**Name of Journal: *World Journal of Nephrology***

**ESPS Manuscript NO: 23152**

**Manuscript Type: Review**

**Stop chronic kidney disease progression: Time is approaching**

Sharaf El Din UAA *et al.* Stop chronic kidney disease progression

**Usama Abdel Azim Sharaf El Din, Mona Mansour Salem, Dina Ossama Abdulazim**

**Usama Abdel Azim Sharaf El Din,** Departments of Nephrology, School of Medicine, Cairo University, Manial, Cairo 11759, Egypt

**Mona Mansour Salem,** Departments of Endocrinology, School of Medicine, Cairo University, Manial, Cairo 11759, Egypt

**Dina Ossama Abdulazim,** Departments of Rheumatology and Rehabilitation, School of Medicine, Cairo University, Manial, Cairo 11759, Egypt

**Author contributions:** Sharaf El Din UAA and Salem MM performed the majority of writing the manuscript; Abdulazim DO collected the references and highlighted the points of relevance in each article and revised the manuscript after being prepared.

**Conflict-of-interest** **statement:** Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Usama Abdel Azim Sharaf El Din, MD, Professor,** Departments of Nephrology, School of Medicine, Cairo University, 58th Abbas El Akkad St., Manial, Cairo 11759, Egypt. usamaaas@gmail.com

**Telephone:** +20-11-11333800

**Fax:** +20-22-2753890

**Received:** October 25, 2015

**Peer-review started:** October 27, 2015

**First decision:** January 18, 2016

**Revised:** January 26, 2016

**Accepted:** February 23, 2016

**Article in press:**

**Published online:**

**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; Diabetic nephropathy; *Klotho*; Amyloidosis; Micro RNA

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Sharaf El Din UAA, Salem MM, Abdulazim DO. Stop chronic kidney disease progression: Time is approaching. *World J Nephrol* 2016; In press

**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[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 vascular calcification 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 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), 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 (PDGF), 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 (CTGF), and myofibroblast activation[59-63] or enhancing factors that attenuate fibrosis, such as bone morphogenetic protein 7 (BMP 7) and hepatocyte growth factor (HGF)[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]. Renin-angiotensin system (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 angiotensin1-7[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 cardiovascular 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 lead 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 melieu[114]. Higher CPP levels are thus associated with reduced renal function, higher scores of vascular calcification, 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 vascular calcification 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 vascular calcification (V.C.)[119,120]. Thus, their use in cases suffering V.C., hypercalcemia, low level of parathormone (PTH) 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 Fermagate (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 (NAM) 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 leucocytes[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 leucocyte 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 macrophage chemoattractant protein (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 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 5years 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 epithelial-mesenchymal transition 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 (MDA)[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 anti-oxidant 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 iohexol 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, msangial matrix expansion, urine IP10, TNFα, 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 vitamin D receptor 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 to be answered in this review is: “Are we approaching the time to change the pessimistic concept of (inevitable progression)?”

**REFERENCES**

1 **Coresh J**, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038-2047 [PMID: 17986697 DOI: 10.1001/jama.298.17.2038]

2 Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia) *Lancet* 1997; **349**: 1857-1863 [PMID: 9217756 DOI: 10.1016/S0140-6736(96)11445-8]

3 **Brenner BM**, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861-869 [PMID: 11565518 DOI: 10.1056/NEJMoa011161]

4 **Lewis EJ**, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851-860 [PMID: 11565517]

5 **Haller H**. CCL2 inhibition with emapticap pegol (NOX‐E36) in type 2 diabetic patients with albuminuria. Late breaking clinical trials. The ERA-EDTA 51st congress, 2014, Sunday, June 1st. Available from: URL: http://www.era-edta2014.org/en-US/symposium-1.

6 **De Zeeuw D**. CCR2 inhibitor CCX140 effective in phase 2 clinical trial in diabetic nephropathy. Late breaking clinical trials. The ERA-EDTA 52nd congress, 2015, Friday, May 29th. Available from: URL: http://www.era-edta2015.org/en-US/symposium-6

7 **Saito H**, Kusano K, Kinosaki M, Ito H, Hirata M, Segawa H, Miyamoto K, Fukushima N. Human fibroblast growth factor-23 mutants suppress Na+-dependent phosphate co-transport activity and 1alpha,25-dihydroxyvitamin D3 production. *J Biol Chem* 2003; **278**: 2206-2211 [PMID: 12419819]

8 **Kuro-o M**, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H, Iida A, Shiraki-Iida T, Nishikawa S, Nagai R, Nabeshima YI. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* 1997; **390**: 45-51 [PMID: 9363890]

9 **Razzaque MS**, Sitara D, Taguchi T, St-Arnaud R, Lanske B. Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D-mediated process. *FASEB J* 2006; **20**: 720-722 [PMID: 16436465]

10 **Nasrallah MM**, El-Shehaby AR, Salem MM, Osman NA, El Sheikh E, Sharaf El Din UA. Fibroblast growth factor-23 (FGF-23) is independently correlated to aortic calcification in haemodialysis patients. *Nephrol Dial Transplant* 2010; **25**: 2679-2685 [PMID: 20176609 DOI: 10.1093/ndt/gfq089]

11 **Faul C**, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; **121**: 4393-4408 [PMID: 21985788 DOI: 10.1172/JCI46122]

12 **Hu MC**, Kuro-o M, Moe OW. The emerging role of Klotho in clinical nephrology. *Nephrol Dial Transplant* 2012; **27**: 2650-2657 [PMID: 22802580 DOI: 10.1093/ndt/gfs160]

13 **Sugiura H**, Yoshida T, Shiohira S, Kohei J, Mitobe M, Kurosu H, Kuro-o M, Nitta K, Tsuchiya K. Reduced Klotho expression level in kidney aggravates renal interstitial fibrosis. *Am J Physiol Renal Physiol* 2012; **302**: F1252-F1264 [PMID: 22338084 DOI: 10.1152/ajprenal.00294.2011]

14 **Pahl MV**, Vaziri ND. The Chronic Kidney Disease - Colonic Axis. *Semin Dial* 2015; **28**: 459-463 [PMID: 25855516 DOI: 10.1111/sdi.12381]

15 **Lau WL**, Kalantar-Zadeh K, Vaziri ND. The Gut as a Source of Inflammation in Chronic Kidney Disease. *Nephron* 2015; **130**: 92-98 [PMID: 25967288 DOI: 10.1159/000381990]

16 **Mafra D**, Lobo JC, Barros AF, Koppe L, Vaziri ND, Fouque D. Role of altered intestinal microbiota in systemic inflammation and cardiovascular disease in chronic kidney disease. *Future Microbiol* 2014; **9**: 399-410 [PMID: 24762311 DOI: 10.2217/fmb.13.165]

17 [**Nasrallah MM**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Nasrallah%20MM%5BAuthor%5D&cauthor=true&cauthor_uid=24348506), [El-Shehaby AR](http://www.ncbi.nlm.nih.gov/pubmed/?term=El-Shehaby%20AR%5BAuthor%5D&cauthor=true&cauthor_uid=24348506)2, [Osman NA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Osman%20NA%5BAuthor%5D&cauthor=true&cauthor_uid=24348506)1, [Fayad T](http://www.ncbi.nlm.nih.gov/pubmed/?term=Fayad%20T%5BAuthor%5D&cauthor=true&cauthor_uid=24348506)1, [Nassef A](http://www.ncbi.nlm.nih.gov/pubmed/?term=Nassef%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24348506)3, [Salem MM](http://www.ncbi.nlm.nih.gov/pubmed/?term=Salem%20MM%5BAuthor%5D&cauthor=true&cauthor_uid=24348506)4, [Sharaf El Din UA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Sharaf%20El%20Din%20UA%5BAuthor%5D&cauthor=true&cauthor_uid=24348506). The Association between Fibroblast Growth Factor-23 and Vascular Calcification Is Mitigated by Inflammation Markers. *Nephron Extra* 2013; **3**: 106-112 [PMID: 24348506 DOI: 10.1159/000356118]

18 **Thurston RD**, Larmonier CB, Majewski PM, Ramalingam R, Midura-Kiela M, Laubitz D, Vandewalle A, Besselsen DG, Mühlbauer M, Jobin C, Kiela PR, Ghishan FK. Tumor necrosis factor and interferon-gamma down-regulate Klotho in mice with colitis. *Gastroenterology* 2010; **138**: 1384-1394, 1384-1394 [PMID: 20004202 DOI: 10.1053/j.gastro.2009.12.002]

19 **Torres VE**, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; **367**: 2407-2418 [PMID: 23121377 DOI: 10.1056/NEJMoa1205511]

20 **Richards DB**, Cookson LM, Berges AC, Barton SV, Lane T, Ritter JM, Fontana M, Moon JC, Pinzani M, Gillmore JD, Hawkins PN, Pepys MB. Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component. *N Engl J Med* 2015; **373**: 1106-1114 [PMID: 26176329 DOI: 10.1056/NEJMoa1504942]

21 **Bodin K**, Ellmerich S, Kahan MC, Tennent GA, Loesch A, Gilbertson JA, Hutchinson WL, Mangione PP, Gallimore JR, Millar DJ, Minogue S, Dhillon AP, Taylor GW, Bradwell AR, Petrie A, Gillmore JD, Bellotti V, Botto M, Hawkins PN, Pepys MB. Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. *Nature* 2010; **468**: 93-97 [PMID: 20962779 DOI: 10.1038/nature09494]

22 **Gomez IG**, MacKenna DA, Johnson BG, Kaimal V, Roach AM, Ren S, Nakagawa N, Xin C, Newitt R, Pandya S, Xia TH, Liu X, Borza DB, Grafals M, Shankland SJ, Himmelfarb J, Portilla D, Liu S, Chau BN, Duffield JS. Anti-microRNA-21 oligonucleotides prevent Alport nephropathy progression by stimulating metabolic pathways. *J Clin Invest* 2015; **125**: 141-156 [PMID: 25415439 DOI: 10.1172/JCI75852]

23 **National Kidney Foundation**. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1-266 [PMID: 11904577]

24 **Matsushita K**, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073-2081 [PMID: 20483451 DOI: 10.1016/S0140-6736(10)60674-5]

25 **Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group**. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; **3**: 1-150 [DOI: 10.1038/kisup.2012.74]

26 **Jha V**, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; **382**: 260-272 [PMID: 23727169 DOI: 10.1016/S0140-6736(13)60687-X]

27 **Lozano R**, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095-2128 [PMID: 23245604 DOI: 10.1016/S0140-6736(12)61728-0]

28 **Afkarian M**, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, de Boer IH. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013; **24**: 302-308 [PMID: 23362314 DOI: 10.1681/ASN.2012070718]

29 **Go AS**, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296-1305 [PMID: 15385656 DOI: 10.1056/NEJMoa041031]

30 MMWR, Prevalence of Chronic Kidney Disease and Associated Risk Factors - United States, 1999-2004, March 2, 2007; **56**: 161-165. Available from: URL: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5608a2.htm

31 **Ruggenenti P**, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). *Kidney Int* 1998; **53**: 1209-1216 [PMID: 9573535 DOI: 10.1046/j.1523-1755.1998.00874.x]

32 **Culleton BF**, Larson MG, Parfrey PS, Kannel WB, Levy D. Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. *Am J Med* 2000; **109**: 1-8 [PMID: 10936471 DOI: 10.1016/S0002-9343(00)00444-7]

33 **Noronha IL**, Fujihara CK, Zatz R. The inflammatory component in progressive renal disease--are interventions possible? *Nephrol Dial Transplant* 2002; **17**: 363-368 [PMID: 11865077]

34 **Sánchez-Lozada LG**, Tapia E, Johnson RJ, Rodríguez-Iturbe B, Herrera-Acosta J. Glomerular hemodynamic changes associated with arteriolar lesions and tubulointerstitial inflammation. *Kidney Int Suppl* 2003; **(86)**: S9-14 [PMID: 12969121]

35 **Harris RC**, Neilson EG. Toward a unified theory of renal progression. *Annu Rev Med* 2006; **57**: 365-380 [PMID: 16409155 DOI: 10.1146/annurev.med.57.121304.131342]

36 **Taal MW**, Omer SA, Nadim MK, Mackenzie HS. Cellular and molecular mediators in common pathway mechanisms of chronic renal disease progression. *Curr Opin Nephrol Hypertens* 2000; **9**: 323-331 [PMID: 10926167]

37 **Wilson HM**, Walbaum D, Rees AJ. Macrophages and the kidney. *Curr Opin Nephrol Hypertens* 2004; **13**: 285-290 [PMID: 15073486 DOI: 10.1097/00041552-200405000-00004]

38 **Holdsworth SR**, Summers SA. Role of mast cells in progressive renal diseases. *J Am Soc Nephrol* 2008; **19**: 2254-2261 [PMID: 18776124 DOI: 10.1681/ASN.2008010015]

39 **Eremina V**, Quaggin SE. The role of VEGF-A in glomerular development and function. *Curr Opin Nephrol Hypertens* 2004; **13**: 9-15 [PMID: 15090854 DOI: 10.1097/00041552-200401000-00002]

40 **Ohashi K**, Iwatani H, Kihara S, Nakagawa Y, Komura N, Fujita K, Maeda N, Nishida M, Katsube F, Shimomura I, Ito T, Funahashi T. Exacerbation of albuminuria and renal fibrosis in subtotal renal ablation model of adiponectin-knockout mice. *Arterioscler Thromb Vasc Biol* 2007; **27**: 1910-1917 [PMID: 17626903 DOI: 10.1161/ATVBAHA.107.147645]

41 **Floege J**, Burns MW, Alpers CE, Yoshimura A, Pritzl P, Gordon K, Seifert RA, Bowen-Pope DF, Couser WG, Johnson RJ. Glomerular cell proliferation and PDGF expression precede glomerulosclerosis in the remnant kidney model. *Kidney Int* 1992; **41**: 297-309 [PMID: 1313122]

42 **Daoussis D**, Andonopoulos AP, Liossis SN. Targeting CD40L: a promising therapeutic approach. *Clin Diagn Lab Immunol* 2004; **11**: 635-641 [PMID: 15242934]

43 **Malek AM**, Greene AL, Izumo S. Regulation of endothelin 1 gene by fluid shear stress is transcriptionally mediated and independent of protein kinase C and cAMP. *Proc Natl Acad Sci USA* 1993; **90**: 5999-6003 [PMID: 8392184 DOI: 10.1073/pnas.90.13.5999]

44 **Hirschberg R**, Wang S. Proteinuria and growth factors in the development of tubulointerstitial injury and scarring in kidney disease. *Curr Opin Nephrol Hypertens* 2005; **14**: 43-52 [PMID: 15586015 DOI: 10.1097/00041552-200501000-00008]

45 **Kliem V**, Johnson RJ, Alpers CE, Yoshimura A, Couser WG, Koch KM, Floege J. Mechanisms involved in the pathogenesis of tubulointerstitial fibrosis in 5/6-nephrectomized rats. *Kidney Int* 1996; **49**: 666-678 [PMID: 8648907 DOI: 10.1038/ki.1996.95]

46 **Donadelli R**, Abbate M, Zanchi C, Corna D, Tomasoni S, Benigni A, Remuzzi G, Zoja C. Protein traffic activates NF-kB gene signaling and promotes MCP-1-dependent interstitial inflammation. *Am J Kidney Dis* 2000; **36**: 1226-1241 [PMID: 11096048]

47 **Shimizu H**, Maruyama S, Yuzawa Y, Kato T, Miki Y, Suzuki S, Sato W, Morita Y, Maruyama H, Egashira K, Matsuo S. Anti-monocyte chemoattractant protein-1 gene therapy attenuates renal injury induced by protein-overload proteinuria. *J Am Soc Nephrol* 2003; **14**: 1496-1505 [PMID: 12761250 DOI: 10.1097/01.ASN.0000069223.98703.8E]

48 **Bechtel W**, McGoohan S, Zeisberg EM, Müller GA, Kalbacher H, Salant DJ, Müller CA, Kalluri R, Zeisberg M. Methylation determines fibroblast activation and fibrogenesis in the kidney. *Nat Med* 2010; **16**: 544-550 [PMID: 20418885 DOI: 10.1038/nm.2135]

49 **Chen YX**, Li Y, Wang WM, Zhang W, Chen XN, Xie YY, Lu J, Huang QH, Chen N. Phosphoproteomic study of human tubular epithelial cell in response to transforming growth factor-beta-1-induced epithelial-to-mesenchymal transition. *Am J Nephrol* 2010; **31**: 24-35 [PMID: 19864886 DOI: 10.1159/000253865]

50 **Hu MC**, Shi M, Zhang J, Quiñones H, Kuro-o M, Moe OW. Klotho deficiency is an early biomarker of renal ischemia-reperfusion injury and its replacement is protective. *Kidney Int* 2010; **78**: 1240-1251 [PMID: 20861825 DOI: 10.1038/ki.2010.328]

51 **Shimizu H**, Bolati D, Adijiang A, Adelibieke Y, Muteliefu G, Enomoto A, Higashiyama Y, Higuchi Y, Nishijima F, Niwa T. Indoxyl sulfate downregulates renal expression of Klotho through production of ROS and activation of nuclear factor-ĸB. *Am J Nephrol* 2011; **33**: 319-324 [PMID: 21389697]

52 **Cantaluppi V**, Quercia AD, Dellepiane S, Ferrario S, Camussi G, Biancone L. Interaction between systemic inflammation and renal tubular epithelial cells. *Nephrol Dial Transplant* 2014; **29**: 2004-2011 [PMID: 24589723 DOI: 10.1093/ndt/gfu046]

53 **Karalliedde J**, Maltese G, Hill B, Viberti G, Gnudi L. Effect of renin-angiotensin system blockade on soluble Klotho in patients with type 2 diabetes, systolic hypertension, and albuminuria. *Clin J Am Soc Nephrol* 2013; **8**: 1899-1905 [PMID: 23929932 DOI: 10.2215/CJN.02700313]

54 **Yoon HE**, Choi BS. The renin-angiotensin system and aging in the kidney. *Korean J Intern Med* 2014; **29**: 291-295 [PMID: 24851061 DOI: 10.3904/kjim.2014.29.3.291]

55 **Komaba H**, Fukagawa M. Vitamin D and secreted Klotho: a long-awaited panacea for vascular calcification? *Kidney Int* 2012; **82**: 1248-1250 [PMID: 23203019 DOI: 10.1038/ki.2012.338]

56 **Mitani H**, Ishizaka N, Aizawa T, Ohno M, Usui S, Suzuki T, Amaki T, Mori I, Nakamura Y, Sato M, Nangaku M, Hirata Y, Nagai R. In vivo klotho gene transfer ameliorates angiotensin II-induced renal damage. *Hypertension* 2002; **39**: 838-843 [PMID: 11967236 DOI: 10.1161/01.HYP.0000013734.33441.EA]

57 **Chuang PY**, Menon MC, He JC. Molecular targets for treatment of kidney fibrosis. *J Mol Med* (Berl) 2013; **91**: 549-559 [PMID: 23179685 DOI: 10.1007/s00109-012-0983-z]

58 **Rutherford WE**, Blondin J, Miller JP, Greenwalt AS, Vavra JD. Chronic progressive renal disease: rate of change of serum creatinine concentration. *Kidney Int* 1977; **11**: 62-70 [PMID: 839654]

59 **Ziyadeh FN**, Hoffman BB, Han DC, Iglesias-De La Cruz MC, Hong SW, Isono M, Chen S, McGowan TA, Sharma K. Long-term prevention of renal insufficiency, excess matrix gene expression, and glomerular mesangial matrix expansion by treatment with monoclonal antitransforming growth factor-beta antibody in db/db diabetic mice. *Proc Natl Acad Sci USA* 2000; **97**: 8015-8020 [PMID: 10859350 DOI: 10.1073/pnas.120055097]

60 **Chen S**, Iglesias-de la Cruz MC, Jim B, Hong SW, Isono M, Ziyadeh FN. Reversibility of established diabetic glomerulopathy by anti-TGF-beta antibodies in db/db mice. *Biochem Biophys Res Commun* 2003; **300**: 16-22 [PMID: 12480514]

61 **Guan Q**, Li S, Gao S, Chen H, Nguan CY, Du C. Reduction of chronic rejection of renal allografts by anti-transforming growth factor-β antibody therapy in a rat model. *Am J Physiol Renal Physiol* 2013; **305**: F199-F207 [PMID: 23552866 DOI: 10.1152/ajprenal.00665.2012]

62 **Williams SJ**, Zammit SC, Cox AJ, Shackleford DM, Morizzi J, Zhang Y, Powell AK, Gilbert RE, Krum H, Kelly DJ. 3',4'-Bis-difluoromethoxycinnamoylanthranilate (FT061): an orally-active antifibrotic agent that reduces albuminuria in a rat model of progressive diabetic nephropathy. *Bioorg Med Chem Lett* 2013; **23**: 6868-6873 [PMID: 24169234 DOI: 10.1016/j.bmcl.2013.09.100]

63 **Sharma K**, McCue P, Dunn SR. Diabetic kidney disease in the db/db mouse. *Am J Physiol Renal Physiol* 2003; **284**: F1138-F1144 [PMID: 12736165 DOI: 10.1152/ajprenal.00315.2002]

64 **Negri AL**. Prevention of progressive fibrosis in chronic renal diseases: antifibrotic agents. *J Nephrol* 2004; **17**: 496-503 [PMID: 15372410]

65 **Zeisberg M**, Kalluri R. Reversal of experimental renal fibrosis by BMP7 provides insights into novel therapeutic strategies for chronic kidney disease. *Pediatr Nephrol* 2008; **23**: 1395-1398 [PMID: 18446379 DOI: 10.1007/s00467-008-0818-x]

66 **Declèves AE**, Sharma K. Novel targets of antifibrotic and anti-inflammatory treatment in CKD. *Nat Rev Nephrol* 2014; **10**: 257-267 [PMID: 24662433 DOI: 10.1038/nrneph.2014.31]

67 **Klahr S**, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994; **330**: 877-884 [PMID: 8114857 DOI: 10.1056/NEJM199403313301301]

68 **Menon V**, Kopple JD, Wang X, Beck GJ, Collins AJ, Kusek JW, Greene T, Levey AS, Sarnak MJ. Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis* 2009; **53**: 208-217 [PMID: 18950911 DOI: 10.1053/j.ajkd.2008.08.009]

69 **Bakris GL**, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; **36**: 646-661 [PMID: 10977801]

70 **Ruggenenti P**, Perna A, Remuzzi G. Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. *Kidney Int* 2003; **63**: 2254-2261 [PMID: 12753315 DOI: 10.1046/j.1523-1755.2003.00033.x]

71 **Ruggenenti P**, Perna A, Benini R, Bertani T, Zoccali C, Maggiore Q, Salvadori M, Remuzzi G. In chronic nephropathies prolonged ACE inhibition can induce remission: dynamics of time-dependent changes in GFR. Investigators of the GISEN Group. Gruppo Italiano Studi Epidemiologici in Nefrologia. *J Am Soc Nephrol* 1999; **10**: 997-1006 [PMID: 10232685]

72 **Bakris GL**. Slowing nephropathy progression: focus on proteinuria reduction. *Clin J Am Soc Nephrol* 2008; **3** Suppl 1: S3-10 [PMID: 18178794 DOI: 10.2215/CJN.03250807]

73 **Ruggenenti P**. Angiotensin-converting enzyme inhibition and angiotensin II antagonism in nondiabetic chronic nephropathies. *Semin Nephrol* 2004; **24**: 158-167 [PMID: 15017528]

74 **Sochett EB**, Cherney DZ, Curtis JR, Dekker MG, Scholey JW, Miller JA. Impact of renin angiotensin system modulation on the hyperfiltration state in type 1 diabetes. *J Am Soc Nephrol* 2006; **17**: 1703-1709 [PMID: 16672313 DOI: 10.1681/ASN.2005080872]

75 **Erman A**, Veksler S, Gafter U, Boner G, Wittenberg C, van Dijk DJ. Renin-angiotensin system blockade prevents the increase in plasma transforming growth factor beta 1, and reduces proteinuria and kidney hypertrophy in the streptozotocin-diabetic rat. *J Renin Angiotensin Aldosterone Syst* 2004; **5**: 146-151 [PMID: 15526251 DOI: 10.3317/jraas.2004.032]

76 **Scaglione R**, Argano C, Corrao S, Di Chiara T, Licata A, Licata G. Transforming growth factor beta1 and additional renoprotective effect of combination ACE inhibitor and angiotensin II receptor blocker in hypertensive subjects with minor renal abnormalities: a 24-week randomized controlled trial. *J Hypertens* 2005; **23**: 657-664 [PMID: 15716710 DOI: 10.1097/01.hjh.0000160225.01845.26]

77 **de Borst MH**, van Timmeren MM, Vaidya VS, de Boer RA, van Dalen MB, Kramer AB, Schuurs TA, Bonventre JV, Navis G, van Goor H. Induction of kidney injury molecule-1 in homozygous Ren2 rats is attenuated by blockade of the renin-angiotensin system or p38 MAP kinase. *Am J Physiol Renal Physiol* 2007; **292**: F313-F320 [PMID: 16896183]

78 **Vieitez P**, Gómez O, Uceda ER, Vera ME, Molina-Holgado E. Systemic and local effects of angiotensin II blockade in experimental diabetic nephropathy. *J Renin Angiotensin Aldosterone Syst* 2008; **9**: 96-102 [PMID: 18584585 DOI: 10.3317/jraas.2008.018]

79 **Capettini LS**, Montecucco F, Mach F, Stergiopulos N, Santos RA, da Silva RF. Role of renin-angiotensin system in inflammation, immunity and aging. *Curr Pharm Des* 2012; **18**: 963-970 [PMID: 22283774 DOI: 10.2174/138161212799436593]

80 **Zimmerman D**, Burns KD. Angiotensin-(1-7) in kidney disease: a review of the controversies. *Clin Sci* (Lond) 2012; **123**: 333-346 [PMID: 22639821 DOI: 10.1042/CS20120111]

81 **Velkoska E**, Dean RG, Burchill L, Levidiotis V, Burrell LM. Reduction in renal ACE2 expression in subtotal nephrectomy in rats is ameliorated with ACE inhibition. *Clin Sci* (Lond) 2010; **118**: 269-279 [PMID: 19698082 DOI: 10.1042/CS20090318]

82 **Schindler C**, Brosnihan KB, Ferrario CM, Bramlage P, Maywald U, Koch R, Oertel R, Kirch W. Comparison of inhibitory effects of irbesartan and atorvastatin treatment on the renin angiotensin system (RAS) in veins: a randomized double-blind crossover trial in healthy subjects. *J Clin Pharmacol* 2007; **47**: 112-120 [PMID: 17192509 DOI: 10.1177/0091270006294280]

83 **Bolignano D**, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev* 2014; **4**: CD007004 [PMID: 24782282 DOI: 10.1002/14651858.CD007004.pub3]

84 **Hirsch JS**, Drexler Y, Bomback AS. Aldosterone blockade in chronic kidney disease. *Semin Nephrol* 2014; **34**: 307-322 [PMID: 25016401 DOI: 10.1016/j.semnephrol.2014.04.006]

85 **Bakris GL**, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, Remuzzi G, Rossing P, Schmieder RE, Nowack C, Kolkhof P, Joseph A, Pieper A, Kimmeskamp-Kirschbaum N, Ruilope LM. Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy: A Randomized Clinical Trial. *JAMA* 2015; **314**: 884-894 [PMID: 26325557 DOI: 10.1001/jama.2015.1008]

86 **Mathialahan T**, Sandle GI. Dietary potassium and laxatives as regulators of colonic potassium secretion in end-stage renal disease. *Nephrol Dial Transplant* 2003; **18**: 341-347 [PMID: 12543890]

87 **Weir MR**, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ-Schmidt H, Berman L, Pitt B. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015; **372**: 211-221 [PMID: 25415805 DOI: 10.1056/NEJMoa]

88 **Packham DK**, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, Qunibi W, Pergola P, Singh B. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015; **372**: 222-231 [PMID: 25415807 DOI: 10.1056/NEJMoa1411487]

89 **McGowan CE**, Saha S, Chu G, Resnick MB, Moss SF. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. *South Med J* 2009; **102**: 493-497 [PMID: 19373153 DOI: 10.1097/SMJ.0b013e31819e8978]

90 **Chatelain D**, Brevet M, Manaouil D, Yzet T, Regimbeau JM, Sevestre H. Rectal stenosis caused by foreign body reaction to sodium polystyrene sulfonate crystals (Kayexalate). *Ann Diagn Pathol* 2007; **11**: 217-219 [PMID: 17498597 DOI: 10.1016/j.anndiagpath.2006.02.001]

91 **KDIGO Blood Pressure Work Group**. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2012; **2** (Suppl): 337–414

92 **Schrier RW**, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, Winklhofer FT, Brosnahan G, Czarnecki PG, Hogan MC, Miskulin DC, Rahbari-Oskoui FF, Grantham JJ, Harris PC, Flessner MF, Bae KT, Moore CG, Chapman AB. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med* 2014; **371**: 2255-2266 [PMID: 25399733 DOI: 10.1056/NEJMoa1402685]

93 **Fioretto P**, Sutherland DE, Najafian B, Mauer M. Remodeling of renal interstitial and tubular lesions in pancreas transplant recipients. *Kidney Int* 2006; **69**: 907-912 [PMID: 16518350 DOI: 10.1038/sj.ki.5000153]

94 **Shurraw S**, Hemmelgarn B, Lin M, Majumdar SR, Klarenbach S, Manns B, Bello A, James M, Turin TC, Tonelli M. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. *Arch Intern Med* 2011; **171**: 1920-1927 [PMID: 22123800 DOI: 10.1001/archinternmed.2011.537]

95 **Lee CL**, Li TC, Lin SY, Wang JS, Lee IT, Tseng LN, Song YM, Tsai SF, Sheu WH. Dynamic and dual effects of glycated hemoglobin on estimated glomerular filtration rate in type 2 diabetic outpatients. *Am J Nephrol* 2013; **38**: 19-26 [PMID: 23817017 DOI: 10.1159/000351803]

96 **Haynes R**, Wanner C. Chronic kidney disease: Statins in chronic kidney disease: time to move on? *Nat Rev Nephrol* 2015; **11**: 262-263 [PMID: 25802077 DOI: 10.1038/nrneph.2015.36]

97 **Altemtam N**, Russell J, El Nahas M. A study of the natural history of diabetic kidney disease (DKD). *Nephrol Dial Transplant* 2012; **27**: 1847-1854 [PMID: 22058177 DOI: 10.1093/ndt/gfr561]

98 **Shi Y**, Chen W, Jalal D, Li Z, Chen W, Mao H, Yang Q, Johnson RJ, Yu X. Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. *Kidney Blood Press Res* 2012; **35**: 153-160 [PMID: 22116196 DOI: 10.1159/000331453]

99 **Ohno I**, Hosoya T, Gomi H, Ichida K, Okabe H, Hikita M. Serum uric acid and renal prognosis in patients with IgA nephropathy. *Nephron* 2001; **87**: 333-339 [PMID: 11287777 DOI: 10.1159/000045939]

100 **Nacak H**, van Diepen M, Qureshi AR, Carrero JJ, Stijnen T, Dekker FW, Evans M. Uric acid is not associated with decline in renal function or time to renal replacement therapy initiation in a referred cohort of patients with Stage III, IV and V chronic kidney disease. *Nephrol Dial Transplant* 2015; **30**: 2039-2045 [PMID: 26185050 DOI: 10.1093/ndt/gfv225]

101 **Rodenbach KE**, Schneider MF, Furth SL, Moxey-Mims MM, Mitsnefes MM, Weaver DJ, Warady BA, Schwartz GJ. Hyperuricemia and Progression of CKD in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort Study. *Am J Kidney Dis* 2015; **66**: 984-992 [PMID: 26209544 DOI: 10.1053/j.ajkd.2015.06.015]

102 **Goicoechea M**, Garcia de Vinuesa S, Verdalles U, Verde E, Macias N, Santos A, Pérez de Jose A, Cedeño S, Linares T, Luño J. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis* 2015; **65**: 543-549 [PMID: 25595565]

103 **Kanji T**, Gandhi M, Clase CM, Yang R. Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis. *BMC Nephrol* 2015; **16**: 58 [PMID: 25928556 DOI: 10.1186/s12882-015-0047-z]

104 **Sircar D**, Chatterjee S, Waikhom R, Golay V, Raychaudhury A, Chatterjee S, Pandey R. Efficacy of Febuxostat for Slowing the GFR Decline in Patients With CKD and Asymptomatic Hyperuricemia: A 6-Month, Double-Blind, Randomized, Placebo-Controlled Trial. *Am J Kidney Dis* 2015; **66**: 945-950 [PMID: 26233732 DOI: 10.1053/j.ajkd.2015.05.017]

105 **de Brito-Ashurst I**, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009; **20**: 2075-2084 [PMID: 19608703 DOI: 10.1681/ASN.2008111205]

106 **Jeong J**, Kwon SK, Kim HY. Effect of bicarbonate supplementation on renal function and nutritional indices in predialysis advanced chronic kidney disease. *Electrolyte Blood Press* 2014; **12**: 80-87 [PMID: 25606047 DOI: 10.5049/EBP.2014.12.2.80]

107 **Barsotti G**, Giannoni A, Morelli E, Lazzeri M, Vlamis I, Baldi R, Giovannetti S. The decline of renal function slowed by very low phosphorus intake in chronic renal patients following a low nitrogen diet. *Clin Nephrol* 1984; **21**: 54-59 [PMID: 6705274]

108 **Lezaic V**, Tirmenstajn-Jankovic B, Bukvic D, Vujisic B, Perovic M, Novakovic N, Dopsaj V, Maric I, Djukanovic Lj. Efficacy of hyperphosphatemia control in the progression of chronic renal failure and the prevalence of cardiovascular calcification. *Clin Nephrol* 2009; **71**: 21-29 [PMID: 19203546 DOI: 10.5414/CNP71021]

109 **Voormolen N**, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, Boeschoten EW, Huisman RM, Krediet RT, Dekker FW. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrol Dial Transplant* 2007; **22**: 2909-2916 [PMID: 17517792 DOI: 10.1093/ndt/gfm286]

110 **Da J**, Xie X, Wolf M, Disthabanchong S, Wang J, Zha Y, Lv J, Zhang L, Wang H. Serum Phosphorus and Progression of CKD and Mortality: A Meta-analysis of Cohort Studies. *Am J Kidney Dis* 2015; **66**: 258-265 [PMID: 25804679 DOI: 10.1053/j.ajkd.2015.01.009]

111 **Six I**, Maizel J, Barreto FC, Rangrez AY, Dupont S, Slama M, Tribouilloy C, Choukroun G, Mazière JC, Bode-Boeger S, Kielstein JT, Drüeke TB, Massy ZA. Effects of phosphate on vascular function under normal conditions and influence of the uraemic state. *Cardiovasc Res* 2012; **96**: 130-139 [PMID: 22822101 DOI: 10.1093/cvr/cvs240]

112 **Reynolds JL**, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnen-Dechent W, Weissberg PL, Shanahan CM. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. *J Am Soc Nephrol* 2004; **15**: 2857-2867 [PMID: 15504939 DOI: 10.1097/01.ASN.0000141960.01035.28]

113 **Smith ER**, Hanssen E, McMahon LP, Holt SG. Fetuin-A-containing calciprotein particles reduce mineral stress in the macrophage. *PLoS One* 2013; **8**: e60904 [PMID: 23577176 DOI: 10.1371/journal.pone.0060904]

114 **Smith ER**, Ford ML, Tomlinson LA, Rajkumar C, McMahon LP, Holt SG. Phosphorylated fetuin-A-containing calciprotein particles are associated with aortic stiffness and a procalcific milieu in patients with pre-dialysis CKD. *Nephrol Dial Transplant* 2012; **27**: 1957-1966 [PMID: 22105144 DOI: 10.1093/ndt/gfr609]

115 **Smith ER**. The Isolation and Quantitation of Fetuin-A-Containing Calciprotein Particles from Biological Fluids. *Methods Mol Biol* 2016; **1397**: 221-240 [PMID: 26676136 DOI: 10.1007/978-1-4939-3353-2\_15]

116 **Adema AY**, de Borst MH, Ter Wee PM, Vervloet MG. Dietary and pharmacological modification of fibroblast growth factor-23 in chronic kidney disease. *J Ren Nutr* 2014; **24**: 143-150 [PMID: 24216259 DOI: 10.1053/j.jrn.2013.09.001]

117 **Block GA**, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, Allison MA, Asplin J, Smits G, Hoofnagle AN, Kooienga L, Thadhani R, Mannstadt M, Wolf M, Chertow GM. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol* 2012; **23**: 1407-1415 [PMID: 22822075 DOI: 10.1681/ASN.2012030223]

118 **Locatelli F**, Del Vecchio L, Violo L, Pontoriero G. Phosphate binders for the treatment of hyperphosphatemia in chronic kidney disease patients on dialysis: a comparison of safety profiles. *Expert Opin Drug Saf* 2014; **13**: 551-561 [PMID: 24702470 DOI: 10.1517/14740338.2014.907791]

119 **Floege J**, Ketteler M. Vascular calcification in patients with end-stage renal disease. *Nephrol Dial Transplant* 2004; **19** Suppl 5: V59-V66 [PMID: 15284362 DOI: 10.1093/ndt/gfh1058]

120 **London GM**, Marchais SJ, Guérin AP, Boutouyrie P, Métivier F, de Vernejoul MC. Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol* 2008; **19**: 1827-1835 [PMID: 18480316 DOI: 10.1681/ASN.2007050622]

121 **Cozzolino M**, Rizzo MA, Stucchi A, Cusi D, Gallieni M. Sevelamer for hyperphosphataemia in kidney failure: controversy and perspective. *Ther Adv Chronic Dis* 2012; **3**: 59-68 [PMID: 23251769 DOI: 10.1177/2040622311433771]

122 **Di Iorio B**, Bellasi A, Russo D. Mortality in kidney disease patients treated with phosphate binders: a randomized study. *Clin J Am Soc Nephrol* 2012; **7**: 487-493 [PMID: 22241819 DOI: 10.2215/CJN.03820411]

123 **Massy ZA**, Maizel J. [Pleiotropic effects of sevelamer: a model of intestinal tract chelating agent]. *Nephrol Ther* 2014; **10**: 441-450 [PMID: 25070605 DOI: 10.1016/j.nephro.2014.04.001]

124 **Ferramosca E**, Burke S, Chasan-Taber S, Ratti C, Chertow GM, Raggi P. Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients. *Am Heart J* 2005; **149**: 820-825 [PMID: 15894962]

125 **Navarro-González JF**, Mora-Fernández C, Muros de Fuentes M, Donate-Correa J, Cazaña-Pérez V, García-Pérez J. Effect of phosphate binders on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients. *Clin J Am Soc Nephrol* 2011; **6**: 2272-2279 [PMID: 21784820 DOI: 10.2215/CJN.01650211]

126 **Garg JP**, Chasan-Taber S, Blair A, Plone M, Bommer J, Raggi P, Chertow GM. Effects of sevelamer and calcium-based phosphate binders on uric acid concentrations in patients undergoing hemodialysis: a randomized clinical trial. *Arthritis Rheum* 2005; **52**: 290-295 [PMID: 15641045 DOI: 10.1002/art.20781]

127 **Zayed BM**, Fishawy H, Al-Shihaby AR, Salem MA3, Sharaf El Din UA1, Salem MM efficacy of sevelamer hydrochloride and calcium carbonate as phosphate binders on FGF23 and coronary calcification in hemodialysis patients. WCN, Cape Town, South Aferica March 13-15, 2015. Available from: URL: http://www.abstracts2view.com/wcn/lookup\_view.php?word=Zayed&where=authors&return=/wcn/authorindex.php?num=25

128 **Oliveira RB**, Cancela AL, Graciolli FG, Dos Reis LM, Draibe SA, Cuppari L, Carvalho AB, Jorgetti V, Canziani ME, Moysés RM. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? *Clin J Am Soc Nephrol* 2010; **5**: 286-291 [PMID: 19965540 DOI: 10.2215/CJN.05420709]

129 **Lin HH**, Liou HH, Wu MS, Lin CY, Huang CC. Long-term sevelamer treatment lowers serum fibroblast growth factor 23 accompanied with increasing serum Klotho levels in chronic haemodialysis patients. *Nephrology* (Carlton) 2014; **19**: 672-678 [PMID: 25113414 DOI: 10.1111/nep.12319]

130 **Rastogi A**. Sevelamer revisited: pleiotropic effects on endothelial and cardiovascular risk factors in chronic kidney disease and end-stage renal disease. *Ther Adv Cardiovasc Dis* 2013; **7**: 322-342 [PMID: 24327730 DOI: 10.1177/1753944713513061]

131 **Ossareh S**. Clinical and economic aspects of sevelamer therapy in end-stage renal disease patients. *Int J Nephrol Renovasc Dis* 2014; **7**: 161-168 [PMID: 24855385 DOI: 10.2147/IJNRD.S41626]

132 **Ruggeri M**, Cipriani F, Bellasi A, Russo D, Di Iorio B. Sevelamer is cost-saving vs. calcium carbonate in non-dialysis-dependent CKD patients in italy: a patient-level cost-effectiveness analysis of the INDEPENDENT study. *Blood Purif* 2014; **37**: 316-324 [PMID: 25171148 DOI: 10.1159/000365746]

133 **Toussaint ND**, Lau KK, Polkinghorne KR, Kerr PG. Attenuation of aortic calcification with lanthanum carbonate versus calcium-based phosphate binders in haemodialysis: A pilot randomized controlled trial. *Nephrology* (Carlton) 2011; **16**: 290-298 [PMID: 21342323 DOI: 10.1111/j.1440-1797.2010.01412.x]

134 **Zhang C**, Wen J, Li Z, Fan J. Efficacy and safety of lanthanum carbonate on chronic kidney disease-mineral and bone disorder in dialysis patients: a systematic review. *BMC Nephrol* 2013; **14**: 226 [PMID: 24134531 DOI: 10.1186/1471-2369-14-226]

135 **Finn WF**. Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. *Clin Nephrol* 2006; **65**: 191-202 [PMID: 16550750 DOI: 10.5414/CNP65191]

136 **Ureña-Torres P**, Prié D, Keddad K, Preston P, Wilde P, Wan H, Copley JB. Changes in fibroblast growth factor 23 levels in normophosphatemic patients with chronic kidney disease stage 3 treated with lanthanum carbonate: results of the PREFECT study, a phase 2a, double blind, randomized, placebo-controlled trial. *BMC Nephrol* 2014; **15**: 71 [PMID: 24885942 DOI: 10.1186/1471-2369-15-71]

137 **Isakova T**, Barchi-Chung A, Enfield G, Smith K, Vargas G, Houston J, Xie H, Wahl P, Schiavenato E, Dosch A, Gutiérrez OM, Diego J, Lenz O, Contreras G, Mendez A, Weiner RB, Wolf M. Effects of dietary phosphate restriction and phosphate binders on FGF23 levels in CKD. *Clin J Am Soc Nephrol* 2013; **8**: 1009-1018 [PMID: 23471131 DOI: 10.2215/CJN.09250912]

138 **Gonzalez-Parra E**, Gonzalez-Casaus ML, Galán A, Martinez-Calero A, Navas V, Rodriguez M, Ortiz A. Lanthanum carbonate reduces FGF23 in chronic kidney disease Stage 3 patients. *Nephrol Dial Transplant* 2011; **26**: 2567-2571 [PMID: 21436379 DOI: 10.1093/ndt/gfr144]

139 **Soriano S**, Ojeda R, Rodríguez M, Almadén Y, Rodríguez M, Martín-Malo A, Aljama P. The effect of phosphate binders, calcium and lanthanum carbonate on FGF23 levels in chronic kidney disease patients. *Clin Nephrol* 2013; **80**: 17-22 [PMID: 23391319 DOI: 10.5414/CN107764]

140 **Negri AL**, Ureña Torres PA. Iron-based phosphate binders: do they offer advantages over currently available phosphate binders? *Clin Kidney J* 2015; **8**: 161-167 [PMID: 25815172 DOI: 10.1093/ckj/sfu139]

141 **Floege J**, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S, Lisk LJ, Sprague SM. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. *Kidney Int* 2014; **86**: 638-647 [PMID: 24646861 DOI: 10.1038/ki.2014.58]

142 **Lenglet A**, Liabeuf S, Guffroy P, Fournier A, Brazier M, Massy ZA. Use of nicotinamide to treat hyperphosphatemia in dialysis patients. *Drugs R D* 2013; **13**: 165-173 [PMID: 24000048 DOI: 10.1007/s40268-013-0024-6]

143 **Takahashi Y**, Tanaka A, Nakamura T, Fukuwatari T, Shibata K, Shimada N, Ebihara I, Koide H. Nicotinamide suppresses hyperphosphatemia in hemodialysis patients. *Kidney Int* 2004; **65**: 1099-1104 [PMID: 14871431 DOI: 10.1111/j.1523-1755.2004.00482.x]

144 **Cheng SC**, Young DO, Huang Y, Delmez JA, Coyne DW. A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in hemodialysis patients. *Clin J Am Soc Nephrol* 2008; **3**: 1131-1138 [PMID: 18385391 DOI: 10.2215/CJN.04211007]

145 **Nomiyama H**, Yoshie O. Functional roles of evolutionary conserved motifs and residues in vertebrate chemokine receptors. *J Leukoc Biol* 2015; **97**: 39-47 [PMID: 25416815 DOI: 10.1189/jlb.2RU0614-290R]

146 **Anders HJ**, Ninichuk V, Schlöndorff D. Progression of kidney disease: blocking leukocyte recruitment with chemokine receptor CCR1 antagonists. *Kidney Int* 2006; **69**: 29-32 [PMID: 16374420 DOI: 10.1038/sj.ki.5000053]

147 **Ninichuk V**, Gross O, Reichel C, Khandoga A, Pawar RD, Ciubar R, Segerer S, Belemezova E, Radomska E, Luckow B, Perez de Lema G, Murphy PM, Gao JL, Henger A, Kretzler M, Horuk R, Weber M, Krombach F, Schlöndorff D, Anders HJ. Delayed chemokine receptor 1 blockade prolongs survival in collagen 4A3-deficient mice with Alport disease. *J Am Soc Nephrol* 2005; **16**: 977-985 [PMID: 15716328 DOI: 10.1681/ASN.2004100871]

148 **Eis V**, Luckow B, Vielhauer V, Siveke JT, Linde Y, Segerer S, Perez De Lema G, Cohen CD, Kretzler M, Mack M, Horuk R, Murphy PM, Gao JL, Hudkins KL, Alpers CE, Gröne HJ, Schlöndorff D, Anders HJ. Chemokine receptor CCR1 but not CCR5 mediates leukocyte recruitment and subsequent renal fibrosis after unilateral ureteral obstruction. *J Am Soc Nephrol* 2004; **15**: 337-347 [PMID: 14747380 DOI: 10.1097/01.ASN.0000111246.87175.32]

149 **Anders HJ**, Frink M, Linde Y, Banas B, Wörnle M, Cohen CD, Vielhauer V, Nelson PJ, Gröne HJ, Schlöndorff D. CC chemokine ligand 5/RANTES chemokine antagonists aggravate glomerulonephritis despite reduction of glomerular leukocyte infiltration. *J Immunol* 2003; **170**: 5658-5666 [PMID: 12759447 DOI: 10.4049/jimmunol.170.11.5658]

150 **Shimizu S**, Nakashima H, Karube K, Ohshima K, Egashira K. Monocyte chemoattractant protein-1 activates a regional Th1 immunoresponse in nephritis of MRL/lpr mice. *Clin Exp Rheumatol* 2005; **23**: 239-242 [PMID: 15895897]

151 **Ninichuk V**, Khandoga AG, Segerer S, Loetscher P, Schlapbach A, Revesz L, Feifel R, Khandoga A, Krombach F, Nelson PJ, Schlöndorff D, Anders HJ. The role of interstitial macrophages in nephropathy of type 2 diabetic db/db mice. *Am J Pathol* 2007; **170**: 1267-1276 [PMID: 17392166 DOI: 10.2353/ajpath.2007.060937]

152 **Oberthür D**, Achenbach J, Gabdulkhakov A, Buchner K, Maasch C, Falke S, Rehders D, Klussmann S, Betzel C. Crystal structure of a mirror-image L-RNA aptamer (Spiegelmer) in complex with the natural L-protein target CCL2. *Nat Commun* 2015; **6**: 6923 [PMID: 25901662 DOI: 10.1038/ncomms7923]

153 **Haller HG**, Menne J, Eulberg D, Baumann M. Anti-infl ammatory and Renoprotective Effects of CCL2 Inhibition with Emapticap Pegol (NOX-E36) in Type 2 Diabetic Patients with Albuminuria, ASN 2014 Abstract book, abstract no. FR-OR120, 2014; 25: 76. Abstract Edition. Available from: URL: https://www.asn-online.org/api/download/?file=/.../KW14Abstracts.pdf

154 **de Zeeuw D**, Bekker P, Henkel E, Hasslacher C, Gouni-Berthold I, Mehling H, Potarca A, Tesar V, Heerspink HJ, Schall TJ. The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial. *Lancet Diabetes Endocrinol* 2015; **3**: 687-696 [PMID: 26268910 DOI: 10.1016/S2213-8587(15)00261-2]

155 **Xiao H**, Dairaghi DJ, Powers JP, Ertl LS, Baumgart T, Wang Y, Seitz LC, Penfold ME, Gan L, Hu P, Lu B, Gerard NP, Gerard C, Schall TJ, Jaen JC, Falk RJ, Jennette JC. C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol* 2014; **25**: 225-231 [PMID: 24179165]

156 **Ghorbani A**, Omidvar B, Beladi-Mousavi SS, Lak E, Vaziri S. The effect of pentoxifylline on reduction of proteinuria among patients with type 2 diabetes under blockade of angiotensin system: a double blind and randomized clinical trial. *Nefrologia* 2012; **32**: 790-796 [PMID: 23169362 DOI: 10.3265/Nefrologia.pre2012.Jun.11242]

157 **Navarro-González JF**, Mora-Fernández C, Muros de Fuentes M, Chahin J, Méndez ML, Gallego E, Macía M, del Castillo N, Rivero A, Getino MA, García P, Jarque A, García J. Effect of pentoxifylline on renal function and urinary albumin excretion in patients with diabetic kidney disease: the PREDIAN trial. *J Am Soc Nephrol* 2015; **26**: 220-229 [PMID: 24970885 DOI: 10.1681/ASN.2014010012]

158 **Shroff R**, Aitkenhead H, Costa N, Trivelli A, Litwin M, Picca S, Anarat A, Sallay P, Ozaltin F, Zurowska A, Jankauskiene A, Montini G, Charbit M, Schaefer F, Wühl E. Normal 25-Hydroxyvitamin D Levels Are Associated with Less Proteinuria and Attenuate Renal Failure Progression in Children with CKD. *J Am Soc Nephrol* 2016; **27**: 314-322 [PMID: 26069294 DOI: 10.1681/ASN.2014090947]

159 **Sanchez-Niño MD**, Bozic M, Córdoba-Lanús E, Valcheva P, Gracia O, Ibarz M, Fernandez E, Navarro-Gonzalez JF, Ortiz A, Valdivielso JM. Beyond proteinuria: VDR activation reduces renal inflammation in experimental diabetic nephropathy. *Am J Physiol Renal Physiol* 2012; **302**: F647-F657 [PMID: 22169009 DOI: 10.1152/ajprenal.00090.2011]

160 **de Zeeuw D**, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T, Parving HH, Pritchett Y, Remuzzi G, Ritz E, Andress D. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. *Lancet* 2010; **376**: 1543-1551 [PMID: 21055801 DOI: 10.1016/S0140-6736(10)61032-X]

161 **Pérez-Gómez MV**, Ortiz-Arduán A, Lorenzo-Sellares V. Vitamin D and proteinuria: a critical review of molecular bases and clinical experience. *Nefrologia* 2013; **33**: 716-726 [PMID: 24089164 DOI: 10.3265/Nefrologia.pre2013.Apr.12025]

162 **Ritter CS**, Zhang S, Delmez J, Finch JL, Slatopolsky E. Differential expression and regulation of Klotho by paricalcitol in the kidney, parathyroid, and aorta of uremic rats. *Kidney Int* 2015; **87**: 1141-1152 [PMID: 25692955 DOI: 10.1038/ki.2015.22]

163 **Matsumura Y**, Aizawa H, Shiraki-Iida T, Nagai R, Kuro-o M, Nabeshima Y. Identification of the human klotho gene and its two transcripts encoding membrane and secreted klotho protein. *Biochem Biophys Res Commun* 1998; **242**: 626-630 [PMID: 9464267 DOI: 10.1006/bbrc.1997.8019]

164 **Imura A**, Iwano A, Tohyama O, Tsuji Y, Nozaki K, Hashimoto N, Fujimori T, Nabeshima Y. Secreted Klotho protein in sera and CSF: implication for post-translational cleavage in release of Klotho protein from cell membrane. *FEBS Lett* 2004; **565**: 143-147 [PMID: 15135068 DOI: 10.1016/j.febslet.2004.03.090]

165 **Hofman-Bang J**, Martuseviciene G, Santini MA, Olgaard K, Lewin E. Increased parathyroid expression of klotho in uremic rats. *Kidney Int* 2010; **78**: 1119-1127 [PMID: 20631679 DOI: 10.1038/ki.2010.215]

166 **Takeshita K**, Fujimori T, Kurotaki Y, Honjo H, Tsujikawa H, Yasui K, Lee JK, Kamiya K, Kitaichi K, Yamamoto K, Ito M, Kondo T, Iino S, Inden Y, Hirai M, Murohara T, Kodama I, Nabeshima Y. Sinoatrial node dysfunction and early unexpected death of mice with a defect of klotho gene expression. *Circulation* 2004; **109**: 1776-1782 [PMID: 15037532]

167 **Hu MC**, Shi M, Zhang J, Addo T, Cho HJ, Barker SL, Ravikumar P, Gillings N, Bian A, Sidhu SS, Kuro-O M, Moe OW. Renal Production, Uptake, and Handling of Circulating αKlotho. *J Am Soc Nephrol* 2016; **27**: 79-90 [PMID: 25977312 DOI: 10.1681/ASN.2014101030]

168 **Buendía P**, Carracedo J, Soriano S, Madueño JA, Ortiz A, Martín-Malo A, Aljama P, Ramírez R. Klotho Prevents NFκB Translocation and Protects Endothelial Cell From Senescence Induced by Uremia. *J Gerontol A Biol Sci Med Sci* 2015; **70**: 1198-1209 [PMID: 25246106 DOI: 10.1093/gerona/glu170]

169 **Zhou L**, Mo H, Miao J, Zhou D, Tan RJ, Hou FF, Liu Y. Klotho Ameliorates Kidney Injury and Fibrosis and Normalizes Blood Pressure by Targeting the Renin-Angiotensin System. *Am J Pathol* 2015; **185**: 3211-3223 [PMID: 26475416 DOI: 10.1016/j.ajpath.2015.08.004]

170 **Kohan DE**, Lambers Heerspink HJ, Coll B, Andress D, Brennan JJ, Kitzman DW, Correa-Rotter R, Makino H, Perkovic V, Hou FF, Remuzzi G, Tobe SW, Toto R, Parving HH, de Zeeuw D. Predictors of Atrasentan-Associated Fluid Retention and Change in Albuminuria in Patients with Diabetic Nephropathy. *Clin J Am Soc Nephrol* 2015; **10**: 1568-1574 [PMID: 26153128 DOI: 10.2215/CJN.00570115]

171 **Vaziri ND**. CKD impairs barrier function and alters microbial flora of the intestine: a major link to inflammation and uremic toxicity. *Curr Opin Nephrol Hypertens* 2012; **21**: 587-592 [PMID: 23010760 DOI: 10.1097/MNH.0b013e328358c8d5]

172 **Xu G**, Luo K, Liu H, Huang T, Fang X, Tu W. The progress of inflammation and oxidative stress in patients with chronic kidney disease. *Ren Fail* 2015; **37**: 45-49 [PMID: 25375354 DOI: 10.3109/0886022X.2014.964141]

173 **Stenvinkel P**, Alvestrand A. Inflammation in end-stage renal disease: sources, consequences, and therapy. *Semin Dial* 2002; **15**: 329-337 [PMID: 12358637 DOI: 10.1046/j.1525-139X.2002.00083.x]

174 **Kim HJ**, Vaziri ND. Contribution of impaired Nrf2-Keap1 pathway to oxidative stress and inflammation in chronic renal failure. *Am J Physiol Renal Physiol* 2010; **298**: F662-F671 [PMID: 20007347 DOI: 10.1152/ajprenal.00421.2009]

175 **de Zeeuw D**, Akizawa T, Audhya P, Bakris GL, Chin M, Christ-Schmidt H, Goldsberry A, Houser M, Krauth M, Lambers Heerspink HJ, McMurray JJ, Meyer CJ, Parving HH, Remuzzi G, Toto RD, Vaziri ND, Wanner C, Wittes J, Wrolstad D, Chertow GM. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med* 2013; **369**: 2492-2503 [PMID: 24206459 DOI: 10.1056/NEJMoa1306033]

176 [**Wing MR**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Wing%20MR%5BAuthor%5D&cauthor=true&cauthor_uid=26337794), [Patel SS](http://www.ncbi.nlm.nih.gov/pubmed/?term=Patel%20SS%5BAuthor%5D&cauthor=true&cauthor_uid=26337794), [Ramezani A](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ramezani%20A%5BAuthor%5D&cauthor=true&cauthor_uid=26337794), [Raj DS](http://www.ncbi.nlm.nih.gov/pubmed/?term=Raj%20DS%5BAuthor%5D&cauthor=true&cauthor_uid=26337794). Gut microbiome in chronic kidney disease. *Exp Physiol* 2015 [PMID: 26337794 DOI: 10.1113/EP085283]

177 **Koppe L**, Mafra D, Fouque D. Probiotics and chronic kidney disease. *Kidney Int* 2015; **88**: 958-966 [PMID: 26376131 DOI: 10.1038/ki.2015.255]

178 **Mishima E**, Fukuda S, Shima H, Hirayama A, Akiyama Y, Takeuchi Y, Fukuda NN, Suzuki T, Suzuki C, Yuri A, Kikuchi K, Tomioka Y, Ito S, Soga T, Abe T. Alteration of the Intestinal Environment by Lubiprostone Is Associated with Amelioration of Adenine-Induced CKD. *J Am Soc Nephrol* 2015; **26**: 1787-1794 [PMID: 25525179 DOI: 10.1681/ASN.2014060530]

179 **Ramezani A**, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol* 2014; **25**: 657-670 [PMID: 24231662 DOI: 10.1681/ASN.2013080905]

180 **Lallès JP**. Intestinal alkaline phosphatase: novel functions and protective effects. *Nutr Rev* 2014; **72**: 82-94 [PMID: 24506153 DOI: 10.1111/nure.12082]

181 **Pickkers P**, Heemskerk S, Schouten J, Laterre PF, Vincent JL, Beishuizen A, Jorens PG, Spapen H, Bulitta M, Peters WH, van der Hoeven JG. Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial. *Crit Care* 2012; **16**: R14 [PMID: 22269279 DOI: 10.1186/cc11159]

182 **Prakash UN**, Srinivasan K. Beneficial influence of dietary spices on the ultrastructure and fluidity of the intestinal brush border in rats. *Br J Nutr* 2010; **104**: 31-39 [PMID: 20178671 DOI: 10.1017/S0007114510000334]

183 **Ghosh SS**, Gehr TW, Ghosh S. Curcumin and chronic kidney disease (CKD): major mode of action through stimulating endogenous intestinal alkaline phosphatase. *Molecules* 2014; **19**: 20139-20156 [PMID: 25474287 DOI: 10.3390/molecules191220139]

184 **Montemurno E**, Cosola C, Dalfino G, Daidone G, De Angelis M, Gobbetti M, Gesualdo L. What would you like to eat, Mr CKD Microbiota? A Mediterranean Diet, please! *Kidney Blood Press Res* 2014; **39**: 114-123 [PMID: 25117687 DOI: 10.1159/000355785]

185 **Brun LR**, Brance ML, Rigalli A. Luminal calcium concentration controls intestinal calcium absorption by modification of intestinal alkaline phosphatase activity. *Br J Nutr* 2012; **108**: 229-233 [PMID: 22018098 DOI: 10.1017/S0007114511005617]

186 **Mineo H**, Morikawa N, Ohmi S, Ishida K, Machida A, Kanazawa T, Chiji H, Fukushima M, Noda T. Ingestion of potato starch containing esterified phosphorus increases alkaline phosphatase activity in the small intestine in rats. *Nutr Res* 2010; **30**: 341-347 [PMID: 20579526 DOI: 10.1016/j.nutres.2010.05.003]

187 **Moore RJ**, Reeves PG, Veum TL. Influence of dietary phosphorus and sulphaguanidine levels on P utilization in rats. *Br J Nutr* 1984; **51**: 453-465 [PMID: 6326799 DOI: 10.1079/BJN19840051]

188 **Sogabe N**, Maruyama R, Hosori T, Goseki-Sone M. Enhancement effects of vitamin K1 (phylloquinone) or vitamin K2 (menaquinone-4) on intestinal alkaline phosphatase activity in rats. *J Nutr Sci Vitaminol* (Tokyo) 2007; **53**: 219-224 [PMID: 17874826 DOI: 10.3177/jnsv.53.219]

189 **Ding W**, Wang B, Zhang M, Gu Y. Tempol, a Superoxide Dismutase-Mimetic Drug, Ameliorates Progression of Renal Disease in CKD Mice. *Cell Physiol Biochem* 2015; **36**: 2170-2182 [PMID: 26279424 DOI: 10.1159/000430183]

190 **Park SY**, Rhee SY, Oh S, Kwon HS, Cha BY, Lee HJ, Lee HC, Kim YS. Evaluation of the effectiveness of sarpogrelate on the surrogate markers for macrovascular complications in patients with type 2 diabetes. *Endocr J* 2012; **59**: 709-716 [PMID: 22673600 DOI: 10.1507/endocrj.EJ12-0047]

191 **Perez-Gomez MV**, Sanchez-Niño MD, Sanz AB, Martín-Cleary C, Ruiz-Ortega M, Egido J, Navarro-González JF, Ortiz A, Fernandez-Fernandez B. Horizon 2020 in Diabetic Kidney Disease: The Clinical Trial Pipeline for Add-On Therapies on Top of Renin Angiotensin System Blockade. *J Clin Med* 2015; **4**: 1325-1347 [PMID: 26239562 DOI: 10.3390/jcm4061325]

192 **Ogawa S**, Mori T, Nako K, Ishizuka T, Ito S. Reduced albuminuria with sarpogrelate is accompanied by a decrease in monocyte chemoattractant protein-1 levels in type 2 diabetes. *Clin J Am Soc Nephrol* 2008; **3**: 362-368 [PMID: 18235151 DOI: 10.2215/CJN.03450807]

193 **Grantham JJ**. Clinical practice. Autosomal dominant polycystic kidney disease. *N Engl J Med* 2008; **359**: 1477-1485 [PMID: 18832246 DOI: 10.1056/NEJMcp0804458]

194 **Deltas C**, Felekkis K. Is suppression of cyst growth in PKD enough to preserve renal function?: STAT6 inhibition is a novel promising target. *JAKSTAT* 2012; **1**: 216-218 [PMID: 24058776 DOI: 10.4161/jkst.21634]

195 **Mochizuki T**, Tsuchiya K, Nitta K. Autosomal dominant polycystic kidney disease: recent advances in pathogenesis and potential therapies. *Clin Exp Nephrol* 2013; **17**: 317-326 [PMID: 23192769 DOI: 10.1007/s10157-012-0741-0]

196 **Gattone VH**, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat Med* 2003; **9**: 1323-1326 [PMID: 14502283 DOI: 10.1038/nm935]

197 **Dember LM**. Amyloidosis-associated kidney disease. *J Am Soc Nephrol* 2006; **17**: 3458-3471 [PMID: 17093068 DOI: 10.1681/ASN.2006050460]

198 **Hawkins PN**, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with 123I-labeled serum amyloid P component. *N Engl J Med* 1990; **323**: 508-513 [PMID: 2377176 DOI: 10.1056/NEJM199008233230803]

199 **Friedman SL**, Sheppard D, Duffield JS, Violette S. Therapy for fibrotic diseases: nearing the starting line. *Sci Transl Med* 2013; **5**: 167sr1 [PMID: 23303606 DOI: 10.1126/scitranslmed.3004700]

200 **Chau BN**, Xin C, Hartner J, Ren S, Castano AP, Linn G, Li J, Tran PT, Kaimal V, Huang X, Chang AN, Li S, Kalra A, Grafals M, Portilla D, MacKenna DA, Orkin SH, Duffield JS. MicroRNA-21 promotes fibrosis of the kidney by silencing metabolic pathways. *Sci Transl Med* 2012; **4**: 121ra18 [PMID: 22344686 DOI: 10.1126/scitranslmed.3003205]

201 [**Mohamed R**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Mohamed%20R%5BAuthor%5D&cauthor=true&cauthor_uid=26334030)**,** [Jayakumar C](http://www.ncbi.nlm.nih.gov/pubmed/?term=Jayakumar%20C%5BAuthor%5D&cauthor=true&cauthor_uid=26334030), [Chen F](http://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20F%5BAuthor%5D&cauthor=true&cauthor_uid=26334030), [Fulton D](http://www.ncbi.nlm.nih.gov/pubmed/?term=Fulton%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26334030), [Stepp D](http://www.ncbi.nlm.nih.gov/pubmed/?term=Stepp%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26334030), [Gansevoort RT](http://www.ncbi.nlm.nih.gov/pubmed/?term=Gansevoort%20RT%5BAuthor%5D&cauthor=true&cauthor_uid=26334030), [Ramesh G](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ramesh%20G%5BAuthor%5D&cauthor=true&cauthor_uid=26334030). Low-Dose IL-17 Therapy Prevents and Reverses Diabetic Nephropathy, Metabolic Syndrome, and Associated Organ Fibrosis. *J Am Soc Nephrol* 2015 [PMID: 26334030 DOI: 10.1681/ASN.2014111136]

**P-Reviewer:** Navarro-Gonzalez JF, Tsuruya K **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Standard of care therapeutic management**

|  |  |  |  |
| --- | --- | --- | --- |
| Drug class | On-target parameter | Off-target parameters | Ref. |
| **Antihypertensive**  RAS blockers  Aldosterone antagonists | BP ↓  BP ↓ | UAE↓ GTP↓, K+↑ AT1-7↑, cytokines↓, Klotho↑  UAE ↓ K+↑ | [53,54,56,69-82]  [83-85] |
| **K+ binders**  Bisacodyl  Patiromer  Na zirconium cyclosilicate | K+↓  K+↓  K+↓ | Diarrhea | [86]  [87]  [88] |
| **Blood sugar control** | Blood sugar↓  HbA1c + 7 | Progression ↓  Postpones need of Dx | [93-95] |
| **Hypocholestrolemic**  Statins | Cholesterol↓, LDL↓ | Cardiovascular events ↓ | [96] |
| **Hypouricemic agents**  Allpurinol  Febuxostst | Uric acid ↓  Uric acid ↓ | Renal events↓, CV events ↓  CKD progression ↓ | [102,103]  [104] |
| **Sod.bicarbonate** | HCO3-↑, PH ↑ | Ptn catabolism↓, GFR decline ↓ | [105,106] |
| **Phosphate binders**  Calcium based  Sevelamer  Lanthanum carbonate  Iron compounds  Nicotinamide | P↓  P↓  P↓  P↓  P↓ | PTH↓, vasc calc. ↑  PTH↓, stop vasc calc, Mortality ↓, Uric acid ↓, Cholesterol↓, LDL↓, inflammation ↓ Cardiovascular events ↓  PTH↓, stop vasc calc,  Iron ↑  TG↓, LDL↓, HDL ↑ | [117-120]  [121-131]  [123-139]  [140,141]  [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. | | | |

**Table 2 Novel therapeutic interventions**

|  |  |  |  |
| --- | --- | --- | --- |
| **Therapeutic modality** | **Mechanism of action** | **Primary end points** | **Ref.** |
| **Chemokine ligand and receptor antagonists** |  |  |  |
| *CCR1 antagonists*  *Emapticap Pegol*  CCX140 | Block CCR1 receptors on leucocyte surface  binds and neutralizes MCP-1  Block CCR2 | Leuc. Inf. ↓, IF↓, TI↓, and improved KFTs  UAE↓, glycemic control in phase IV D.N.  UAE↓, glycemic control in phase IV D.N. | [146]  [5,152,153]  [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*  *Bound phosphorus*  *Vitamin K* | Restores intestinal microbiota, IAP↑  IAP↑  IAP↑ | eGFR loss↓ | [184]  [186]  [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.: Inflamation. | | | |