Overview

- Introduction
- Pathophysiology of Diabetic Nephropathy (DN)
- Current Standard of Approach to Diabetic Nephropathy
- Novel Therapeutic Modalities
- Newer Drugs in DN treatment

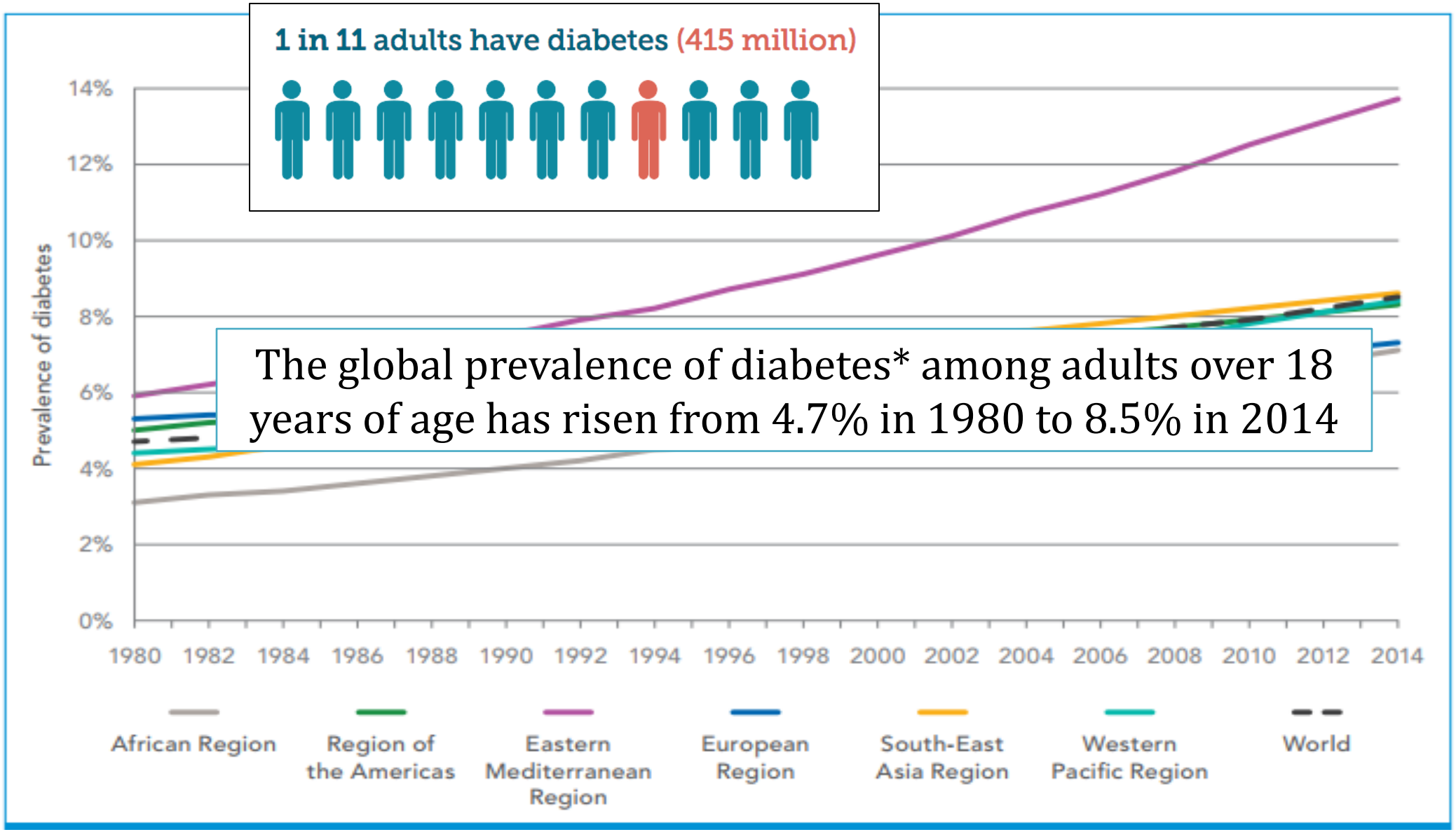
Introduction

Diabetes Mellitus

- The global prevalence of diabetes has risen from 4.7% (108 million) in 1980 to 8.5%(422 million) in 2014

GLOBAL REPORT ON DIABETES , © World Health Organization 2016
http://www.who.int/mediacentre/factsheets/fs312/en/ accessed on 13-03-2020

TRENDS IN PREVALENCE OF DIABETES, 1980–2014, BY WHO REGION



GLOBAL REPORT ON DIABETES , © World Health Organization 2016
http://www.who.int/mediacentre/factsheets/fs312/en/ accessed on 10-01-2018
Sarwar N, et al. Lancet. 2010; 26;375:2215-2222.

Diabetes Mellitus

- The global prevalence of diabetes has risen from 4.7% (108 million) in 1980 to 8.5%(422 million) in 2014
- Most patients are affected with Type 2 DM
  - Epidemic for several decades
  - Associated with many complications
- Diabetic kidney disease (DKD) is a leading complication of diabetes
  - lead to serious consequences, including kidney failure and cardiovascular morbidity and mortality

GLOBAL REPORT ON DIABETES , © World Health Organization 2016
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AMERICAN DIABETES ASSOCIATION 2018

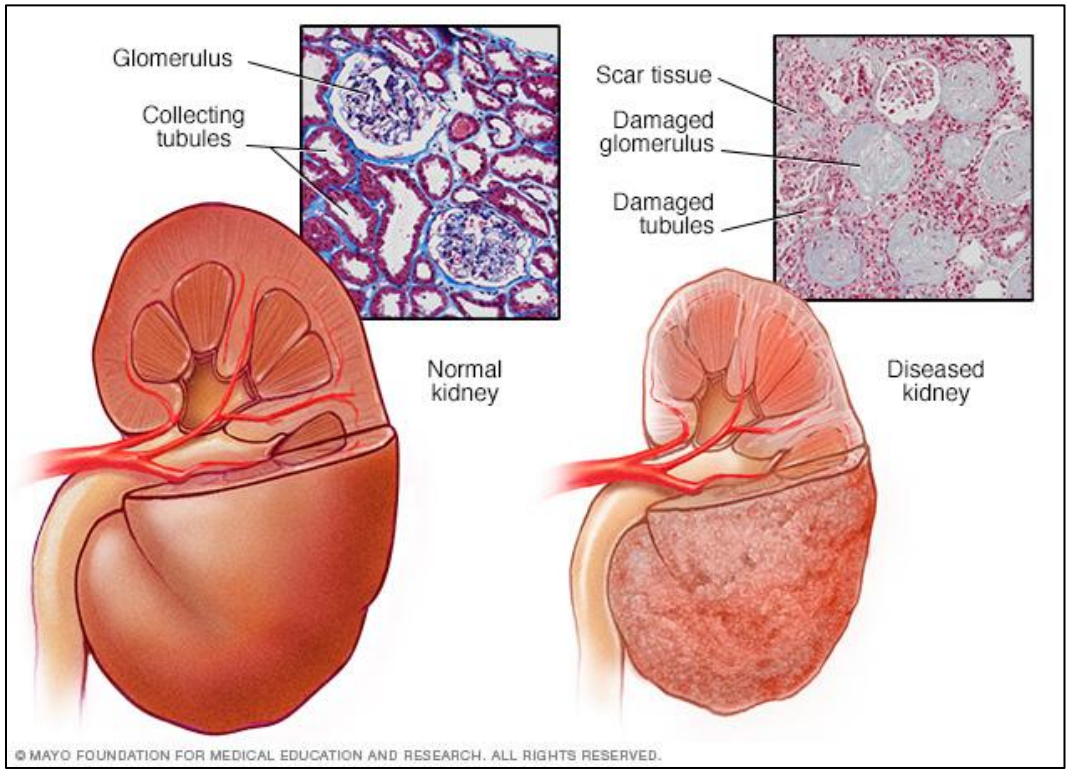
CKD and Diabetes

- Diabetes accounted for approximately 45% of patients with end-stage renal disease (ESRD)
- Prevalence of diabetic nephropathy (DN)
  - Rising dramatically, with concomitant increases in associated mortality and cardiovascular complications
- DN is clinically characterized by
  - Proteinuria (mostly albuminuria),
  - Elevated serum creatinine levels, and
  - Decreased eGFR

- **AMERICAN DIABETES ASSOCIATION 2018**
- *Collins AJ et al, Am J Kidney Dis. 2015 Jan; 63(1 Suppl):A7.*
- *Afkarian M et al, J Am Soc Nephrol. 2016 Feb; 24(2):302-8.*

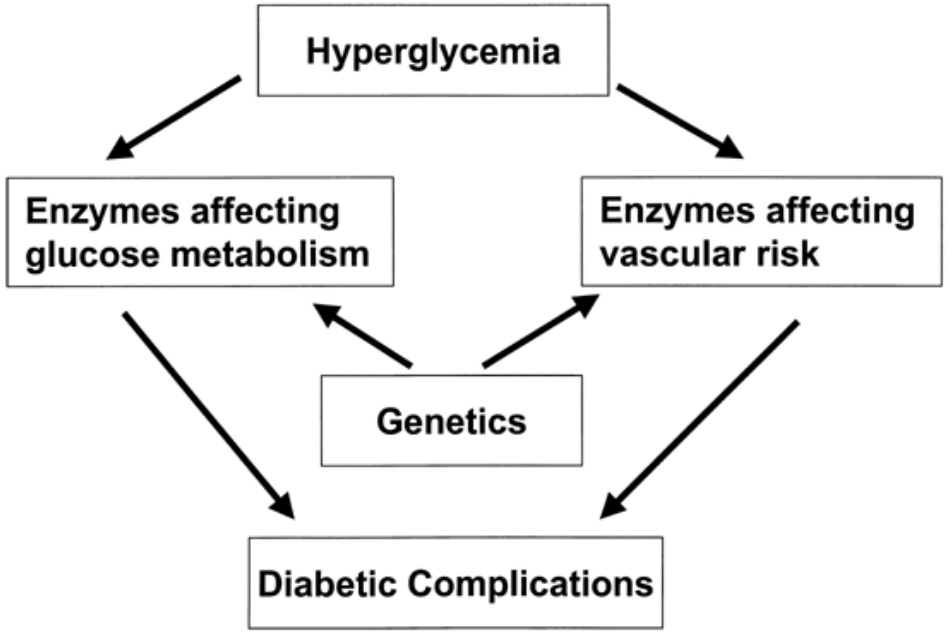
Diabetic Nephropathy

- Affects approx. one-third of individuals with diabetes mellitus
- DN increases
  - Overall 10-year mortality
    - By 6 folds compared to healthy age matched non-diabetic



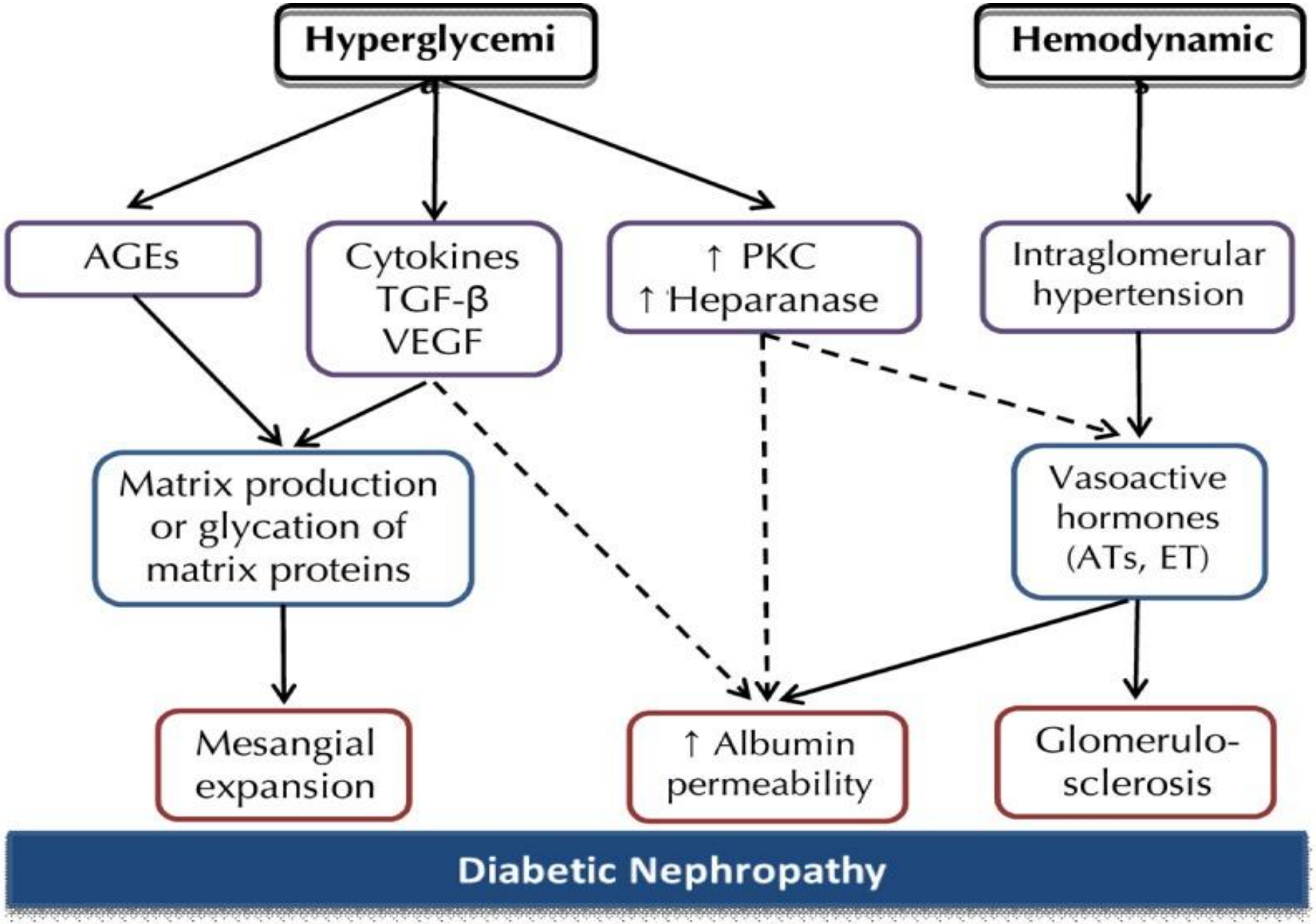
Tang SC et al, F1000Res. 2016 May 31;5.

Diabetic Nephropathy



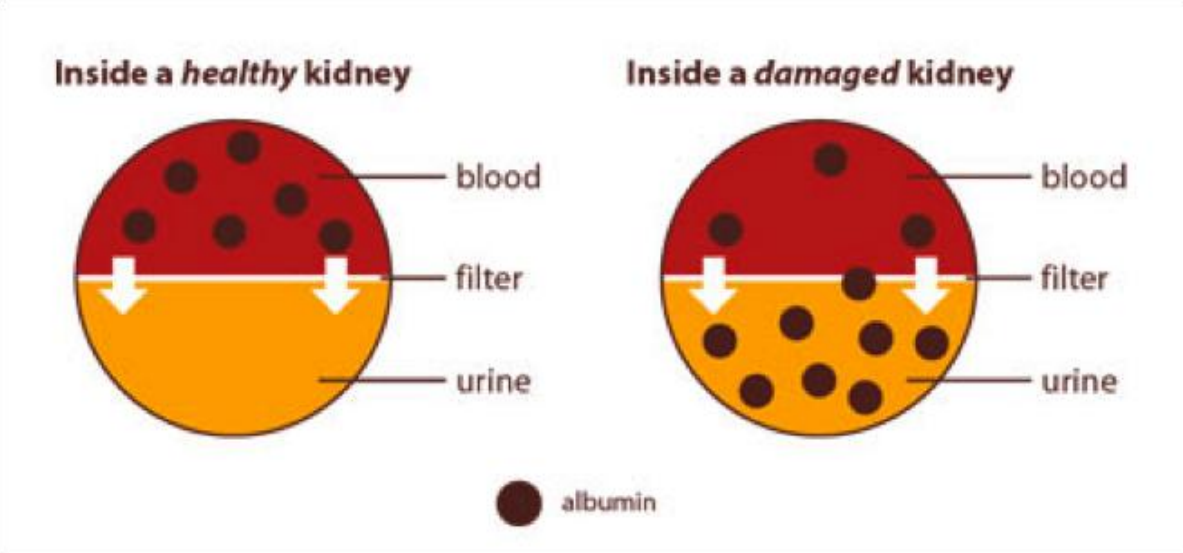
Etiology :

- Diabetic Nephropathy occurs
  - As a result of interaction between both genetic & environmental factors.
  - Hyperglycemia, hypertension, and genetic predisposition are the major risk factors.
  - The aggravating hyperglycemia - high risk factor
    - Development of microvascular complications



Evangelia Dounousi et al, *Rev Diabet Stud, 2015, 12(1-2):119-133*

Pathophysiology of DN



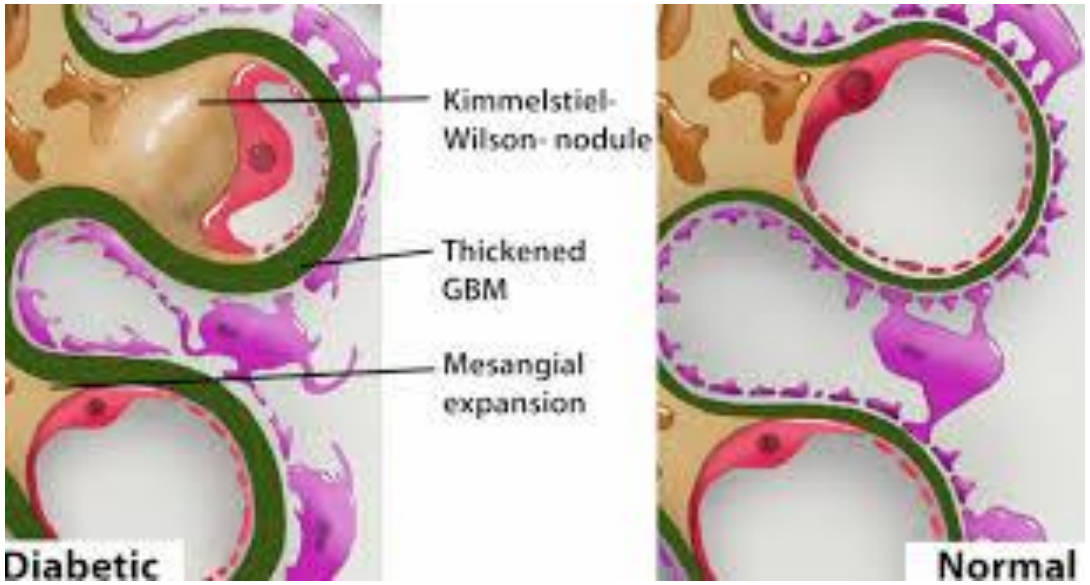
- Diabetic nephropathy is a clinical syndrome characterized by the following:
  - Persistent albuminuria (>300 mg/d or >200 µg/min)
    - Confirmed on at least 2 occasions 3-6 months apart
  - Progressive decline in the glomerular filtration rate (GFR)
  - Elevated arterial blood pressure

Tang SC et al, F1000Res. 2016 May 31;5.

Pathophysiology of DN

3 major histological changes in the glomeruli

- Mesangial expansion - induced by hyperglycemia
- Thickening of the glomerular basement membrane
- Glomerular sclerosis – due to intraglomerular hypertension



Recent evidence shows:

- DN comprises a heavy inflammatory element triggered by metabolic disorders, protein overload & hemodynamic abnormalities

Raptis AE et al, Exp Clin Endocrinol Diabetes. 2001;109 Suppl 2:S424-37.
Lai KN et al, Contrib Nephrol. 2011; 17:135-44.

Diagnosis of diabetic nephropathy

- DN - usually a clinical diagnosis
  - Based on albuminuria and/or reduced eGFR
- Typical presentation of DN
  - long-standing duration of diabetes, retinopathy, albuminuria without hematuria, and gradually progressive kidney disease
- The pathologic changes in DN are:
  - Mesangial expansion, Diffuse glomerular basement membrane thickening
  - Diffuse glomerulosclerosis, Nodular glomerulosclerosis
  - Afferent & efferent arteriolar hyalinosis
  - Interstitial mononuclear cell infiltrate &
  - Interstitial fibrosis together with tubular atrophy

• **AMERICAN DIABETES ASSOCIATION 2018**
•Usama A.A. Sharaf El Din et al, J Adv Res. 2017 Jul; 8(4): 363–373.

Current Standard of Approach to Diabetic Nephropathy

- Glycemic optimization
- Blood pressure control
  - Renin-angiotensin system
- Lipid Lowering Therapy

Tang SC et al, F1000Res. 2016 May 31;5

Glycemic optimization

- Glycemic control plays
  - most momentous role in management of DN

- Several studies have indicated
  - Close relationship been established between poor glycemic control & microvascular complications, including DN.

Rui Xue et al, J Diabetes Res. 2017; 2017: 1839809.

Glycemic optimization

- Study - EDIC (Epidemiology of Diabetes Interventions and Complications- Cohort)
  - Type 1 diabetics
  - Clearly demonstrated - early intensive diabetic control-
    - 44% reduction in developing CKD with eGFR lower than 60 ml/min/1.73m2

• DCCT/EDIC research group. Lancet Diabetes Endocrinol. 2014 Oct; 2(10):793-800.

Glycemic optimization

- Study- UK Prospective Diabetes Study (UKPDS)
  - 3,867 Patients (newly diagnosed)
  - Conventional Group HbA1c 7.9%
- For type 2 diabetics the risk in the intensive group was
  - 12% lower for any diabetes-related endpoint;
  - 10% lower for any diabetes-related death &
  - 6% lower for all-cause mortality

UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12; 352(9131):837-53.

Glycemic optimization

- Study- ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial
  - 11,140 patients
- Demonstrated the value of tight glycaemic control
  - Reduction of albuminuria
    - 9% & 30% for micro- & macro-albuminuria, respectively
    - 65% risk reduction of ESRD

Perkovic V et al, Kidney Int. 2013 Mar; 83(3):517-23.

Glycemic optimization

- The American Association of Clinical Endocrinologists recommends
  - HbA1c target of <6.5%
- American Diabetes Association
  - Goal of HbA1c <7%
- To achieve balance between the risk of hypoglycemia and the clear benefit of renoprotection

Tang sc et al, F1000Res. 2016 May 31;5

Approved treatment Modalities to prevent or withhold progression of DN.		
Drug class	**On-target action**	**Remarks**
•Metformin	Blood sugar ↓	↓ dose by 50% if GFR<60 mL/min, stop if GFR<30
•Pioglitazone	Blood sugar ↓	Salt and water retention, osteopenia, BW↑
•GLP-1 agonists	Blood sugar ↓	Nausea, vomiting, stop if GFR<30
•DPP-4 inhibitors	Blood sugar ↓	Hypoglycemia less likely, dose adjustment with CKD progression except Linagliptin
•SGLT2 inhibitors	Blood sugar ↓	stop if GFR<30
		Sharaf El Din UAA et al, J Adv Res. 2017 Jul;8(4):363-373.

Blood pressure control

Blood pressure control

- Hypertension an independent, modifiable variable
  - Predisposes individuals to the development and acceleration of micro- and macro-vascular problems
  - Various attempts to optimize RAAS inactivation
- Several trials have been conducted to validate the efficacy of following drug groups
  - Angiotensin converting enzyme inhibitors (ACEI) or Angiotensin II type 1
  - receptor blockers (ARBs) alone
  - Combined use of ACEI and ARBs
  - Renin inhibitors
  - Aldosterone inhibitors
  - Angiotensin II type 2 receptor enhancement

Tang SC et al, F1000Res. 2016 May 31;5

Blood pressure control

- UKPDS showed for every 10 mmHg reduction in SBP, there was a decrease in
  - All DM-related complications by 12%
  - Death by 15%
- Echoed in the RENAAL *(Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial*
  - 1,513 type 2 DM patients with confirmed DN & hypertension
    - Risk of ESRD or death was raised by 6.7% for each 10 mmHg increase in baseline SBP

Adler AI et al, BMJ. 2000 Aug 12; 321(7258):412-9.
Bakris GL et al, RENAAL Study Group. Arch Intern Med. 2003 Jul 14; 163(13):1555-65.

Renin-angiotensin-aldosterone Axis Blockade

- Type 2 DM-
  - ACEi or ARB is superior to using other anti-hypertensive agents
  - Provide other renoprotective benefits, (MARVAL -*Micro-Albuminuria Reduction with Valsartan study)*
- Type 1 DM –
  - Study- meta-analysis of 698 non-hypertensive type 1 DM patients with micro-albuminuria
  - Treatment with ACEi restricted development to macro-albuminuria by 60%

Viberti G et al,(MARVAL) Study Investigators. Circulation. 2002 Aug 6; 106(6):672-8.
ACE Inhibitors in Diabetic Nephropathy Trialist Group. Ann Intern Med. 2001 Mar 6; 134(5):370-9.

Renin-angiotensin-aldosterone Axis Blockade

- Sub-study of the IRMA-2 *(Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria) trial*
  - Reduction in micro-albuminuria by RAS blockade persisted even after treatment withdrawal
- *IDNT (Irbesartan Diabetic Nephropathy Trial)*
  - 1,715 hypertensive type 2 DN patients
    - 33% decrease in the risk of serum creatinine doubling
    - 23% decrease in progression to ESRD

Andersen S et al, Diabetes Care. 2003 Dec; 26(12):3296-302.
Lewis EJ et al, N Engl J Med. 2001 Sep 20; 345(12):851-60.

Renin-angiotensin-aldosterone Axis Blockade

Drug	Trial	Notes
Valsartan	MARVAL (Micro-Albuminuria Reduction with Valsartan)	Reduction in BP + micro-albuminuria
Irbesartan	IRMA-2 (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria)	Reduction in micro-albuminuria persisted, even after treatment withdrawal, implies that glomerular structural normalization may be occurring
Irbesartan	IDNT (Irbesartan Diabetic Nephropathy Trial)	GFR decline, 33% and 23% Risk reduction of serum creatinine doubling and progression to ESRD respectively
losartan	RENAAL RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan)	GFR decline, 50% & 45% decrease in albuminuria & risk for ESRD respectively after 6 months treatment

National Kidney Foundation. Am J Kidney Dis. 2012 Nov; 60(5):850-86.

Aldosterone Antagonism

- Mineralocorticoid receptor antagonist (MRA) -
  - Meta-analyses have demonstrated
    - Supplement of MRA (Spirinolactone, Eplerenone)given with ACEi or ARB produces a decrease in proteinuria
- Likewise beneficial effects observed in administration of nonselective and selective MRA
- But, Several studies, in combination with RAS inhibition showed
  - A greater risk of hyperkalemia

Tang SC et al, F1000Res. 2016 May 31;5

Lipid Lowering Therapy

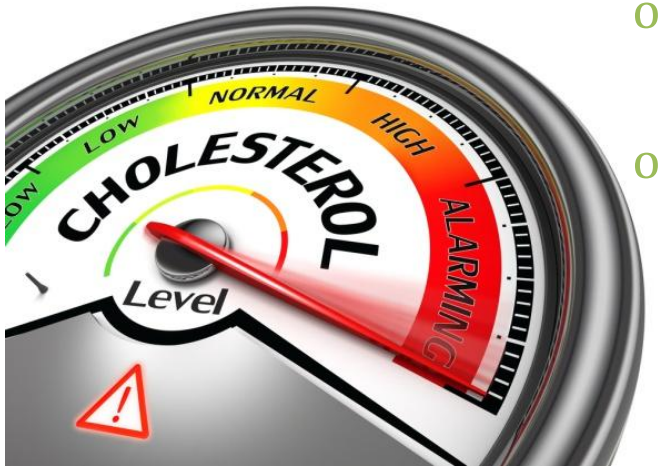
- Statins - most widely used class of drug for lipid lowering in T2DM cases
  - Reflects the indisputable evidence
- Statins-
  - Lowered mortality & cardiovascular events with early stages of CKD
  - Little or no effects in those on dialysis
  - Had uncertain effects in kidney transplant recipients
  - Effects on stroke and kidney function remain to be elucidated

- The role of lipid-lowering treatments in renoprotection for patients with diabetes, however, is debatable.

Collins R et al, Lancet. 2003 Jun 14; 361(9374):2005-16.
Tang sc et al, F1000Res. 2016 May 31;5

Lipid Lowering Therapy

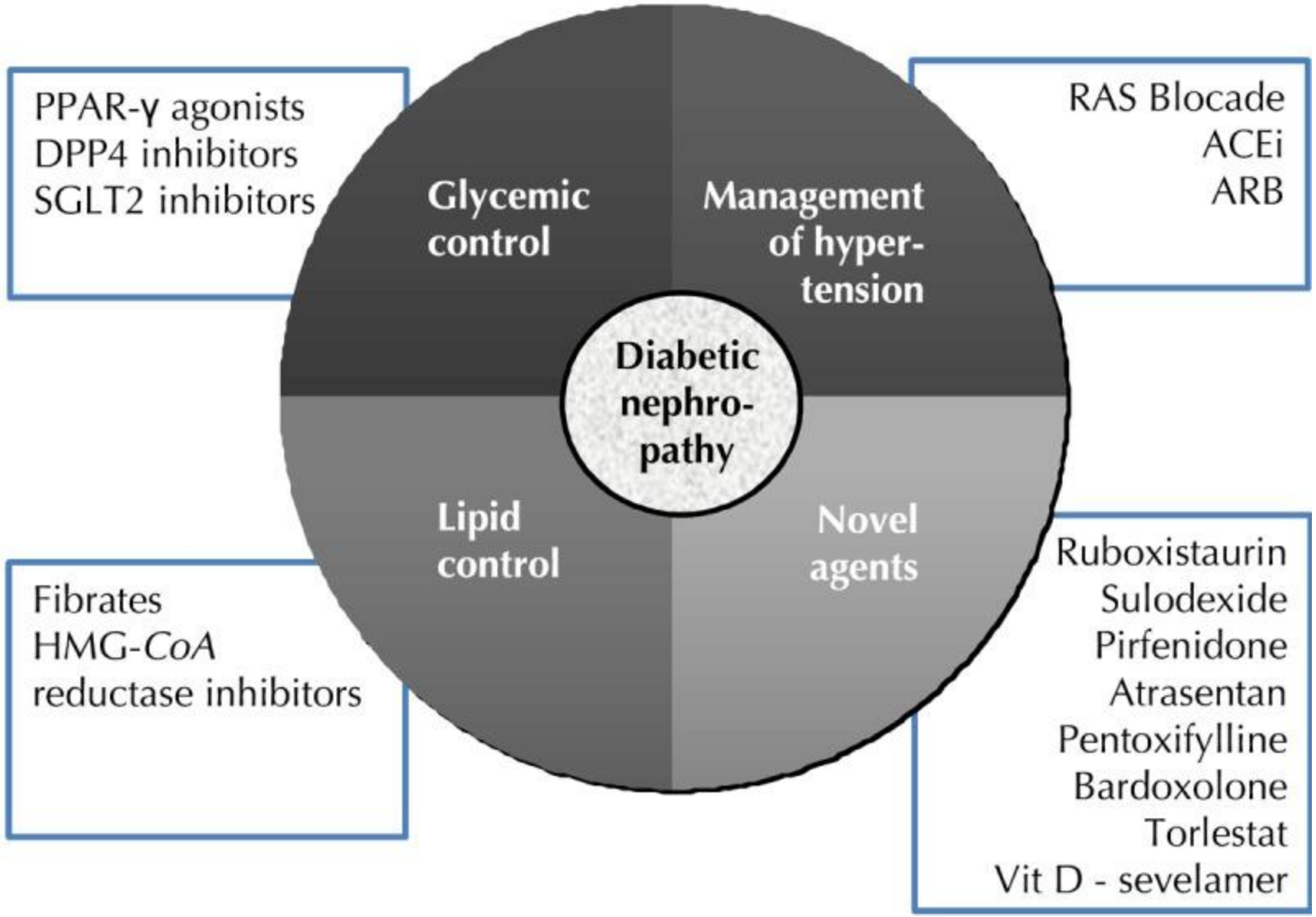
- Studies have shown
  - Atorvastatin
  - Rosuvastatin
  - Simvastatin
    - Significant reduction in urinary albumin excretion
    - Significantly reducing the disease progression



Collins R et al, Lancet. 2003 Jun 14; 361(9374):2005-16.
Athyros VG et al, Clin Pathol. 2004 Jul; 57(7):728-34.

Other Approved treatment Modalities to prevent or withhold progression of DN.		
Drug class	On-target action	Remarks
Hypouricemic agents	↓UA	
Phosphate handling		
↓P intake +sevelamer	↓Serum P	
HCO3 supplement	Treat acidosis	May↑BP, may ↑edema
Pentoxifylline	RBCs rheology	1200 mg/day
Sarpogrelate	↓thromboxane A2	
Paricalcitol	↓PTH	
Statins	↓Serum Cholesterol	No effect on stroke, CKD progession or mortality

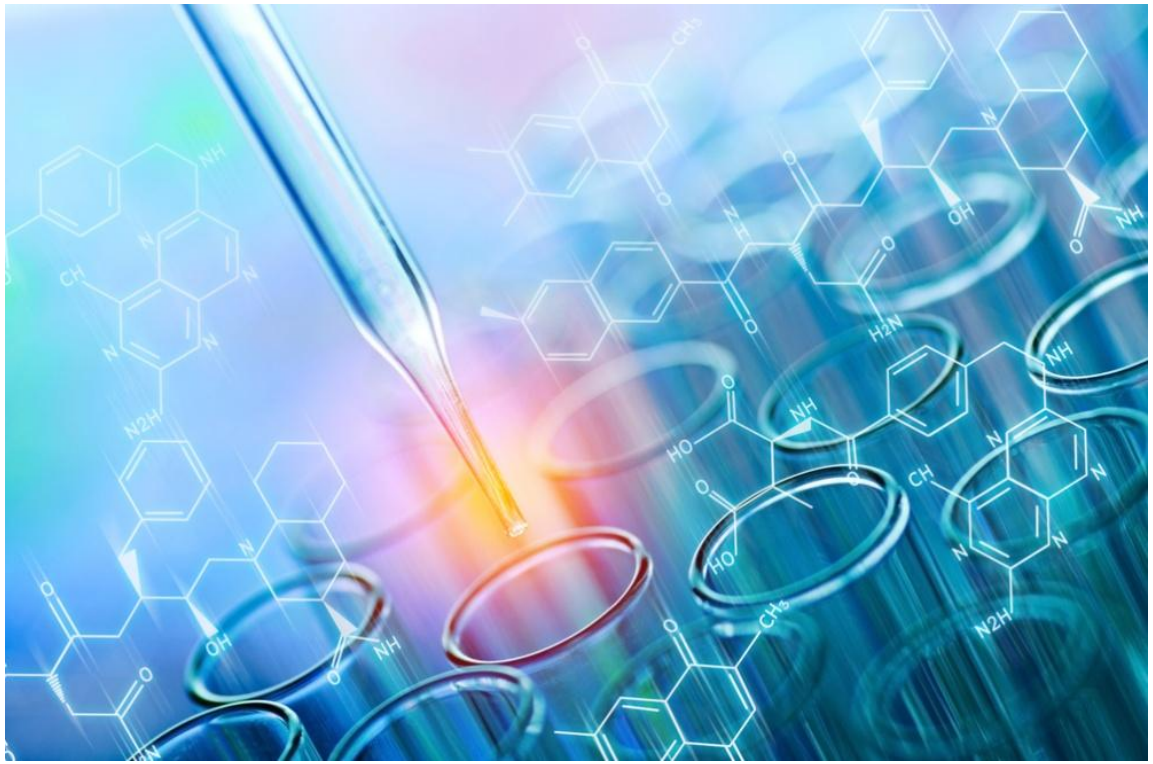
Sharaf El Din UAA et al, J Adv Res. 2017 Jul;8(4):363-373.



Key elements in the management of diabetic nephropathy with established and potential novel therapeutic agents

Evangelia Dounousi et al, *Rev Diabet Stud, 2015, 12(1-2):119-133*

Novel Therapeutic Modalities



New therapeutic agents in diabetic nephropathy beyond conventional RAAS inhibition

Glucose-dependent pathway	
AGEs reduction:	Aminoguanidine, Pyridoxamine
PPAR agonists:	Fenofibrate, Thiazolidinediones
Incretins:	GLP-1 receptor, DPP-4 inhibitor
SGLT2 inhibitor:	Canagliflozin, Dapagliflozin
AMPK activator:	AICAR, Adiponectin, Statins
Vasoactive-pathway	
RAAS system:	Aliskiren, HRP, Spironolactone, Eplerenone
Endothelial antagonism:	Avosentan, Atrasentan
	Glycosaminoglycan, Sulodexide, Paricalcitol

RAAS, renin-angiotensin-aldosterone system; AGE, advanced glycation end product; PPAR, peroxisome proliferator-activated receptor; GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium/glucose cotransporter 2; AMPK, adenosine monophosphate-activated protein kinase; AICAR, 5-aminoimidazole-4-carboxamide ribonucleoside; HRP, hand-region peptide; PKC-β, protein kinase C β; GF, growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; CTGF, connective tissue growth factor; TNF-α, tumor necrosis factor α; mTOR, mammalian target of rapamycin.

Kim Y et al, Korean J Intern Med. 2017 Jan;32(1):11-25.

Intracellular signalling
PKC-β inhibition: ruboxistaurin
Rho kinase inhibitors: Fasudil
Prosclerotic GFs inhibition
Anti-PDGF, anti-TGF-β, anti-CTGF, pirfenidone
Anti-inflammatory pathway
Adenosine, pentoxifylline (TNF-α inhibition), adiponectin, statins, mTORi
Anti-oxidative pathway
Bardoxolone methyl, N-acetylcysteine, probucol
Others - Glycosaminoglycan, sulodexide, paricalcitol

RAAS, renin-angiotensin-aldosterone system; AGE, advanced glycation end product; PPAR, peroxisome proliferator-activated receptor; GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium/glucose cotransporter 2; AMPK, adenosine monophosphate-activated protein kinase; AICAR, 5-aminoimidazole-4-carboxamide ribonucleoside; HRP, hand-region peptide; PKC-β, protein kinase C β; GF, growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; CTGF, connective tissue growth factor; TNF-α, tumor necrosis factor α; mTOR, mammalian target of rapamycin.

Kim Y et al, Korean J Intern Med. 2017 Jan;32(1):11-25.

Pleiotropic Reno-protective Effects of Anti-diabetic Drugs Beyond Glycaemic Control

- Certain hypoglycemic agents
  - Shows to confer independent renoprotective effects beyond their hypoglycemic action.
  - Like
    - PPAR-γ agonists
    - Incretin- based Agents

PPAR-γ Agonists

- TZDs- Pioglitazone and Rosiglitazone
  - Varied reports from clinical studies
  - Heightened cardiovascular risks and malignancy

- TZDs are unlikely to be a major player in the therapeutic armamentarium for DN

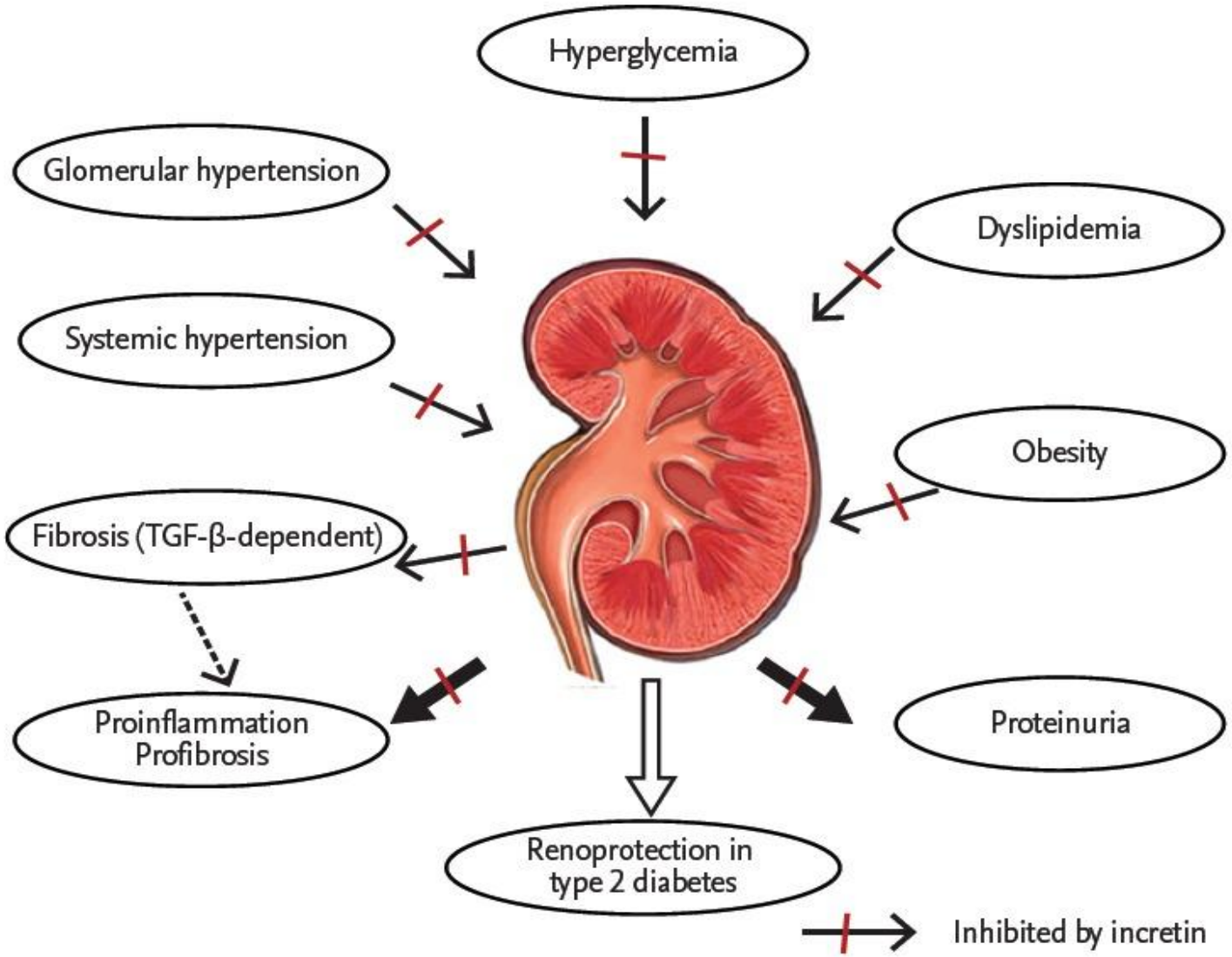
Sarafidis PA et al, Am J Kidney Dis. 2010 May; 55(5):835-47

Incretin- Based Agents

- Incretins secreted into the circulation postprandially
  - Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1)
  - Exert insulinotropic activity
- Impaired incretin regulation is implied in type 2 diabetes
- GLP-1 exerts antidiabetogenic properties by
  - Stimulating insulin secretion, increasing β-cell mass, inhibiting glucagon secretion, delaying gastric emptying and inducing satiety

Tang SC et al, F1000Res. 2016 May 31;5

Favourable renal outcome achieved by Incretin in diabetic nephropathy



Kim Y et al, Korean J Intern Med. 2017 Jan;32(1):11-25.

Incretin- Based Agents

- GLP-1gets rapidly degraded by dipeptidyl peptidase 4 (DPP-4)
- Limitation can be overcome by using
  - DPP-4 resistant GLP-1 receptor agonists &
  - DPP-4 inhibitors.
- Other than glycaemic effects reduce-
  - Blood pressure,
  - Dyslipidemia,
  - Inflammation to a certain degree
  - Risk of hypoglycaemia

Tang sc et al, F1000Res. 2016 May 31;5

Incretin- Based Agents

- Sitagliptin/ Alogliptin/ Saxagliptin
  - Experimental models indicated renoprotective benefits
- Lowered albuminuria in patients with type 2 DM
  - 6 months of sitagliptin or 12 weeks of alogliptin
  - Data from small, uncontrolled studies
- Findings must be interpreted with caution

Tang SC et al, F1000Res. 2016 May 31;5

Incretin- Based Agents

- Four phase III studies, comprising 217 patients with DN on RAS inhibition
  - 24 weeks of linagliptin significantly reduced albuminuria (32% reduction), independent of HbA1c
- Advantages of DPP-4 inhibitors
  - Tolerability
  - Weight neutral benefit
  - Low risk of hypoglycaemia

Groop PH et al, Diabetes Care. 2013 Nov; 36(11):3460-8.

Incretin- Based Agents

- GLP 1 Agonists- Exenatide, Liraglutide, Dulaglutide
- Exenatide treatment in Type 2 DM
  - Reductions in both albuminuria & urinary levels of TGF-β and type IV collagen
- The anti-fibrotic effect of linagliptin
  - In a type 1 model of DN after 4 weeks of treatment
- Limited clinical evidence of the effect of targeting TGF-β

Tang sc et al, F1000Res. 2016 May 31;5

Vitamin D Receptor Activators

- Anti-inflammatory & anti-proteinuric effects in animal models of DN
- Phase III VITAL *trial in Patients with Type 2 Diabetes*
  - Adjuvant *paricalcitol at 2 µg/day lowers residual albuminuria in DN*
  - Drawbacks-
    - Poor tolerance- 42% of patients needed a reduced dose of paricalcitol,
    - High cost of treatment
- Concrete evidence demonstrating the successful use of VDR activators to retard the progression of DN is still awaited

de Zeeuw D et al, Lancet. 2010 Nov 6; 376(9752):1543-51.

Sodium-Glucose Co-transporter 2 Inhibition

- Along with aiding glycemic control, SGLT-2 inhibitors
  - Appear to promote an attractive cardiovascular portfolio

- EMPA-REG study,Empagliflozin added to standard care
  - Over 7,000 type 2 diabetics at high cardiovascular risk
  - Reduced the rates of
    - Death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% RRR)
    - Hospitalization for heart failure (2.7% Vs 4.1%, 35% RRR)
    - Death from any cause (5.7% Vs 8.3%, 32% RRR)

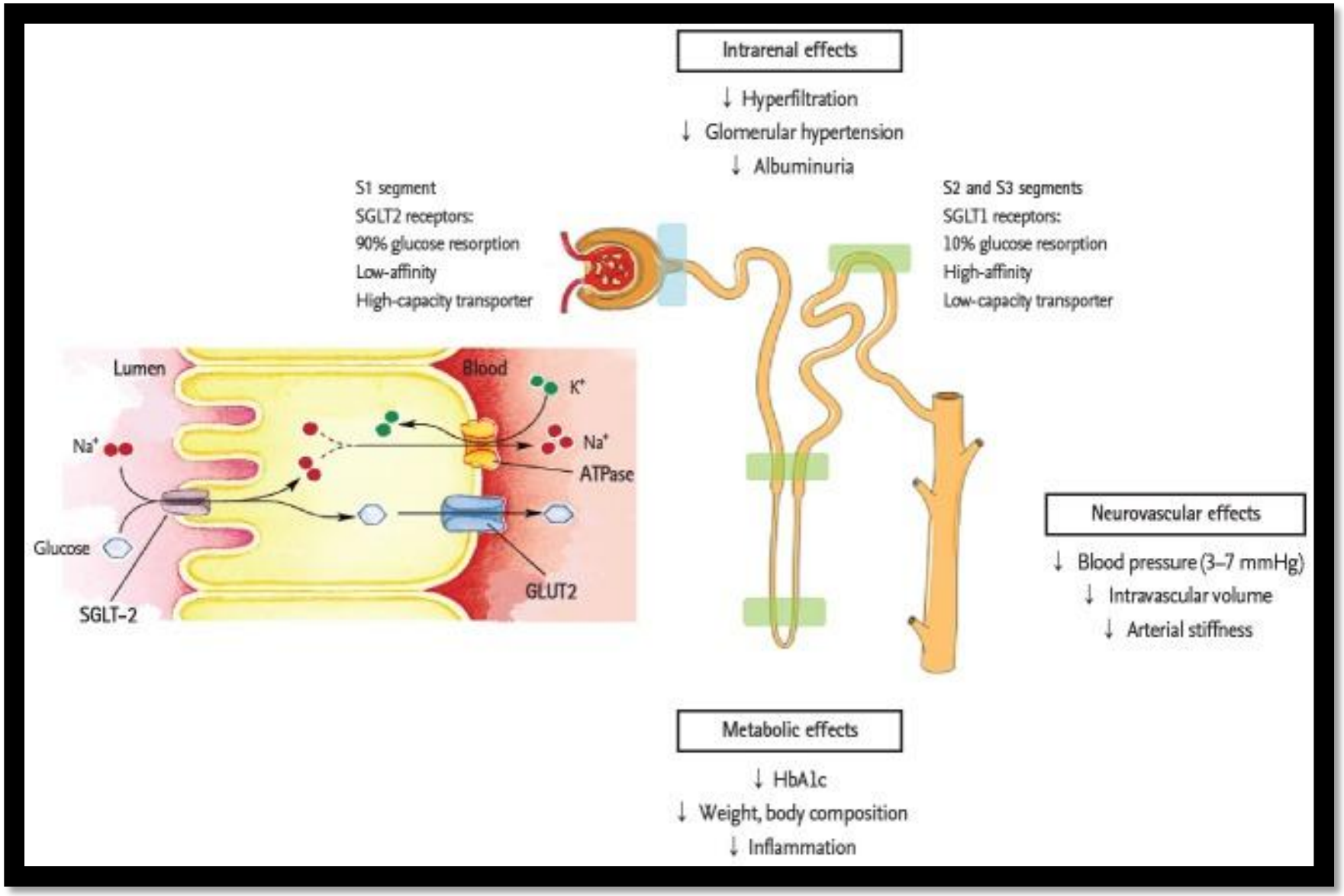
Zinman B et al, EMPA-REG OUTCOME Investigators. N Engl J Med. 2015 Nov 26; 373(22):2117-28.

Sodium-Glucose Co-transporter 2 Inhibition

- Renoprotective effect of SGLT2 inhibitors
  - Attributed to a decrease in high glucose-induced inflammatory & fibrotic markers in human proximal tubular cells

- By blocking glucose entry into the cell empagliflozin attenuated
- High glucose-induced-
  - Expression of Toll-like receptor-4, binding of nuclear deoxyribonucleic acid to nuclear factor κB and activator protein 1, and secretion of collagen IV and interleukin-6

Tang SC et al, F1000Res. 2016 May 31;5



Potential therapeutic effects of sodium/glucose co-transporter 2 (SGLT2) inhibition in diabetic nephropathy

Kim Y et al, Korean J Intern Med. 2017 Jan;32(1):11-25.

Selective C-C Chemokine Receptor Type 2 Antagonism

- MCP-1 over expression plays an indispensable role in promoting monocyte and macrophage migration and activation
- CCR2 antagonist- CCX140-B is a small molecule
  - Inhibits CCR2 and blocks MCP-1-dependent monocyte activation and chemotaxis
  - Improved glycaemia and albuminuria in animal models

Tang SC et al, F1000Res. 2016 May 31;5

5’ Adenosine Monophosphate-activated Protein Kinase Activation

- Evidence of dysregulation of AMPK in relevant tissues
  - Implicated in development of metabolic syndrome and diabetes
- Sirtuin 1 (Sirt1) protein
  - linked to longevity associated with calorie reduction
  - Expression and activity significantly reduced in type 2 diabetic animal models and human kidneys

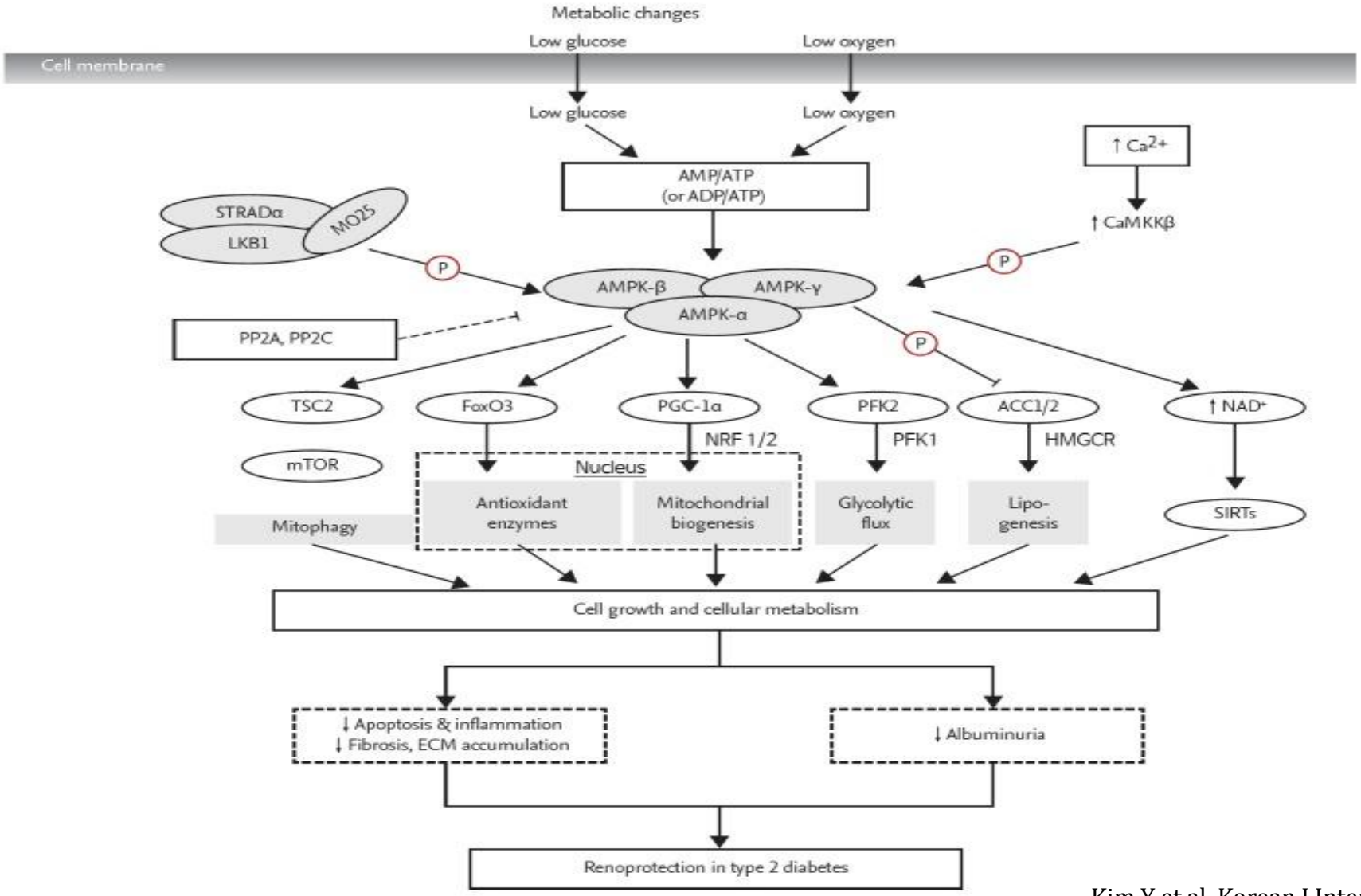
Tang SC et al, F1000Res. 2016 May 31;5

5’ Adenosine Monophosphate-activated Protein Kinase Activat

- Conventional activators of AMPK provides
  - Additional Renoprotective effects in addition to their intrinsic activities –
    - 5-aminoimidazole-4-carboxamide ribonucleoside,
    - Metformin,
    - Adiponectin
    - Resveratrol

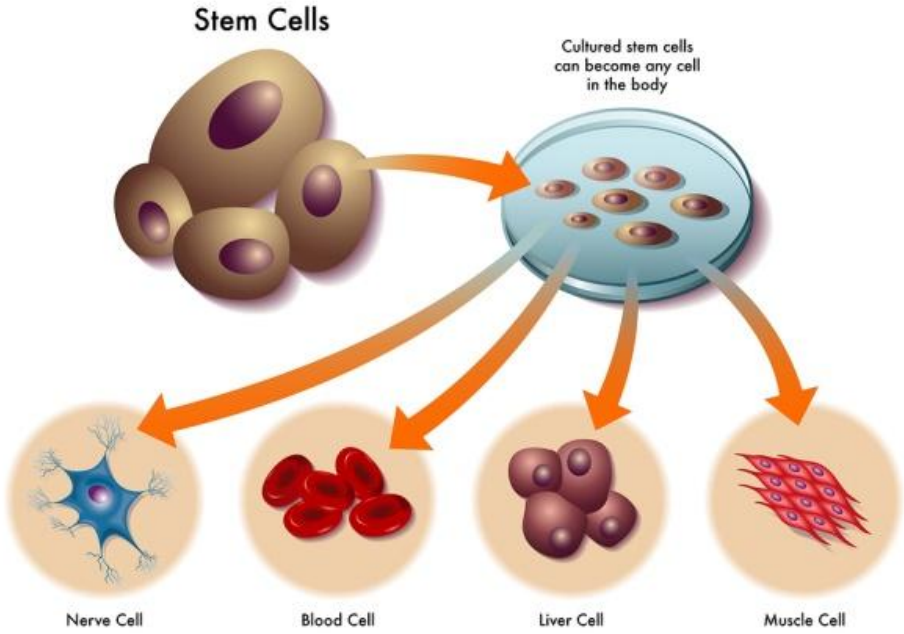
Tang SC et al, F1000Res. 2016 May 31;5

Proposed Renoprotective mechanisms in diabetic nephropathy (DN) through adenosine monophosphate-activated protein kinase (AMPK) activation.



Kim Y et al, Korean J Intern Med. 2017 Jan;32(1):11-25.

Stem Cell Therapy



- Multiple preclinical studies
  - Demonstrated - innovative stem cell therapy using mesenchymal stem cells (MSCs)
- Administration of MSCs
  - Prevent renal injury & promote renal recovery.
- MSC transplantation
  - Promising therapeutic strategy to delay DN progression in animal models
  - however, clinical trials should be performed to investigate the safety and efficacy of MSC transplantation in patients with DN

Xue R et al, J Diabetes Res. 2017;2017:1839809. Epub 2017 Mar 13.

Other Potential therapeutic modalities to prevent or withhold progression of DN

Drug class	On-target action	Remarks
Ruboxistaurin	PKC↓	
Sulodexide		
Atrasentan	Endothelin receptor antagonist	Serious side effects postponed approval
Aldose reductase inhibitors	IC sorbitol↓, IC fructose ↓	No adequate RCTs
Nrf2 activator	ROS↓	
Curcumin	ROS↓	No long term trials
Resveratrol	ROS↓	No clinical trials
Bardoxolone	ROS↓	UAE↑, BP↑, HF↑, mortality↑, nausea, wt loss, muscle spasm
Emapticap Pegol	MCP1↓	I.V administration
CCX140-B	CCR2 antagonist	Oral administration
Exogenous klotho	EMT↓, TGF-β↓	
Low dose IL-17A	MCP1↓	No clinical trials

Sharaf El Din UAA et al, J Adv Res..2017 Jul;8(4):363-373.

Summary (1/2)

- Diabetes is the leading cause of chronic kidney disease (CKD)
- Screened regularly for kidney disease
  - key markers- glomerular filtration rate (eGFR) and urine albumin
- Intensive management of blood glucose has shown great promise for people with diabetes, especially for those in the early stages of CKD.

Summary (2/2)

- Agents proven blood pressure lowering and slowing the progression of kidney disease
- Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin receptor blockers (ARBs)
- ACEi and ARBs dual blockade is not recommended
- When estimated glomerular filtration rate is,60 mL/min/1.73 m2, evaluate and manage potential complications of chronic kidney disease.
- Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate ,30 mL/min/1.73 m2.

Thank you