

Stop chronic kidney disease progression: Time is approaching

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Abstract

Progression of chronic kidney disease (CKD) is inevitable. However, the last decade has witnessed tremendous achievements in this field. Today we are optimistic; the dream of withholding this progression is about to be realistic. The recent discoveries in the field of CKD management involved most of the individual diseases leading the patients to end-stage renal disease. Most of these advances involved patients suffering diabetic kidney disease, chronic glomerulonephritis, polycystic kidney disease, renal amyloidosis and chronic tubulointerstitial disease. The chronic systemic inflammatory status and increased oxidative stress were also investigated. This inflammatory status influences the anti-senescence *Klotho* gene expression. The role of *Klotho* in CKD progression together with its therapeutic value are explored. The role of gut as a major source of inflammation, the pathogenesis of intestinal mucosal barrier damage, the role of intestinal alkaline phosphatase and the dietary and therapeutic implications add a novel therapeutic tool to delay CKD progression.

Key words: Chronic kidney disease; Progression; *Klotho*; Amyloidosis; Diabetic nephropathy; Micro RNA

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Core tip: The problem of chronic kidney disease (CKD) progression is a panic, affecting both patients and physicians. The fact that such patients will sooner or later need RRT terrifies them and makes these patients to survive a continuous mare. All the trials to stop this progression in the past only delayed this progression for some time. However, in the last 2 years many genuine experimental and clinical trials revived the hope to stop the progression almost completely in the vast variety of chronic renal diseases. In this review, we are highlighting most of these trials, stressing on the

different mechanisms that would stop CKD progression.

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INTRODUCTION

Chronic kidney disease (CKD) affects approximately one-seventh of adults above the age of 20 years^[1]. Progression of CKD is a major concern during managing patients in stages G1-4. The suppression of known "causes" of progression by targeting high blood pressure (BP) as well as the renin-angiotensin system (RAS) has achieved some success in REIN, RENAAL, IDNT, and other clinical trials^[2-4]. However, progression to end-stage renal disease (ESRD) is still inevitable. The recent discoveries of novel mechanisms underlying CKD progression opened the gate for more comprehensive understanding of the pathophysiology of CKD progression and the development of new therapeutic strategies. The role of chemokines in the recruitment of inflammatory cells into the kidney of a variety underlying diseases has opened the gate for new promising therapeutic modalities^[5,6]. The intensive studies done on *Klotho* and fibroblast growth factor 23 (FGF23) and their role in the control of renal phosphate handling^[7], and their unique anti-aging properties^[8,9] have disclosed appreciable data concerning their action on vascular calcification (V.C.)^[10], cardiac hypertrophy^[11], renal tubular epithelial- mesenchymal cell transformation^[12], and increased interstitial fibrosis^[13]. The last decade also witnessed the role of the gut in the pathogenesis of systemic inflammation in CKD patients^[14-16]. This chronic inflammatory status might add directly, through absorbed toxins or through its interaction with *Klotho* gene to the risk of V.C. and CKD progression^[17,18]. Therapeutic interventions manipulating such factors, besides the recent introduction of tolvaptan to treat autosomal dominant polycystic kidney disease (ADPKD)^[19], therapeutic IgG anti-SAP for the treatment of amyloidosis^[20,21], and anti-micro RNA for progressive interstitial fibrosis and/or glomerulosclerosis^[22] will expectedly improve the strategy combating CKD progression.

Epidemiology

CKD is inevitably progressive with the consistent decrease of glomerular filtration rate, leading finally to ESRD. In 2002, the United States National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines defined CKD as kidney damage or glomerular filtration rate lower than 60 mL/min per 1.73 m² or the presence of increased urinary

albumin excretion for 3 mo or longer, and proposed a classification scheme based on glomerular filtration rate^[23]. The important impact of albuminuria on CKD progression^[24] prompted the Kidney Disease: Improving Global Outcomes (KDIGO) Work Group on Evaluation and Management of CKD to include albuminuria in the revised 2012 classification^[25]. The estimated prevalence of CKD worldwide is 8%-16%^[26]. CKD is the 18th cause of death in 2010 (annual death rate 16.3 per 100000)^[27]. The 10 years all-cause mortality in diabetic nephropathy patient is around 5 times the rate in age and sex-matched nondiabetic personnel and triple the rate of diabetic patients without kidney disease^[28]. The risk of death increases as the GFR declines < 60 mL/min per 1.73 m² of body-surface area: The adjusted hazard ratio for death is 1.2 in CKD stage G3a, 1.8 in stage G3b, 3.2 in G4, and 5.9 in G5. The adjusted hazard ratio for cardiovascular events also increased inversely with the estimated GFR: 1.4, 2.0, 2.8, and 3.4 respectively. The adjusted risk of hospitalization with a reduced estimated GFR followed a similar pattern^[29]. These results indicate the serious impact of CKD progression on morbidity and mortality of CKD patients. It can also explain the marked discrepancy in the distribution of prevalence among different CKD stages^[30].

Proteinuria is an added risk for both CKD progression^[31] increased cardio-vascular and overall mortality^[32].

Pathogenesis

The mechanism of CKD progression among different CKD entities involves cytokine actions on renal hemodynamics, glomerular, and tubular functions. The characteristic pathologic feature of CKD is glomerular and interstitial infiltration by macrophages^[33]. Angiotensin II contributes to the hemodynamic and glomerular changes following the initial renal insult. This contribution results in progression of glomerular disease^[34]. Glomerular hypertension that follows renal insult results in increased angiotensin II activity. Angiotensin II activates transforming growth factor- β (TGF- β), macrophage chemoattractant protein (MCP-1), and vascular endothelial growth factor (VEGF) within the glomerulus^[35,36]. Accumulation of macrophages and lymphocytes; thus, ensues with further increase in production of IL-1, TNF- α , and MCP-1^[37,38]. Accumulating cytokines cause progressive glomerular damage by targeting podocytes. Although VEGF is a key player in the formation and maintenance of glomerular filtration barrier, elevated levels of VEGF are associated with glomerular hyperfiltration, hypertrophy, and proteinuria^[39]. Increased podocytes VEGF contributes to glomerular sclerosis in transgenic mice^[39]. Cytokines act also on mesangial cells inducing their proliferation or transforming them to fibroblast phenotype^[33]. The mesangial cell fibroblast phenotype secretes extracellular matrix components with consequent glomerular sclerosis^[33,40,41]. Endothelial cells generate endothelin,

TGF- β , and platelet-derived growth factor, in response to shear stress and glomerular hypertension. These cytokines and growth factors can also contribute to progressive glomerular sclerosis^[42,43]. Endothelial cells can also generate IL-1, TNF- α , and MCP-1 that ultimately result in attraction and proliferation of inflammatory cells^[44]. Intracellular adhesion molecule 1 (ICAM-1) secreted by endothelial cells facilitates neutrophil adhesion and enables macrophage infiltration^[35]. Although glomerular sclerosis is the key features of CKD progression; the tubulointerstitial damage correlates better with this progression than glomerular damage^[35]. Tubulointerstitial inflammation leads to tubulointerstitial damage. This inflammation starts as a consequence of glomerular hypertension and hypertrophy^[33]. Interstitial infiltration of inflammatory cells occurs in the early phases of renal diseases irrespective of the initial renal insult. These are primarily macrophages and T and B lymphocytes recruited to the interstitium by chemokines and adhesion molecules expressed by damaged tubular epithelium^[45]. Glomerular proteinuria is the postulated link between glomerular and renal tubular injury. Proteinuria may damage tubular lysosomes and increases MCP-1 release by proximal tubular epithelial cells^[46]. MCP-1 recruits and activates macrophages to release TGF- β . Tubulointerstitial fibrosis eventually starts and progresses^[47]. Fibroblasts maintain their activated phenotype even in the absence of the initial insult, *i.e.*, autonomous progression once the process starts^[48]. Tubular cells injured by lymphocytes and cytokines try to regenerate in a trial to replace damaged cells. This regeneration needs the transition of healthy epithelial cells into mesenchymal cells. This process is called epithelial-mesenchymal transition (EMT). Mesenchymal cells proliferate then transform back to epithelium if microenvironment becomes convenient (as occurs during recovery of acute tubular necrosis); otherwise, if inflammation is still there, mesenchymal cells transform into fibroblasts that continue the process of interstitial fibrosis^[49]. The anti-senescence protein, *Klotho*, favors epithelial regeneration and inhibits fibroblast phenotype transformation during EMT^[50]. Inflammation^[17,18,51,52], angiotensin II^[19,53,54], hyperphosphatemia and vitamin D deficiency^[55] suppress *Klotho* gene. Deficient *Klotho* activity enhances tubulointerstitial fibrosis^[56]. The attempt to repair damage begins with the recruitment of inflammatory cells but ends with an unchecked inflammatory response that activates matrix-producing cells leading to tubular cell apoptosis, irreversible scarring, loss of renal function, and ultimately ESRD^[57]. The extent of damage rather than the underlying disease determines the outcome^[58]. Progressive fibrosis is likely responsible for the disruption of glomerular and tubular architecture. Inhibition of the major mediators responsible for matrix accumulation might slow or arrest the progression of CKD. Support for this concept has been provided by the results of a number of studies in animal models of CKD, in which inhibiting factors that promote fibrosis, such as TGF- β , connective

tissue growth factor, and myofibroblast activation^[59-63] or enhancing factors that attenuate fibrosis, such as bone morphogenetic protein 7 and hepatocyte growth factor^[64,65] improved renal architecture and/or function. The present data indicate that TGF- β is the master regulator of the molecular events that result in renal fibrosis^[66]. So far, clinical trials using TGF- β antibodies did not achieve satisfactory results.

Standard of care management: Table 1

We do not have data to support the role of life style modification procedures (body weight control, exercise, and smoking quitting) on the course of CKD or cardiovascular impact in this population.

Protein restriction did not significantly affect CKD progression^[67]. Very low-protein diet does not delay CKD progression and may increase the risk of death^[68].

BP control significantly decreases the rate of decline in GFR in pre-dialysis CKD patients^[69]. RAS blockers should be used to control BP in CKD patients (diabetic and nondiabetic) with increased urine albumin excretion. RAS blockers have a significant impact on the rate of decline of GFR in CKD patients with proteinuria^[70-72]. They exert their action through many mechanisms including their hemodynamic effect on glomerular tuft pressure^[73,74], inhibition of cytokine overproduction^[75-79], increased serum and tissue angiotensin 1-7^[80-82] and stimulation of *Klotho* gene expression in CKD patients. The RAS-mediated renal damage might be through *Klotho* gene manipulation^[54]. This novel mechanism might clarify the vascular, cardiac and renal protective benefits of such agents^[53,56]. Manipulation of *Klotho* gene, adds a new exciting mechanism for the cardiovascular and renal protective actions of RAS blockers.

The addition of aldosterone antagonists whether non-selective (spironolactone) or selective (eplerenone or Finerenone) to anti-hypertension medications offered better BP and proteinuria control in mild to moderate CKD^[83-85].

Hyperkalemia is not infrequent with RAS blockers and/or aldosterone antagonists treatment in such patients. The use of bisacodyl laxative^[86], patiromer, the nonabsorbed potassium binder^[87] or sodium zirconium cyclosilicate^[88] can control hyperkalemia. These agents are not associated with the potentially serious adverse effects of potassium exchange resins^[89,90].

According to KDIGO guidelines, BP should be kept at 130/80 mmHg or lower^[91]. A much lower BP (less than 110/75 mmHg) is associated with slower rate of annual increase in kidney size and urine protein excretion rate in early cases of ADPKD as shown by a recent study, HALT-PKD^[92].

The strict control of blood sugar has a positive impact on survival of pre-dialysis diabetic CKD patients. Diabetic patients experienced the reversal of renal pathology after pancreas transplantation^[93]. Glycemic control might also delay CKD progression and postpones the need for dialysis^[94,95].

Statins reduce the risk of atherosclerotic cardiovas-

Table 1 Standard of care therapeutic management

Drug class	On-target parameter	Off-target parameters	Ref.
Antihypertensive			
RAS blockers	BP↓	UAE↓, GTP↓, K ⁺ ↑, AT1-7↑, cytokines↓, Klotho↑	[53,54,56,69-82]
Aldosterone antagonists	BP↓	UAE↓, K ⁺ ↑	[83-85]
K ⁺ binders			
Bisacodyl	K ⁺ ↓	Diarrhea	[86]
Patiromer	K ⁺ ↓		[87]
Na zirconium cyclosilicate	K ⁺ ↓		[88]
Blood sugar control	Blood sugar↓ HbA1c + 7	Progression↓ Postpones need of Dx	[93-95]
Hypocholesterolemic			
Statins	Cholesterol↓, LDL↓	Cardiovascular events↓	[96]
Hypouricemic agents			
Allpurinol	Uric acid↓	Renal events↓, CV events↓	[102,103]
Febuxostat	Uric acid↓	CKD progression↓	[104]
Sodium bicarbonate	HCO ₃ ⁻ ↑, PH ↑	Ptn catabolism↓, GFR decline↓	[105,106]
Phosphate binders			
Calcium based	P↓	PTH↓, Vasc calc.↑	[117-120]
Sevelamer	P↓	PTH↓, stop vasc calc, Mortality↓, Uric acid↓, Cholesterol↓, LDL↓, inflammation↓ Cardiovascular events↓	[121-131]
Lanthanum carbonate	P↓	PTH↓, stop vasc calc,	[123-139]
Iron compounds	P↓	Iron↑	[140,141]
Nicotinamide	P↓	TG↓, LDL↓, HDL↑	[142-144]

RAS: Renin angiotensin system; BP: Blood pressure; UAE: Urine albumin excretion; GTP: Glomerular tuft pressure; K: Potassium; AT1-7: Angiotensin 1-7; Dx: Dialysis; LDL: low density lipoprotein; CV: Cardiovascular; CKD: Chronic kidney disease; HCO₃⁻: Bicarbonate; Ptn: Protein; GFR: Glomerular filtration rate; P: Phosphorus; PTH: Parathormone; Vasc calc: Vascular calcification; TG: Triglycerides; HDL: High density lipoproteins.

cular disease in CKD patients; however, clinical trials have suggested a minimal effect of statins on CKD progression^[96].

The association between high serum uric acid (UA) and progression of CKD was suggested by many studies of stage G1 and G2^[97-99]. A more recent study denied this association in stages G3, 4 and 5^[100]. On the other hand, hyperuricemia was found as independent risk factor for CKD progression in children and adolescents^[101]. Treatment of CKD patients with estimated GFR of 40.6 ± 11.3 mL/min with allopurinol 100 mg/d was associated with significant decrease in renal events (need of dialysis, doubling of serum creatinine or > 50% reduction of GFR) and cardiovascular events in comparison to control CKD patients taking only their standard treatment (*P* < 0.004 and 0.02 respectively)^[102]. In addition, a recent meta-analysis showed a significant favorable effect of allopurinol on the rate of GFR decline^[103]. Another recent trial demonstrated the significant impact of febuxostat on CKD progression in stage G3 and G4 patients^[104].

Correction of chronic metabolic acidosis was originally recommended in CKD patient to inhibit excessive protein catabolism and calcium mobilization out of the bone. Sodium bicarbonate supplementation was found to slow the rate of progression of CKD to ESRD^[105]. In the more recent trial, a significant improvement in the rate of decline of GFR was encountered in stage G4 CKD patients treated with sodium bicarbonate to render serum bicarbonate level at 22 mmol/L or above^[106].

High serum phosphorus was suggested as a potential risk factor for a rapid decline in renal function

in CKD patients^[107]. The rate of progression of CKD (measured as 1/serum creatinine) was faster in hyperphosphatemic patients in stage G5 when compared to normophosphatemic patients in the same stage^[108]. In patients in stage G4 and G5, each 1 mg/dL higher serum phosphorus concentration, the mean decline in renal function increased with 0.154 mL/min per month^[109]. In addition, hyperphosphatemia is associated with increased mortality^[110]. Increased phosphate concentration leads to the formation of calcium-phosphate crystals, a process called "nucleation". If this process is left unchecked, calcium phosphate crystals undergo further aggregation to form monetite, brushite, octacalcium phosphate, amorphous calcium phosphate and finally hydroxyapatite. When exposed to such crystals, vascular endothelial cells increase production of reactive oxygen species and eventually undergo apoptosis^[111]. Endothelial cell death can expose underlying smooth muscle cells to the high ambient phosphate. Transformation of such cells to osteochondrocytes consequently develops^[112]. Fetuin-A is α -glycoprotein that binds calcium phosphate crystals, inhibiting the crystal growth and polymerization. Fetuin-A calcium phosphate complex is called calciprotein particles (CPP). In comparison to hydroxyapatite, CPP induce significantly less cytokine secretion when macrophages are exposed to equimolar concentrations of hydroxyapatite and CPP^[113]. In spite of the apparent protective effect of CPP, increased serum level of such particles reflects increased procalcific milieu^[114]. Higher CPP levels are thus associated with reduced renal function, higher scores of V.C., aortic stiffening and increased risk of death^[115].

When phosphate intake was restricted, the rate of decline in creatinine clearance was much less^[107]. Restriction of phosphate intake should start early in the course of CKD before the evident rise in serum phosphorus ensues. The restriction should initially be limited to food ingredients rich in inorganic phosphorus (like food preservatives and tasters). These food additives are found in sodas and processed foods^[116]. Bioavailability of organic phosphorus is higher in animal proteins compared to plant proteins. Phosphorus in the later is tightly bound to phytate, an indigestible ingredient found in plant foods. On the other hand, phosphate binders should only be used when serum phosphorus increases above normal limits. The very early use of the phosphate binders might be associated with progression of V.C. while lowering serum phosphorus and attenuating the progression of secondary hyperparathyroidism^[117]. Calcium-based phosphate binders are still very useful to control hyperphosphatemia, but can lead to hypercalcemia and/or positive calcium balance and cardiovascular calcification^[118]. The higher the dose ingested the greater the extent of V.C.^[119,120]. Thus, their use in cases suffering V.C., hypercalcemia, low level of parathormone and/or adynamic bone disease has to be restricted^[121]. When sevelamer was used in hyperphosphatemic stage 3-4 CKD patients, a significant impact on all-cause mortality and the need of dialysis was observed in comparison to calcium carbonate^[122]. Sevelamer is not just a calcium-free phosphate binder, but it has additional pleiotropic effects such as correcting certain abnormalities of lipid metabolism^[123], significant decrease in inflammatory parameters including interleukin (IL)-6, sCD14 and hs-CRP^[124,125], reduces serum UA concentration^[126], decrease serum FGF23^[127-129] and increases serum level of Klotho^[129]. The role of FGF23 and Klotho on the cardiovascular system and progression of CKD will be discussed later in this review. Compared to calcium-based phosphate binders, sevelamer improves endothelial function in CKD patients^[130]. Although sevelamer is more expensive compared to calcium-based phosphate binders^[131], the significant reduction in all-cause mortality and the significantly fewer hospitalizations in the sevelamer group can offset the higher acquisition cost for sevelamer^[132].

Lanthanum carbonate (LC) is another non-calcium based phosphate binder. LC had no impact on overall mortality in CKD patients^[133-135]. Contrary to sevelamer, LC does not have a consistent effect on FGF23. LC failed to cause reductions in FGF23 in patients with CKD stage G3-4^[136,137]. On the other hand, other studies showed that LC was effective in reducing FGF23 levels in CKD G3^[138] and CKD G4-5 patients^[139]. None of the trials on Lanthanum reported any effect on inflammation or inflammatory biomarkers. We are still waiting for such studies to assure non-inferiority of Lanthanum in this field.

Iron compounds represent the new class of phosphate binders. Ferric Citrate, Sucroferric oxyhydroxide,

and Ferrimagate (Iron-magnesium hydroxycarbonate) were tested in some clinical trials^[140]. Most of the clinical studies done so far were using ferric citrate, stressing on phosphate binding and ferrokinetics after short periods of trial. A single study looked for non-inferiority of Sucroferric oxyhydroxide (PA21) compared to sevelamer carbonate concerning phosphate binding^[141].

The value of nicotinamide in phosphate control (as well as its effects on lipid levels) was explored in some short-term trials on dialysis patients^[142-144]. However, such trials did not look for either pharmacokinetics or safety. None of these trials studied the impact on V.C., FGF23, Klotho or inflammatory mediators.

Novel therapeutic interventions: Table 2

Interstitial inflammatory cell infiltrates are a hallmark CKD of different etiology. Such infiltrates are the consequence of the interaction between chemokines locally produced when renal tissue is injured, and membrane receptors located on the cell membrane of leukocytes. Seven chemokine receptors are recognized, so far, on the surface of leukocytes^[145]. Such leukocytes potentially secrete pro-inflammatory, pro-apoptotic and pro-fibrotic cytokines that perpetuate renal tissue destruction and progression to CKD. A single chemokine receptor can respond and interact with different chemokine ligands. Therapeutic interventions targeting the receptors is thus much preferred to interrupt such renal leukocytes recruitment^[146]. The chemokine receptor CCR1 looks to play a pivotal role in leukocyte migration. This role extends to the interaction of other receptors with their chemokine ligands^[147]. While CCR1 is essential for leukocyte recruitment into the interstitium^[148], CCR2 and CCR5 do the job in case of glomerular infiltration^[149,150]. CCR1 antagonists proved to have a significant impact on leukocyte infiltration, interstitial fibrosis, tubular injury and kidney function tests in different rat models of renal injury (*e.g.*, unilateral ureter ligation, lupus nephritis, Adriamycin-induced renal injury, and collagen 4A3 deficient mice; the synonym of human Alport's syndrome)^[146]. When the CCR1 antagonist, BL5923, was used in mice suffering diabetic nephropathy, the interstitial recruitment of *ex vivo* labeled macrophages was markedly decreased. This was associated with reduced numbers of proliferating tubular epithelial and interstitial cells, tubular atrophy, and interstitial fibrosis. Glomerular pathology and proteinuria were not affected by the CCR1 antagonist^[151].

A mirror-image (Spiegelmer) for MCP1 was *in vitro* built-up using non-natural nucleotides. This RNA oligonucleotide is called Emapticap Pegol. It binds and neutralizes MCP-1 (also called CCL2), a pro-inflammatory chemokine that plays an important role in diabetic kidney disease^[152]. A phase IIa study that looked for safety and efficacy of Emapticap Pegol in phase IV diabetic nephropathy showed statistically significant reduction in urinary albumin excretion after the use of Emapticap Pegol for 12 wk as 3 times/wk subcutaneous injections. The anti-proteinuric effect persisted for 12 wk

Table 2 Novel therapeutic interventions

Therapeutic modality	Mechanism of action	Primary end points	Ref.
Chemokine ligand and receptor antagonists			
CCR1 antagonists	Block CCR1 receptors on leucocyte surface	Leuc. Inf.↓, IF↓, TI↓, and improved KFTs	[146]
Emapticap pegol	Binds and neutralizes MCP-1	UAE↓, glycemic control in phase IV D.N.	[5,152,153]
CCX140	Block CCR2	UAE↓, glycemic control in phase IV D.N.	[6,154]
Pentoxifylline	Anti-inflammatory	UAE↓, eGFR loss↓	[156,157]
VDRA			
Paricalcitol	Improves G.M. sieving, antifibrotic	UAE↓, eGFR loss↓	[160-162]
IAP			
Mediterranean diet	Restores intestinal microbiota, IAP↑	eGFR loss↓	[184]
Bound phosphorus	IAP↑		[186]
Vitamin K	IAP↑		[188]
S.O.D. mimetic			
Tempol	Oxidative stress↓	UAE↓, GS↓, TID↓	[189]
SRA			
Sarpogrelate	Antiplatelet	UAE↓	[192]
V2RA			
Tolvaptan	V2 receptor blocker	No. of cysts↓, growth of cysts↓	[19]
IgG anti-SAP antibodies	Binds SAP within amyloid tissue	Clearance of tissue amyloid deposits	[20]
RG-012	Inhibitor of miR-21	GS↓, IF↓, TI↓, Infl.↓	[22]

Leuc. Inf.: Leucocyte infiltration; IF: Interstitial fibrosis; TI: Tubular injury; KFTs: Kidney function tests; UAE: Urine albumin excretion; D.N.: Diabetic nephropathy; eGFR: Estimated glomerular filtration rate; VDRA: Vitamin D receptor agonists; G.M.: Glomerular membrane; IAP: Intestinal alkaline phosphatase; S.O.D.: Superoxide dismutase; GS: Glomerulosclerosis; TID: Tubulointerstitial disease; SRA: Serotonin receptor antagonist; V2RA: Vasopressin receptor antagonist; SAP: Serum amyloid protein; miR: Micro RNA; infl.: Inflammation.

after discontinuation of treatment. It also succeeded to improve glycemic control^[5,153]. A novel CCR2 antagonist was tried in diabetic kidney disease patients having type 2 diabetes. This antagonist is called CCX140. The results of phase II showed that the use of CCX140 given orally in a dose 5 mg/d on top of the standard of care treatment was associated with an additional significant reduction of urine albumin excretion rate. This improvement started after 12 wk and continued for the whole period of the study (52 wk). These patients were already treated with RAS blockers. Significant improvement in the slope of decline of GFR over that achieved with the standard of care treatment was also observed beside the improved glycemic control^[6]. The results of phase 3, however, did not confirm the significant impact on GFR but did confirm the anti-proteinuric and the glycemic favorable outcomes reported in phase 2^[154]. CCX168 is another inhibitor that targets C5aR, the chemoattractant receptor that binds to the complement fragment C5a. Oral administration of CCX168 ameliorated anti-MPO-induced mesangiocapillary glomerulonephritis in mice^[155]. In addition, this inhibitor is in phase 2 trials in patients with aHUS, IgA nephropathy, and ANCA-associated vasculitis.

Pentoxifylline is a phosphodiesterase inhibitor with anti-inflammatory action. It is used as a treatment of peripheral vascular disease. The addition of low-dose pentoxifylline, 400 mg/d, to losartan plus enalapril resulted in a significant decrease of urine protein excretion rate from a baseline of 616 mg/d to 192 mg/d 6 mo later in type 2 diabetic patients^[156]. Another

clinical trial explored add-on pentoxifylline to maximized RAS blockade on renal disease progression in stage G3-4 CKD T2DM patients. Pentoxifylline dose in this trial is 1200 mg/d. After 24 mo of follow-up, treatment with pentoxifylline was associated with a slower rate of eGFR loss together with the significant reduction in urine protein excretion^[157].

An inverse relationship was observed between serum level of 25(OH) vitamin D and the rate of GFR decline in children suffering CKD. Serum levels higher than 50 nmol/L were associated with 75% renal survival at 5 years of observation in contrast to 50% in case of levels below 50 nmol/L ($P < 0.001$). Higher serum levels of 25(OH) vitamin D were associated with lower urine protein/creatinine ratio. Renal survival increased 8.2% for every 10 nmol/L increase in 25(OH) vitamin D ($P = 0.03$), independent of eGFR; proteinuria, and underlying renal diagnosis^[158]. It seems that activation of vitamin D receptors (VDR) on podocytes improves glomerular membrane sieving of proteins and has an anti-fibrotic effect^[159]. Paricalcitol in a dose of 2 µg/d showed a significant effect on urine albumin excretion in type 2 diabetic patients with overt nephropathy^[160]. PROCEED trial is another prospective controlled study of paricalcitol in type 2 diabetes patients in phase IV diabetic nephropathy on low or high salt intake and already treated with RAS blockers^[161]. This trial has already completed and results are expected within few weeks.

Paricalcitol treatment of uremic mice restores deficient Klotho synthesis in CKD renal tissue^[162].

Klotho is an anti-senescence protein^[6]. It exists in 2 forms: The transmembrane and the soluble secreted form^[163]. Klotho is detected as a soluble protein in body fluids including blood, CSF and urine^[164]. The highest expression of Klotho is in the kidney and the brain^[6], but it is also expressed in parathyroid gland^[165] and heart^[166] with less abundance. Klotho protein is a β -glucuronidase. Reduced klotho expression in chronically diseased kidneys is associated with chronic inflammatory cell infiltrate, sclerosis of intrarenal small sized arteries, interstitial fibrosis and renal tubular atrophy^[16]. Decreased klotho expression underlies excessive fibroblast emergence as a consequence of EMT following acute insults posed on renal tubular epithelium^[12]. The kidney produces and releases Klotho into the circulation and clears Klotho from the blood into the urine^[167]. Exogenous Klotho prevents senescence of endothelial cells induced by uremic milieu^[168]. In different models of mouse CKD (5/6 nephrectomy, Adriamycin nephropathy and unilateral ureteric ligation) exogenous Klotho abolished the induction of the different RAS proteins, including angiotensinogen, renin, angiotensin-converting enzyme, and angiotensin II type 1 receptor, and normalized BP. Klotho also ameliorated renal fibrotic lesions^[169].

Endothelin receptor antagonists, avosentan, and atrasentan, have a significant anti-proteinuric effect when added to RAS blockers. However, dose-dependent peripheral edema is a major obstacle limiting their routine use in CKD patients^[170].

CKD is associated with inflammation and oxidative stress which contribute to CKD progression^[171]. A positive correlation was encountered between the rate of rise in serum creatinine and 2 markers of inflammation, namely, hs-CRP and malondialdehyde^[172]. Uremic status is incriminated in the pathogenesis of chronic inflammation; however, the exact mechanisms are not fully understood. Inflammation can result from multiple co-morbid conditions activating inflammation (like infections and autoimmune systemic diseases)^[173]. Impaired activity of the nuclear 1 factor (erythroid-derived 2)-related factor 2 (Nrf2) transcription factor was associated with inflammation and impaired antioxidant activity in CKD animals^[174]. Bardoxolone methyl is a potent activator of the Nrf2. When patients with type 2 diabetes mellitus and G4 CKD (GFR 15 to < 30 mL/min) were treated with bardoxolone methyl, at a daily dose of 20 mg, there was a significant increase in GFR. However, the treatment group had a significant increase in urine albumin excretion, BP and in the incidence of congestive heart failure and cardiovascular mortality. The last 2 adverse events forced the steering committee to prematurely stop the trial 7 mo after its onset^[175].

The gut has recently emerged as a major instigator of systemic inflammation in CKD. Postmortem examination of gut wall disclosed inflammatory changes throughout the digestive tract in patients on regular dialysis^[15]. The human intestine is now recognized

as an important metabolic organ powered by gut microbiota^[176]. Altered gut microbiome might affect the integrity of the intestinal barrier leading to facilitated blood translocation of bacteria and uremic toxins^[15]. In this context, the intestinal barrier function has not yet been carefully studied. However, recent studies have demonstrated marked disintegration of the colonic epithelial barrier structure and significant alteration of the colonic bacterial flora in humans and animals with advanced CKD^[171]. The fact that circulating lipopolysaccharides (LPS) levels and bacteria-derived uremic retention solutes (indoxyl sulfate, p-cresol, and trimethylamine n-oxide) increase with CKD stages suggests a link between the intestinal barrier and renal dysfunction^[177]. Many uremic toxins are derived from gut microbes. The imbalance of gut microbiota (dysbiosis) is provoked by dietary restrictions in CKD. Prescribed diet is poor in plant fibers and symbiotic organisms (to avoid potassium and phosphorus). Gut bacterial DNA and endotoxin were detected in the CKD serum. Endotoxin levels increase with the CKD stage and correlate with the severity of systemic inflammation^[15]. When lubiprostone (a laxative) was used in uremic mice, reduction in the elevated BUN and protection against tubulointerstitial damage, renal fibrosis, and inflammation were observed. Change in the intestinal microbial composition in favor of Lactobacilli and Prevotella genus was also encountered beside a significant decrease in serum level of indoxyl sulfate, hippurate, and trans-aconitate. All these uremic toxins are of intestinal bacterial origin. These results indicate the possible value of change of gut microbiota in improving the rate of progression of CKD^[178]. Thus, by targeting of the gut microbiome in a trial to restore symbiosis may prove as a potent strategy in reducing inflammation and disease progression in CKD. The efficacy of probiotics to decrease uremic toxin production and to improve renal function has been investigated in some human CKD studies^[177]. However, none of the clinical studies, so far, looked for the impact of probiotics on inflammation and CKD progression in pre-dialysis population. We would like to emphasize that probiotic treatment might decrease serum urea and creatinine by direct degradation. The use of estimated GFR in the assessment will obviously give erroneous results. GFR should be measured using iothexol in such trials. Another critical issue concerning the use of probiotics is the possible production of urease enzyme. Bacterial urease would increase ammonia production. This later product can attack the tight junctions in between intestinal epithelium rendering the intestinal mucosal barrier looser allowing excess translocation of bacterial products and uremic toxins to the intestinal wall and then into circulation. We are still looking for randomized prospective trials targeting the colonic microenvironment in CKD aiming at modulation of gut microbiota, to block LPS absorption to attenuate inflammation, or to target rate of production and adsorption of uremic toxins^[179].

Intestinal alkaline phosphatase (IAP) displays anti-inflammatory properties. This property may be related to detoxification of LPS, resulting in amelioration of intestinal and systemic inflammation; and to the regulation of gut microbial communities and their translocation. Enteral and systemic administration of exogenous IAP attenuates systemic inflammation. Dietary intervention can stimulate IAP and minimize low-grade systemic inflammation^[180]. Intravenous administration of IAP improved kidney function and systemic inflammation in cases of sepsis^[181]. Various spices (*e.g.*, black pepper, red pepper, and ginger) increase IAP activity in the small intestine^[182]. Curcumin; the active ingredient in the herbal remedy and dietary spice turmeric (*Curcuma longa*) increases the expression of IAP and tight junction proteins and corrects gut permeability. These effects would explain the anti-inflammatory effect of dietary curcumin in spite of its' poor bioavailability^[183]. It seems clear from this discussion; that a Mediterranean diet rich in indigestible fibers and in saccharolytic bacterial species fortified by spices like black pepper, red pepper, ginger or curcumin represents an innovative approach in CKD, potentially restoring microbiota balance, ameliorating CKD symptoms and slowing down CKD progression^[184]. Dietary calcium and bound phosphate stimulate IAP^[185,186]. In contrast, free unbound phosphorus in food inhibits IAP^[187]. Vitamin K stimulates IAP^[188].

The superoxide dismutase-mimetic drug, Tempol, improved elevation on serum creatinine, blood urea nitrogen, urine albumin, segmental sclerosis and tubulointerstitial damage that were induced by 5/6 nephrectomy. These results indicate the value of the increased oxidative stress commonly encountered in CKD on the progression of the renal disease. They also highlight the possible value of antioxidant treatment to delay CKD progression^[189].

Sarpogrelate is a serotonin (5-hydroxy tryptamine) receptor antagonist. It inhibits the production of thromboxane A₂ and is used as anti-platelet agent instead of aspirin^[190]. Experimental studies showed Sarpogrelate effect on mesangial type IV collagen production, on albuminuria in DKD, on antibody-mediated glomerular injury and on nephrotoxin-induced kidney fibrosis^[191]. A clinical trial showed a significant decrease of urine albumin excretion in diabetic kidney disease after addition of Sarpogrelate^[192].

ADPKD is the most common inherited disease that leads to dialysis or kidney transplantation. ADPKD is the fourth leading cause of ESRD^[193]. The disease manifests by one or more cysts in each kidney usually during the 3rd decade of life. The number and size of the cysts steadily progress to interfere with the structure and function of individual nephrons. This distraction in the structure and function leads finally to ESRD usually between the 4th and 7th decades of life^[194]. Many clinical trials were planned using different agents to stop the growth in number and size of cysts. All these trials failed to show significant results^[195]. On the other hand, animal studies highlighted the role of the antidiuretic

hormone arginine vasopressin and its second messenger adenosine-3', 5'-cyclic monophosphate (cAMP) as promoters of kidney cyst development and accumulation of secretions within existent cysts. These studies also showed that suppression of vasopressin by either increase of water intake, posterior pituitary ablation or using the vasopressin receptor antagonists inhibit cyst development and growth and hence preserve kidney function^[196]. The first phase 3 prospective double-blinded clinical study of tolvaptan (vasopressin receptor antagonist, V₂-receptor antagonist) demonstrated a significant slowing in the rate of increase in total kidney volume and the decline in kidney function over a 3-year period compared to placebo in patients with ADPKD^[19]. These results beside the more recent trial on BP, HALT-PKD^[92], open a big hope to ADPKD patients, especially if their disease is checked in early stages.

The kidney is the most frequent site of amyloid fibril deposition in AL, AA, and several of the hereditary amyloidoses. Amyloid fibrils are a group of soluble proteins that aggregate and deposit extracellularly in tissues as insoluble fibrils, causing progressive organ dysfunction. Substantial progress in understanding the process of amyloid fibril formation and the mechanisms underlying disease manifestations have led to important advances in treatment^[197]. In cases of systemic amyloidosis, the amyloid fibril deposits always contain the non-fibrillar serum amyloid P component (SAP). SAP binds avidly but reversibly to all types of amyloid fibrils and is thus specifically concentrated in all amyloid deposits^[198]. The binding of monoclonal anti-SAP antibodies to the SAP in amyloid deposits activates complement and triggers the rapid clearance of amyloid by macrophage-derived multinucleated giant cells^[20]. The drug (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (CPHPC) efficiently depletes SAP from the plasma but leaves SAP in tissue amyloid deposits. Therapeutic IgG anti-SAP antibodies can subsequently target tissue SAP. An open-label, single-dose-escalation, phase 1 trial was conducted in patient with systemic amyloidosis mainly affecting the liver. One patient had renal involvement. A reduction in kidney amyloid load was observed. The authors are planning a next trial phase, in which patients with clinically significant renal amyloidosis will be included and will receive larger and, if necessary, repeated doses of anti-SAP antibody, with the aim of achieving effective exposure in tissues that do not have the highly permeable sinusoidal endothelium of the liver and spleen^[20].

Micro RNA (miRNA) are non-coding short RNA molecules (average 22 nucleotides) found in plants, animals, some viruses, and human being. Their main function is RNA silencing and post-transcriptional regulation of gene expression. A number of miRNAs are dysregulated in response to acute kidney injury and in CKD. This dysregulation probably contributes to maintenance and progression of CKD of different pathologic entities^[199]. One of such miRNAs is miR-21,

probably involved in regulating kidney tissue response after injury. MiR-21 is expressed in many cell types in the kidney and is upregulated in CKD of different underlying etiology. MiR-21 knockout mice showed far less interstitial fibrosis in response to kidney injury. Similar results were demonstrated in wild-type mice treated with anti-miR-21 oligonucleotides^[200]. These oligonucleotides are administered subcutaneously and have high affinity to renal tissues. When a murine model of Alport syndrome was treated with anti-miR-21 oligonucleotides, no adverse effects were encountered after miR-21 silencing. The treated mice showed substantially milder renal disease compared to vehicle treated mice. The treated Alport mice had improved survival and reduced pathological end points including glomerulosclerosis, interstitial fibrosis, tubular injury, and inflammation^[22]. These results demonstrate that inhibition of miR-21 is a potential therapeutic modality for CKDs in general and Alport nephropathy in specific. Currently, RG-012; the potent inhibitor of miR-21 is being evaluated in a first-in-human Phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of subcutaneous dosing in healthy volunteers. This will be followed by a clinical multicenter study in cases of Alport syndrome.

During September 2015, a new hope was created to diabetic patients. Treatment with low doses of IL-17A succeeded to reverse diabetic nephropathy in genetic models of diabetes in mice. Administration of low doses of IL-17A significantly decreased urine albumin excretion, kidney size, mesangial matrix expansion, urine IP10, TNF α , IL-6, MCP1 and serum urea level in comparison to vehicle^[201].

CONCLUSION

Today, clinical nephrologists appreciate the impact of BP and blood sugar control, the value of RAS blockers and VDR agonists on the outcome of diabetic kidney disease. Chemokine ligand or receptor blockers are about to make the progression of diabetic nephropathy very slow or even completely suppressed. In the time being, CKD patients are irreversibly driven to renal replacement therapy. The question answered in this review is: "Are we approaching the time to change the pessimistic concept of (inevitable progression)?"

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