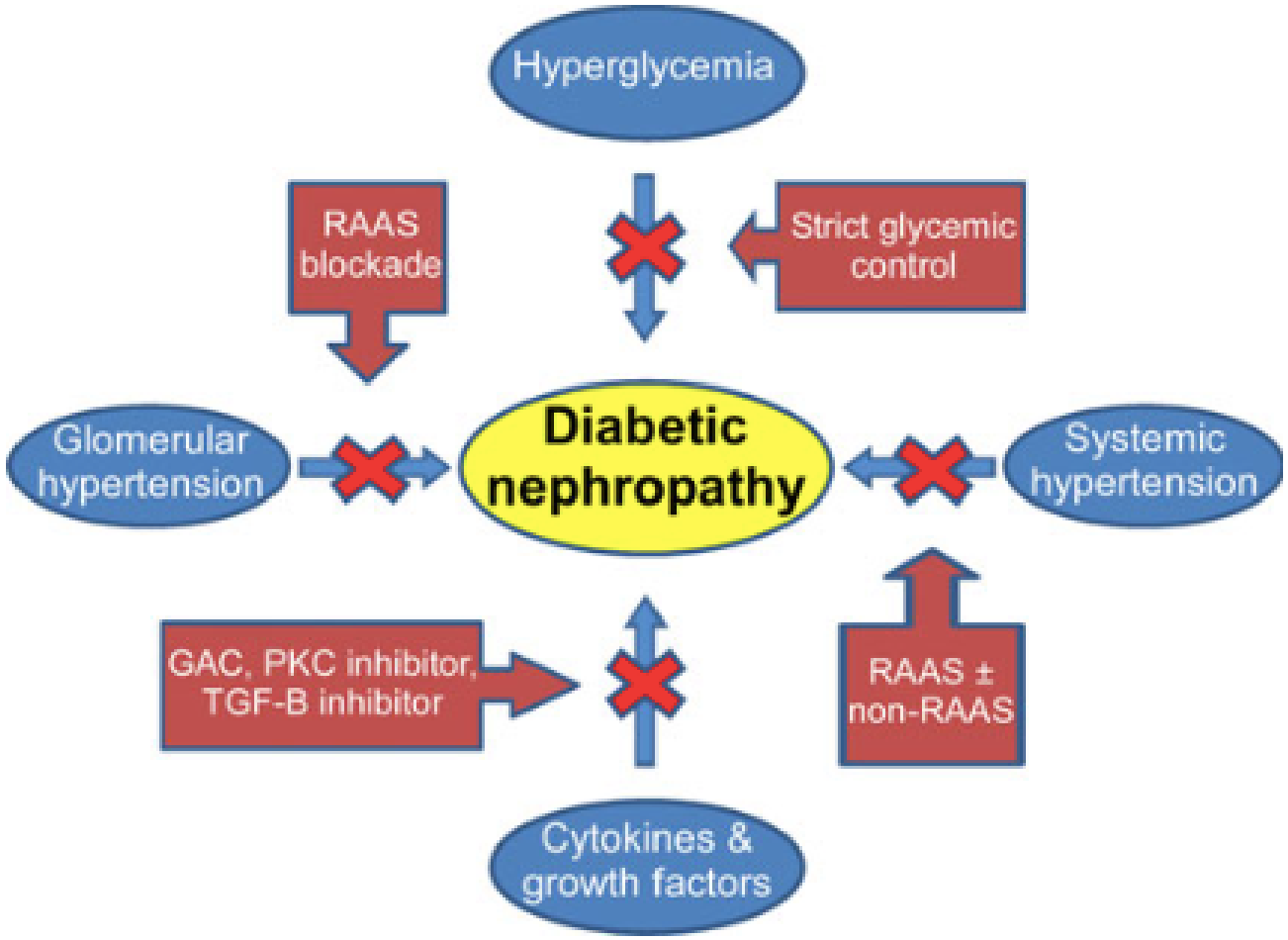
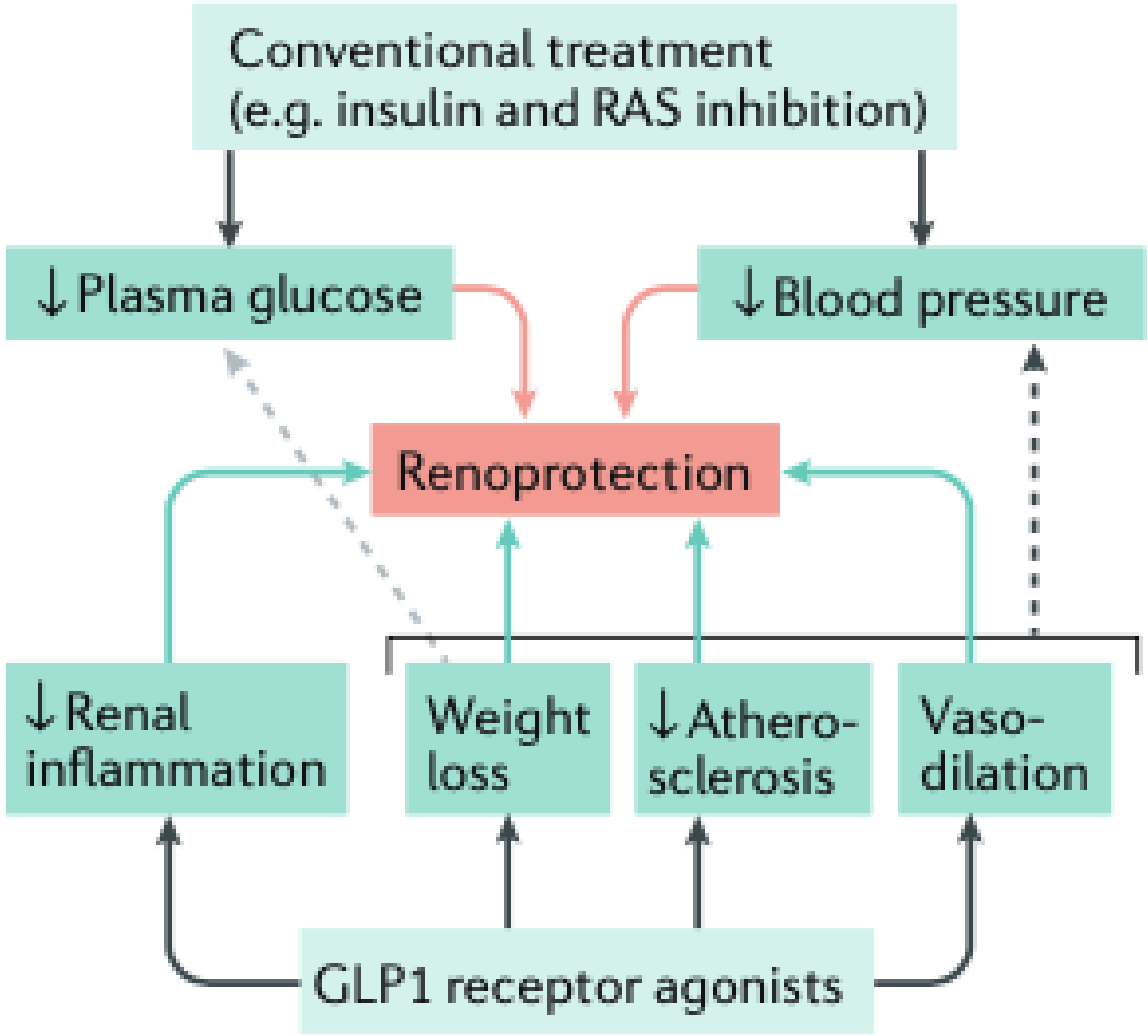
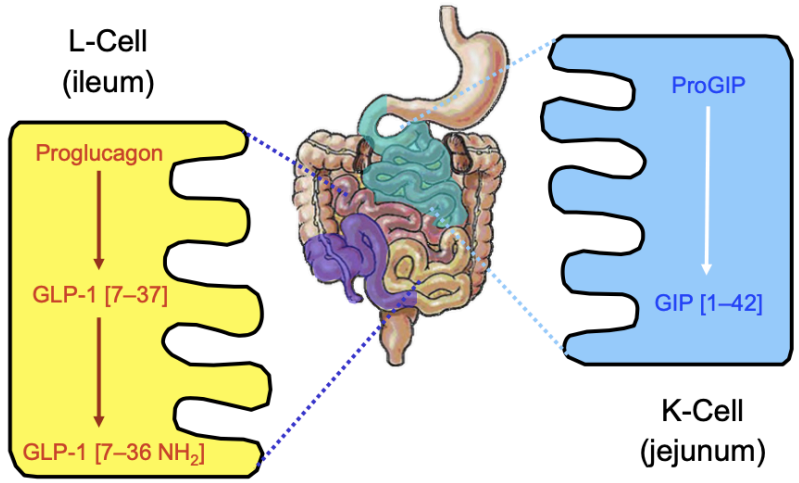


Figure 1. Pathogenesis of diabetic nephropathy and steps to slow its onset and progression. Abbreviations: RAAS, Renin-Angiotensin-Aldosterone System; GAC, Sulodexide; PKC, Protein Kinase C; TGF-β, Transforming growth Factor-beta.

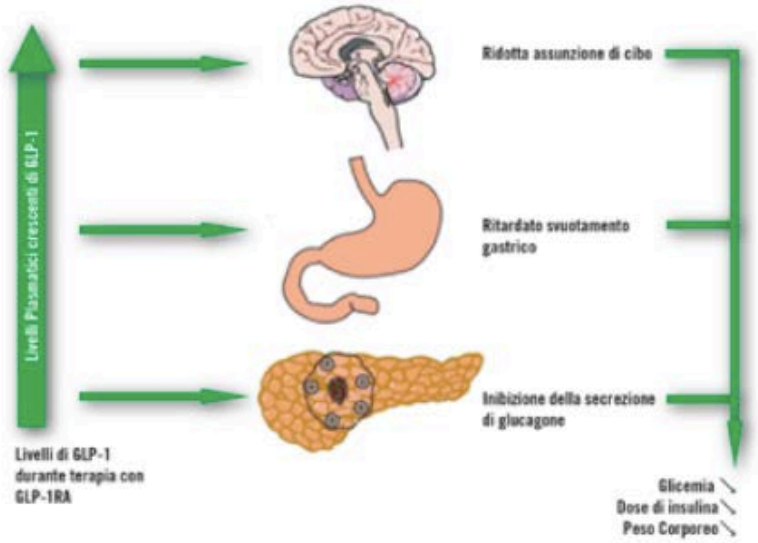

Conventional treatment
(e.g. insulin and RAS inhibition)
↓Plasma glucose
↓Blood pressure
Renoprotection
↓Renal inflammation
Weight loss
↓Athero-sclerosis
Vaso-dilation
GLP1 receptor agonists

GLP-1 and GIP Are Synthesized and Secreted from the Gut in Response to Food Intake



GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1
Adapted from Drucker DJ. *Diabetes Care.* 2003; 26: 2929–2940.

Figura 20. Razionale dell'aggiunta di GLP-1 RA alla terapia con insulina nei pazienti con diabete tipo 1.
Adattato da Frandsen et al. Lancet Diabetes Endocrinol. 2016



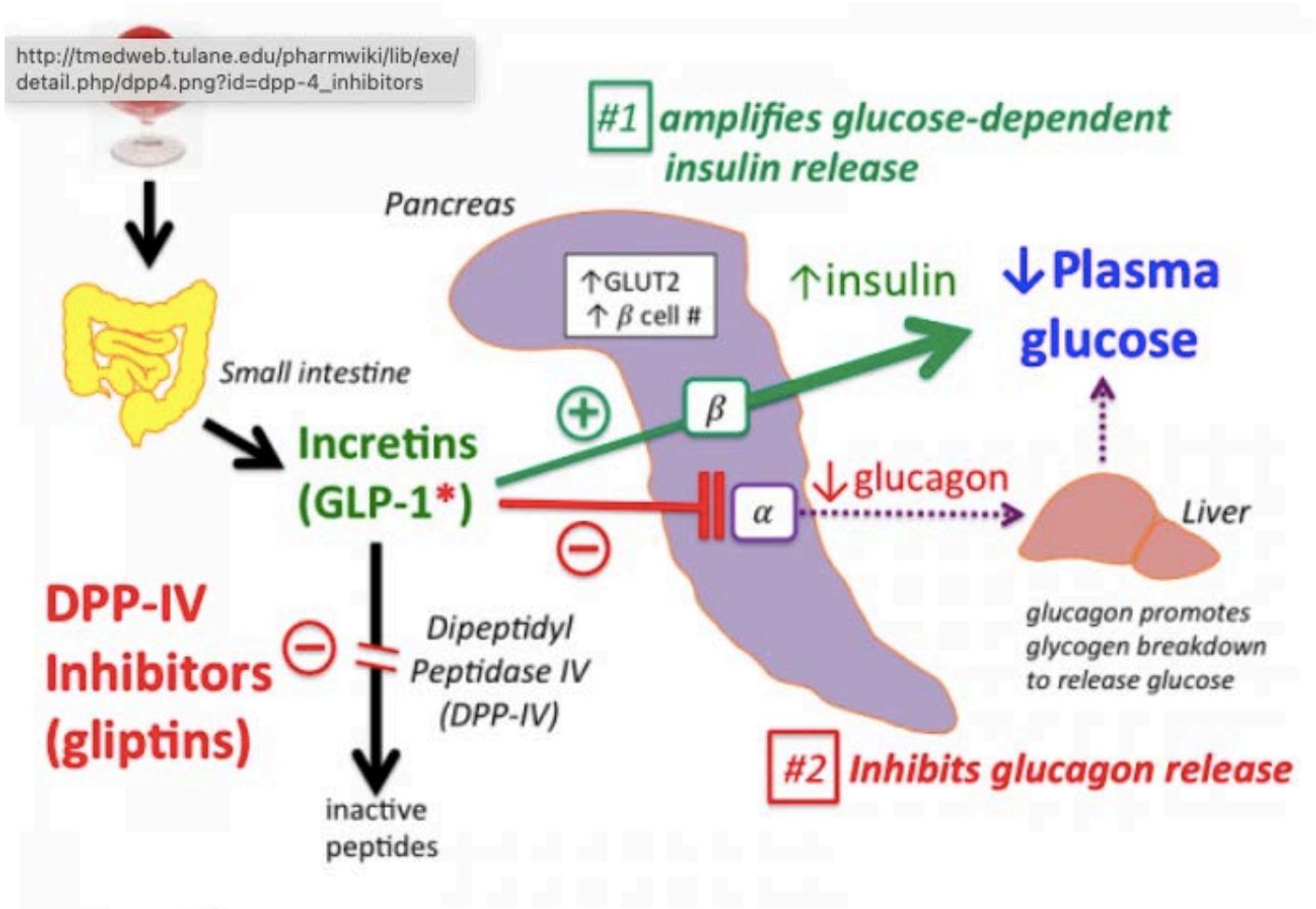
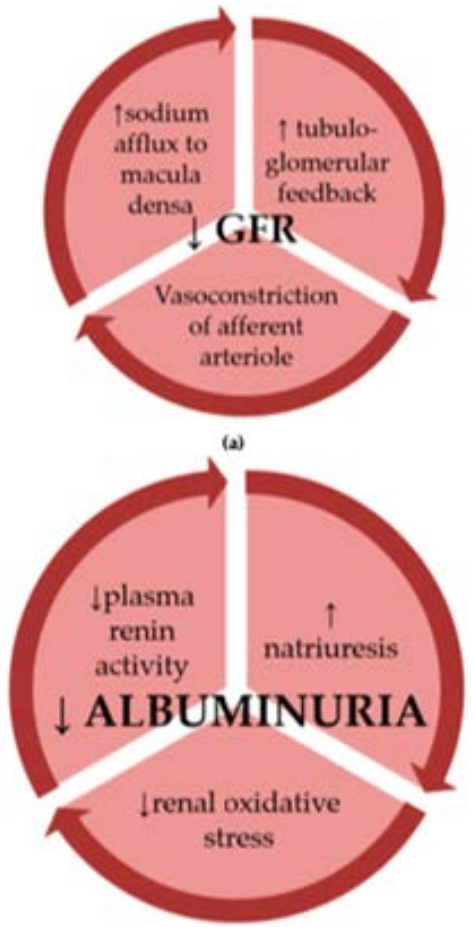

http://tmedweb.tulane.edu/pharmwiki/lib/exe/detail.php/dpp4.png?id=dpp-4_inhibitors
#1 amplifies glucose-dependent insulin release
Pancreas
↑GLUT2
↑ β cell #
↑insulin
↓Plasma glucose
Small intestine
β
Incretins (GLP-1*)
↓glucagon
α
Liver
glucagon promotes glycogen breakdown to release glucose
DPP-IV Inhibitors (gliptins)
Dipeptidyl Peptidase IV (DPP-IV)
inactive peptides
#2 Inhibits glucagon release

Tabella I. Potenziali meccanismi di nefroprotezione delle terapie a base di incretine.

Fattore di rischio renale	Agonisti dei recettori del GLP-1	Inibitori della DPP-4	Possibili meccanismi GLP-1 dipendenti	Possibili effetti propri dei DPP-4 inibitori
Ipertensione arteriosa	Riduzione	Riduzione o effetto neutrale	Calo ponderale Vasodilatazione ↑ Natriuresi ↓ Assorbimento intestinale di sodio ↓ Introito di sodio (possibile effetto diretto sul SNC) ↓ Attività del RAAS? ↑ ANP?	↑ Natriuresi (↑ SDF-1α? ↓ NHE3? ↑ BNP?) ↑ Vasodilazione (↑ BNP? ↑ bradichinina)
Iperfiltrazione glomerulare	Riduzione o effetto neutrale	Effetto neutrale	Ripristino del feedback tubulo-glomerulare (↓ NHE3) ↓ Glucagone post-prandiale ↓ Peso corporeo Rallentamento dello svuotamento gastrico (↓ iperfiltrazione post-prandiale?) ↓ Attività del RAAS?	
Infiammazione e fibrosi	Riduzione	Riduzione	↓ Produzione di ROS a livello renale ↓ AGE	↑ SDF-1α ↓ Transizione epitelio-mesenchimale



- ✓ Natriuresi
- ✓ Rilascio di fattori vasoattivi NO e ANP/BNP
- ✓ Riduzione di ET-1

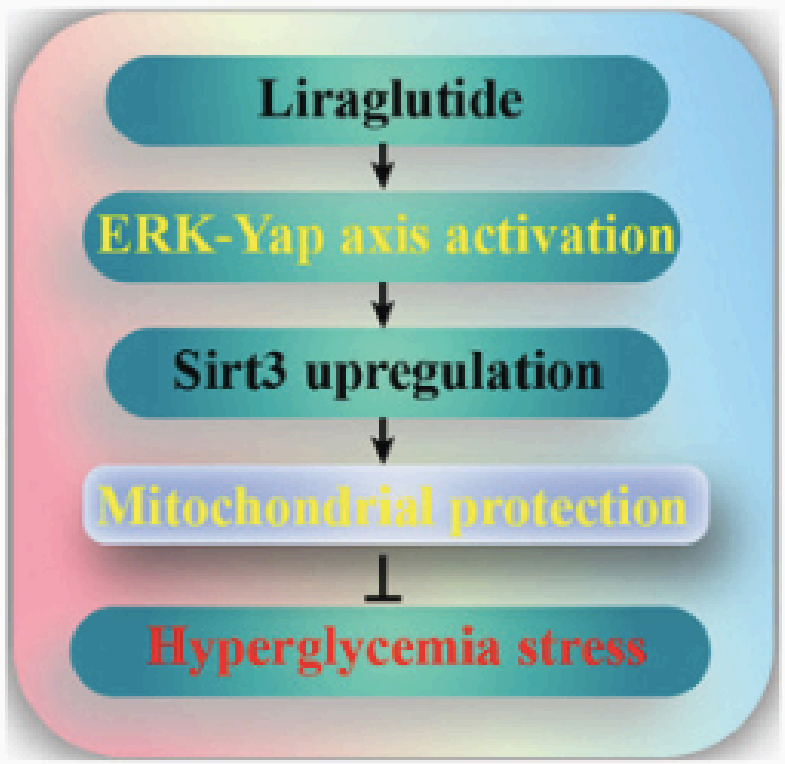


Figure 6. Liraglutide alleviates high glucose-mediated mitochondrial damage in human renal mesangial cells. Mechanistically, liraglutide supplementation augments Sirt3 expression via the ERK-Yap signaling pathway and protects mitochondria against hyperglycemic injury. From a therapeutic perspective, the preservation of mitochondrial integrity is of utmost importance in patients with diabetes with kidney malfunction receiving liraglutide treatment. ERK, extracellular signal-regulated kinase; Yap, Yes associated protein; Sirt3, sirtuin 3.

	Insufficienza renale lieve (GFR 80–50 ml/min)	Insufficienza renale moderata (GFR 50–30 ml/min)	Insufficienza renale severa (GFR < 30 ml/min)	Dialisi
Sitagliptin	100 mg × 1	50 mg × 1	25 mg × 1	25 mg × 1
Vildagliptin	50 mg × 2	50 mg × 1	50 mg × 1	50 mg × 1
Saxagliptin	5 mg × 1	2,5 mg × 1	2,5 mg × 1	Non raccomandato
Linagliptin	5 mg × 1	5 mg × 1	5 mg × 1	5 mg × 1
Exenatide	No variazione dose	Riduzione della dose	Non raccomandato	Non raccomandato
Liraglutide	No variazione dose	Non raccomandato	Non raccomandato	Non raccomandato

Farmaco	Emivita (h)	Inibizione DPP-4	Eliminazione
Sitagliptin	8-24	Max 97% (>80% 24 h post-dose)	Renale (80% immodificato)
Vildagliptin	1.5-4.5	Max 95% (>80% 24 h post-dose)	Metabolizzato a metabolita inattivo, escrezione renale (22% immodificato)
Linagliptin	10-40	Max 80% (~70% 24 h post-dose)	Renale (5%), fecale (85%)
Saxagliptin	2.2-3.8	Max 80% (~70% 24 h post-dose)	Metabolizzato a metabolita attivo, escrezione renale (12-29% immodificato, 21-52% metabolita)
Alogliptin	12.5-21.1	Max 90% (~75% 24 h post-dose)	Renale (>70% immodificato)

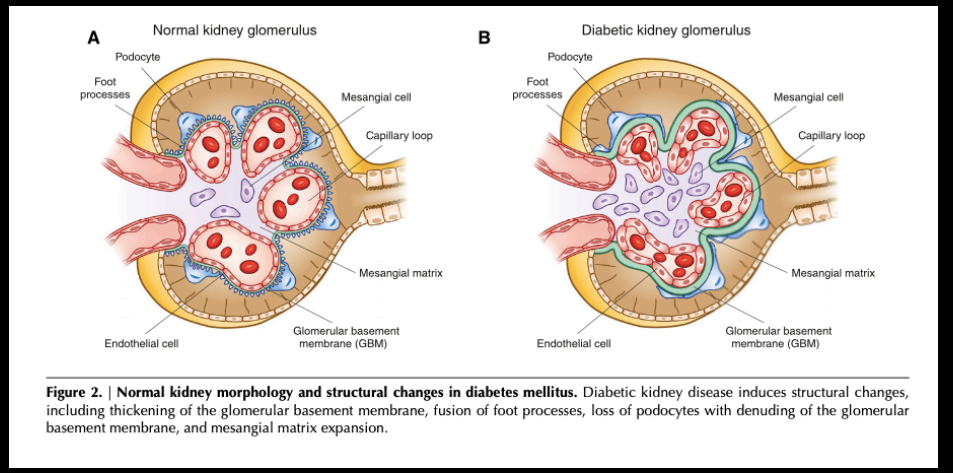
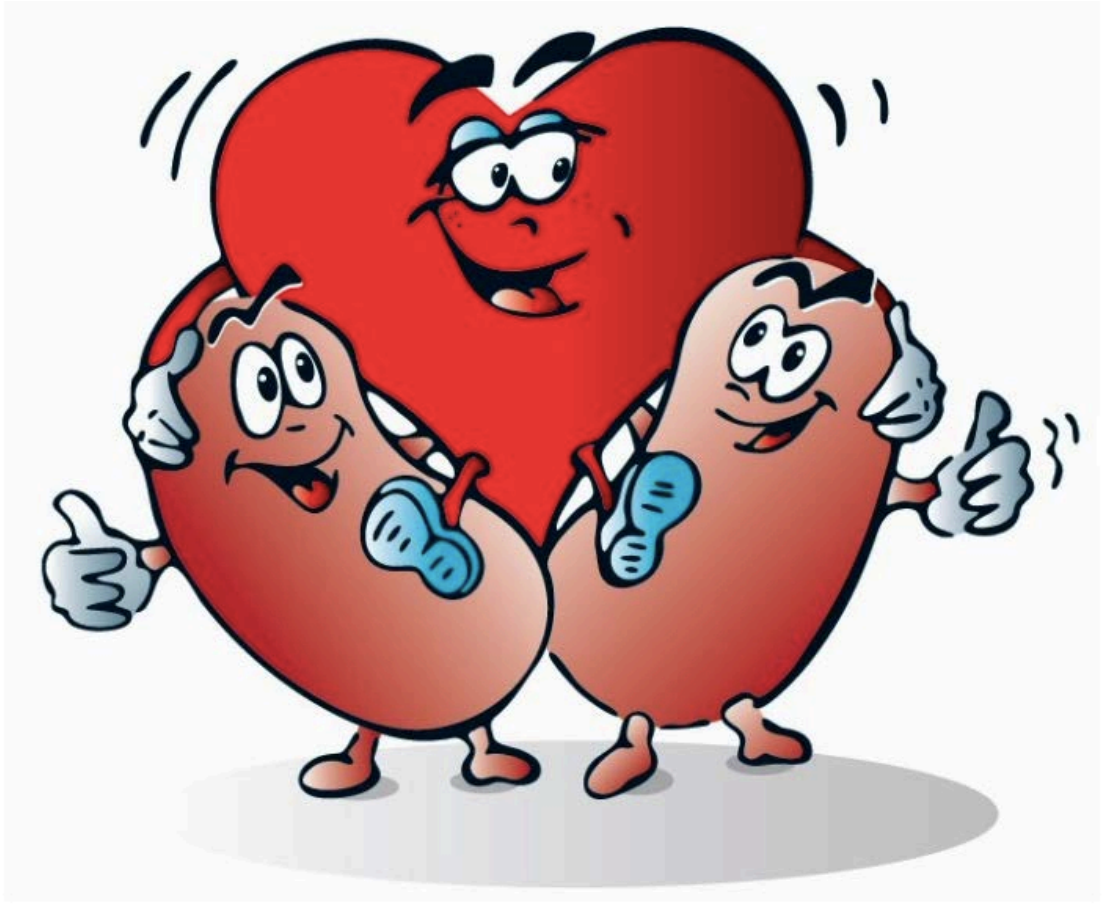


Figure 2. | Normal kidney morphology and structural changes in diabetes mellitus. Diabetic kidney disease induces structural changes, including thickening of the glomerular basement membrane, fusion of foot processes, loss of podocytes with denuding of the glomerular basement membrane, and mesangial matrix expansion.

"Every battle is won **BEFORE** it is fought."

Sun Tzu



Grazie per l’attenzione!