A Review: Prevention of chronic kidney disease (CKD) & novel treatment

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Abstract: CKD is a common disorder and its prevalence is increasing worldwide. Early diagnosis could permit early intervention to reduce the risks of cardiovascular events, kidney failure, and death which associated with chronic kidney disease. The progression of established CKD is variable and depends on several risk factors or markers. Non modifiable factors include genetics, race, age, and sex. The modifiable factors include systemic hypertension, Proteinuria, Metabolic factors (The Diabetes Control, hyperlipidaemia, hyperuricaemia, obesity). Primary prevention will rely on controlling the global epidemic of obesity and associated type 2 diabetes as well as hypertension, Lifestyle modifications. Secondary prevention of progression. In patients with established CKD, there is a wide range of interventions that offer the possibility of slowing progression.

Definition and classification of chronic kidney disease

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for>3 months, with implications for health. Excretory, endocrine and metabolic functions decline together in most chronic kidney diseases. The GFR is one component of excretory function, but is widely accepted as the best overall index of kidney function because it is generally reduced after widespread structural damage and most other kidney functions decline in parallel with GFR in CKD. A threshold of GFR<60 ml/min/1.73m^2 (GFR categories G3a-G5) for >3 months to indicate CKD[1].

Damage to the kidney can be within the parenchyma, large blood vessels or collecting systems, and is most often inferred from markers rather than direct examination of kidney tissue. The markers of kidney damage often provide a clue to the likely site of damage within the kidney and in association with other clinical findings, the cause of kidney disease [2].

CKD is classified based on cause, GFR category, and albuminuria category (CGA).this can be used to inform the need for specialist referral, general medical management, and indications for investigation and therapeutic interventions. It will also be a tool for the study of the epidemiology, natural history, and prognosis of CKD[3].

Risk factors for CKD include genetic or socio demographic predisposition, or the presence of diseases which can initiate and propagate kidney disease. Kidney failure is the end-stage of CKD and is define as severely reduced kidney function or treatment with dialysis. The term "end-stage renal disease" (ESRD) generally refers to chronic kidney failure treated with either dialysis or transplantation. Acute kidney injury (AKI) may complicate CKD and hasten its progression[4].

CKD is usually asymptomatic in its early stages. Symptoms appear in later stages in association with complications. In addition to commonly recognized hormonal and metabolic complications such as anemia and hyperparathyroidism, CKD complications include increased risks for systemic drug toxicity, cardiovascular disease, infection, cognitive impairment, and impaired physical function[5].

Complications are more likely to occur at later stages, and may lead to death before kidney disease progresses to kidney failure. Complications may also arise from the adverse effects of interventions used to prevent or treat the disease[6].

Definition, identification, and prediction of CKD progression

Much epidemiological and clinical evidence has shown a link between several factors and the initiation and the progression of CKD. These can be classified into two distinct categories: those proven to be causal (risk factors) and those that are associated with CKD in the absence of established causal relations (risk markers)[7].

The progression of established CKD is variable and depends on several risk factors or markers. Non modifiable factors include genetics, race, age, and sex. For instance, there is much evidence that the rate of progression of CKD is faster among patients who are elderly, male, or African-American[8].

Most notable among the modifiable progression factors is systemic hypertension. Proteinuria is a reliable marker of the severity of CKD and a powerful and independent predictor of its

progression. Controversy prevails as to whether proteinuria is a risk factor for the progression of clinical nephropathies. Patients with persistently high rates of urinary protein excretion (>3–5 g in 24 h) in general have a much faster rate of progression than those with mild or moderate proteinuria (<1–3 g in 24 h)[9].

Metabolic factors have been implicated in the progression of CKD. The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study established that poor diabetes control accelerates the progression of diabetic nephropathy in both type 1 and type 2 diabetes. Experimental evidence has also shown a link between hyperlipidemia and the progression of diabetic and non-diabetic nephropathies. A link between hyperuricaemia and the development of systemic hypertension, cardiovascular disease, and renal disease has been postulated[10].

Cigarette smoking has been implicated in the initiation and progression of CKD. A graded increased risk of ESRD was noted in non-diabetic nephropathies with increasing cigarette smoking; the incidence of ESRD was increased by 5·9 times among heavy smokers(>15 pack-years). In another study, heavy smokers (>20 pack-years) had a risk of developing albuminuria three times that of non-smokers[11].

Definition and Identification of CKD Progression:

There is variability in the presence of or rate of decline of kidney function in those with CKD. The rate at which this decline occurs also varies based on the underlying population, cause of CKD, presence of albuminuria/proteinuria, comorbidities and age. The Work Group searched the literature for longitudinal studies that evaluated decline in kidney function. As outlined in the study populations included healthy adults, those with comorbidity, as well as a subgroup of adults aged 65 and older[12].

In general these studies suggest progression rates of approximately 0.3 to 1 ml/min/1.73m2/ year among participants without proteinuria or comorbidity and rates of approximately two to three times higher among participants with proteinuria or comorbidity. The somewhat surprising finding that eGFR had low rates of progression among the group with impaired renal function at baseline has been shown in other studies and may relate to the statistical phenomenon of regression to the mean. There is also a concern that it is hard to maintain consistent calibration of the SCr assay over time and progression results are highly sensitive to drift in the creatinine assay[13].

Recognize that small fluctuations in GFR are common and are not necessarily indicative of

progression. Define CKD progression based on one of more of the following:

- Decline in GFR category (>90 [G1], 60-89 [G2], 45-59 [G3a], 30-44 [G3b], 15-29 [G4], <15 [G5] ml/min/1.73 m2).
- A certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline.
- Rapid progression is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m2/year.
- The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up[14].

There are several factors that influence the likelihood and rate of CKD progression including GFR and albuminuria category, the degree of albuminuria, the cause of kidney disease, ongoing exposure to nephrotoxic agents, obesity, hypertension, age, race/ethnicity and laboratory parameters such as Hb (hemoglobin), albumin, calcium, phosphate, and bicarbonate. As some of these risk factors are modifiable they should be actively identified and, if present, be treated as they may impact long-term outcomes including cardiovascular conditions, QOL, and progression of CKD. This holds true for lifestyle measures such as cessation of smoking and prevention of obesity. It also subtends to lowering of BP, lowering of albuminuria and prevention of hyperglycemia. A further fact or that may be modifiable is the underlying cause of CKD. As various causes may respond to targeted treatment, finding the cause of CKD is the starting point of the work-up of a subject with CKD. If this causal disease is modifiable, for example by immunosuppressive treatment, then such treatment is the first step to consider[15].

Most recently, studies have focused on the development of risk scores for identifying progressive decreases in GFR and progressive increases in albuminuria. It has not yet been established which prediction formula could best be used. Some formulas use just simple demographic and clinical measures, while others also include laboratory tests. Some were developed for high-risk populations, such as people with known underlying CVD, with CKD in general, or with specific causes of CKD, such as IgA nephropathy, diabetic nephropathy, or renal artery stenosis. Others developed a risk prediction model in the general population. This latter model included age, race, gender, and in dichotomized version, the presence of anemia, hypertension, diabetes, and CVD history[16].

More recently, two studies used more accurate laboratory parameters in addition to demographic characteristics. The first study was in patients with an

eGFR of 15-60 ml/min/1.73 m2/year, and included age, gender, eGFR, albuminuria, and serum calcium, phosphate, bicarbonate and albumin. The second study was in subjects from the general population and included age, eGFR, albuminuria, measured levels of BP and C-reactive protein (CRP)[17,18].

Management of progression and complications of CKD:

Initial management of chronic kidney disease entails identification of reversible disorders (such as urinary-tract obstruction, infection, or autoimmune disease) that could respond to specific treatment and lead to stabilization or improvement in kidney function. Irrespective of underlying cause, typical goals of management for all patients with chronic kidney disease include prevention of cardiovascular events and reduction of the rate of progression of the disorder (thereby delaying or preventing kidney failure and other complications)[19].

Primary prevention:
 Life style modification

Primary prevention will rely on controlling the global epidemic of obesity and associated type 2 diabetes as well as hypertension. Lifestyle modifications, such as weight reduction, exercise, and dietary manipulations can be effective, as shown in clinical trials in which the incidence of type 2 diabetes in overweight individuals with impaired glucose tolerance was substantially lowered by these means[20].

Approaches to control hypertension by means of dietary salt restrictions and diets rich in fruit and vegetables and low in saturated fat have been recommended[21].

Improved public-health education with reduction of excessive bodyweight, regular exercise, and dietary approaches should lead in the long term to a reduction in the growing numbers of people with diabetes and hypertension who constitute the major future pool of CKD cases[7].

Limitation of dietary sodium intake to less than 100 mmol per day is advocated frequently to prevent or manage hypertension[22].

The effects of dietary protein restriction on prevention of progression of chronic kidney disease have been controversial owing to the features of study design and because of inconclusive and conflicting data of individual randomised controlled trials. Results from meta-analyses suggest that kidney failure or death could be reduced with severe or very low protein intake in trial settings. Nonetheless, because of the risks of malnutrition and need for additional nutritional monitoring, severe protein restriction is not generally implemented for patients with chronic kidney disease[23].

Data from a small single center randomized trial reported that oral supplementation with sodium bicarbonate slowed the rate of decline in kidney function and reduced the rate of progression to kidney failure in individuals with a glomerular filtration rate lower than 30 mL per min per 1·73 m² and low concentration in serum of bicarbonate[24].

Smoking is associated with increased risk of progressive chronic kidney disease and kidney failure or death related to chronic kidney disease and thus smoking cessation is encouraged[25].

Findings of large observational studies suggest that obesity is associated with development of chronic kidney disease, progression to kidney failure, and mortality related to chronic kidney disease, although how much of this effect is mediated by diabetes, hypertension, and dyslipidaemia remains uncertain. Weight gain increases the risk of chronic kidney disease, even in patients with normal starting weight, and should be avoided, whereas weight loss is recommended for individuals who are overweight because of its known benefits for glycaemic control and blood pressure[26,27].

Secondary prevention of progression:
pharmacological approaches
 Treatment of the complications of renal dysfunction:

A wide range of disorders may develop as a consequence of the loss of renal function. These include disorders of fluid and electrolyte balance, such as volume overload, hyperkalemia, metabolic acidosis, and hyperphosphatemia, as well as abnormalities related to hormonal or systemic dysfunction, such as anorexia, nausea, vomiting, fatigue, hypertension, anemia, malnutrition, hyperlipidemia, and bone disease. Attention needs to be paid to all of these issues[28].

Volume overload:

Sodium and intravascular volume balance are usually maintained via homeostatic mechanisms until the GFR falls below 10 to 15 mL/min. However, the patient with mild to moderate chronic kidney disease, despite being in relative volume balance, is less able to respond to rapid infusions of sodium and is therefore prone to fluid overload[29].

Patients with chronic kidney disease and volume overload generally respond to the combination of dietary sodium restriction and diuretic therapy, usually with a loop diuretic given daily. Some investigators have also claimed that limiting sodium intake may also help decrease progression of chronic kidney disease by lowering intraglomerularpressure[30].

Hyperkalemia:

The ability to maintain potassium excretion at near normal levels is generally maintained in patients

with renal disease as long as both aldosterone secretion and distal flow are maintained[31].

Thus, hyperkalemia generally develops in the patient who is oliguric or who has an additional problem such as a high potassium diet, increased tissue breakdown, or hypoaldosteronism (due in some cases to the administration of an ACE inhibitor or ARB). Impaired cell uptake of potassium also may contribute to the development of hyperkalemia in advanced chronic kidney disease[32].

Hyperkalemia due to ACE inhibitor or ARB therapy is most likely to occur in patients in whom the serum potassium concentration is elevated or in the high normal range prior to therapy[29]

Metabolic acidosis:

Chronic metabolic acidosis is associated with increased protein catabolism, uremic bone disease, muscle wasting, chronic inflammation, impaired glucose homeostasis, impaired cardiac function, progression of CKD, and increased mortality[33,34].

Previously, exogenous alkali was not usually given to treat the generally mild metabolic acidosis (arterial pH generally above 7.25) in asymptomatic adults with chronic kidney disease. This was primarily due to concerns related to the exacerbation of volume expansion and hypertension. However, these concerns appear to be overstated[28].

Oral sodium bicarbonate may protect the proximal renal tubule and help delay kidney disease progression. randomized 40 subjects with mild to moderate CKD to oral bicarbonate (1.2 mEq/kg of body weight) or placebo for 3 months and suggested that correction of metabolic acidosis significantly attenuates the rise in blood urea[35].

A larger study randomly assigned 134 adults with moderate to severe CKD (CrCl 15 to 30ml/min/1.73 m2) and serum bicarbonate 16 to 20mmol/l to either supplementation with oral sodium bicarbonate (1.82 ± 0.80 g/day) or standard care for 2 years. Serum bicarbonate increased significantly in the bicarbonate group but despite the associated sodium load there was no difference in BP control, prescription of antihypertensives and loop diuretics, or hospitalization for heart failure compared with the control group. The decline in CrCl was significantly slowed in the bicarbonate group compared with controls[24].

Alkali therapy is recommended to maintain the serum bicarbonate concentration above 23 meq/L[36].

If alkali is given, sodium bicarbonate (in a daily dose of 0.5 to 1 meq/kg per day) is the agent of choice. Sodium citrate (citrate is rapidly metabolized to bicarbonate) may be used in patients who are unable to tolerate sodium bicarbonate, since it does not produce the bloating associated with bicarbonate therapy Sodium citrate should be avoided in the rare patient who may be taking aluminum-containing antacids since it markedly enhances intestinal aluminum absorption[37].

CKD Metabolic Bone Disease:

Abnormalities of calcium and phosphate appear to occur relatively later in the course of CKD than do abnormalities in values of 1,25(OH)2D, 25(OH)D, and PTH. Thus, the recommendation is to evaluate these parameters relatively early in the trajectory of CKD, as an assessment of burden of illness. In dialysis patients, the highest risks for mortality have been reported with combinations of high serum phosphate and calcium together with either high PTH (RR 3.71; 95% CI 1.53-9.03; P= 0.004) or low PTH (RR 4.30; 95% CI 2.01-9.22; P<0.001) compared with the combination of high PTH with normal serum calcium and phosphate which had the lowest mortality and was used as the index category. The importance of examining combinations of parameters of mineral metabolism is likely to be no different in patients with less severe CKD, but this has not been tested in non-dialysis populations[38].

There are also racial differences in the parameters of mineral metabolism. blacks had similar 1,25(OH)2D levels compared with non-blacks but significantly lower levels of 25(OH)D with higher levels of calcium, phosphate, and PTH, and were significantly more likely to have hyperphosphatemia than non-blacks[39].

Decreased bone mass and changes in bone microarchitecture occur early in CKD and worsen with progression of disease such that patients with CKD are at increased risk of bone fracture[40].

Treatment of CKD-MBD:

Two principal modalities are used in an attempt to prevent and/or reverse the hyperphosphatemia of renal failure: Restricting dietary phosphate intake. The administration of different agents, named phosphate binders, to bind ingested phosphate in the gut[41].

Phosphate restriction:

Factors affecting gastrointestinal phosphate absorption include 1,25(OH)2D, food content, phosphate bioavailability and phosphate binders (natural and prescribed). Sources of dietary phosphate are protein-rich foods, including dairy products, meat, and fish as well as legumes, nuts, chocolates and inorganic phosphate additives such as those found in carbonated drinks. In a non-vegetarian Western diet, over half the dietary intake of phosphate comes from animal protein. Although the phosphate content of plant-derived phosphate is higher than animal derived, its bioavailability in terms of gastrointestinal absorption is lower[42].

Inorganic phosphate additives have the highest bioavailability. A number of clinical studies detail

benefit from dietary phosphate and protein control in terms of secondary hyperparathyroidism and progression of CKD in people with moderate CKD[43].

Few studies have evaluated the impact of dietary phosphate restriction on bone disease or vascular calcification and only one has addressed survival. In people on hemodialysis, a post hoc analysis suggested that more restrictive prescribed dietary phosphate was associated with poorer indices of nutritional status and a greater need for nutritional supplementation. There was a stepwise trend toward greater survival with more liberal phosphate prescription, which reached statistical significance among subjects prescribed 1001 to 2000mg/d and those with no specified phosphate restriction, raising concerns about protein energy malnutrition with dietary phosphate restriction. The means used to achieve phosphate restriction may therefore be important[44].

Phosphate binders:

There are a number of agents available for phosphate binding which are listed in the table ranked in order of relative cost, appreciating that both availability and specific costs are country- and era-specific. A Cochrane meta-analysis considered 60 RCTs or quasiRCTs (7631 participants) that assessed the effects of various phosphate binders in adults with CKD. The authors concluded that all available phosphate-binders reduced serum phosphate concentrations in comparison to placebo but that data to date do not support superiority of novel non-calcium binding agents for patient-level outcomes such as all-cause mortality and cardiovascular end points in CKD[45].

Vitamin D supplementation and bisphosphonates in people with CKD:

There is a substantial amount of data to support 25(OH)D deficiency in general and CKD populations which is likely multifactorial. In addition to 25(OH)D deficiency, note has been made that there is a progressive increase in prevalence of 1,25(OH)2D deficiency with lower GFR category, which occurs earlier than 25(OH)D deficiency[46].

No relationship between 25(OH)D levels and 1,25(OH)2D levels was apparent but there was a strong association between 1,25(OH)2D deficiency and PTH concentration. Of particular note, a higher urinary ACR was associated with lower levels of 1,25(OH)2D at GFR values of o60ml/min/ 1.73 m2[47].

Despite the associations with mortality, systematic review of published data to date on vitamin D supplementation in patients with CKD not on dialysis has only shown an improvement in biochemical end points. A series of publications have attempted to summarize the efficacy of vitamin D therapy on biochemical, bone, cardiovascular, and mortality outcomes in people with CKD and not requiring dialysis[48].

No formulation, route, or schedule of vitamin D compound was found to alter the mortality risk or need for dialysis although vitamin D compounds significantly lowered serum PTH concentrations. None of the studies assessed reported outcomes related to CVD, bone disease, or mortality[49].

The risk-benefit ratio of bisphosphonates has not been well studied in CKD populations. Indications for bisphosphonate therapy include osteoporosis, corticosteroid therapy, malignant disease and Paget's disease. In people with CKD and GFR categories >60ml/min/1.73 m2 with osteoporosis and/ or at high risk of fractures, and in people with GFRs between 30-60ml/min/1.73 m2 with normal PTH, osteoporosis and/or at high risk of fracture, treatment should be the same as for the general population (although dose modification may be necessary)[50].

Glycemic control:

Diabetes is the leading cause of CKD worldwide. Diabetic nephropathy occurs in 25–40% of patients with type 1 or type 2 diabetes within 20–25 years of disease onset and is an independent risk factor for early death due to CVD. The mortality rate in people with diabetes and urinary ACR 430mg/g (43mg/mmol) is more than twice that in those with normal urinary albumin levels[51].

It should be noted that the evidence that intensive glycemic control reduces the microvascular complications of diabetes is based almost exclusively on prevention of development of albuminuria (ACR 430mg/g or 43mg/mmol) and prevention of increasing albuminuria. Evidence from the three most recent studies, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and the Veterans Affairs Diabetes Trial (VADT)[52].

Hyperuricemia:

Hyperuricemia is common in people with CKD and is defined by urate concentrations above 7.0mg/dl (420mmol/l) as measured by automated enzymatic (uricase) laboratory methods. Concentrations obtained with colorimetric methods are approximately 1mg/dl (60mmol/l) lower. The Work Group believe it important to acknowledge the accumulating body of evidence describing the association of hyperuricemia with CKD and adverse cardiovascular outcomes, and thus list hyperuricemia as a potential contributor to progression. However, at the time of current writing, there is not a reliable body of evidence from which to recommend treatment of hyperuricemia for the specific goal of delaying progression of CKD[53].

Published data implicate elevated serum uric acid (SUA) concentrations in the progression of CKD[54].

Reduction of SUA by allopurinol has been reported to delay progression of CKD in people with both diabetic and nondiabeticCKD[55].

Treatment of asymptomatic hyperuricemia has also been reported to improve kidney function even in subjects with normal levels of GFR. Both GFR and endothelial function significantly improved in asymptomatic hyperuricemic subjects randomly assigned to 300mg/day of allopurinol in comparison to placebo[56].

A separate doubleblind, placebo-controlled, parallel-group study in 67 people with CKD (GFR 30-60ml/min/1.73 m2) and left ventricular hypertrophy (LVH) randomly assigned subjects to treatment with allopurinol (300mg/day) or placebo for 9 months. In comparison to placebo, the allopurinol-treated subjects had significant reductions in left ventricular mass assessed by magnetic resonance imaging (MRI), and improvements in endothelial function assessed by flow-mediated dilation of the brachial artery and in central arterial stiffness assessed by pulse-wave analysis[57].

Another study randomized 70 subjects with known hyperuricemia or SUA concentrations ≥ 7.0mg/dl (≥ 420mmol/l) to treatment with either allopurinol monotherapy (100-200mg/day) or a combination of allopurinol and a citrate preparation (3 g/day). SUA concentrations were decreased in both groups but to a significantly lower level by combination treatment. GFR assessed by CrCl increased in the combination therapy group but remained unchanged in those treated with allopurinol alone. Other uric acid lowering agents have also been reported to improve outcomes in people with CKD[58].

In an 8-week, placebo-controlled group comparison of rasburicase and placebo, a single 4.5mg dose of rasburicase significantly lowered SUA and resulted in a significant improvement in kidney function assessed by CrCl[59].

Hypertension:

There is a strong association between chronic kidney disease (CKD) and an elevated blood pressure (BP) whereby each can cause or aggravate the other. BP control is fundamental to the care of patients with CKD and is relevant at all stages of CKD regardless of the underlying cause. Some BP-lowering agents are particular effective at reducing albuminuria or proteinuria, suggesting that BP management should differ depending on the amount of albumin or protein in the urine[60].

Patients with CKD, particularly the elderly and diabetic patients with autonomic neuropathy, are prone to orthostatic hypotension, which may be exacerbated by volume depletion. Many CKD patients will require combinations of drugs to control BP including vasodilators, which can cause or exacerbate postural hypotension. This can lead to postural dizziness, reduced adherence and in extreme cases, syncope or falls with consequent injury. Accordingly, it is sensible to regularly check for symptoms of postural dizziness and to compare lying, sitting and standing BP in CKD patients, particularly before and after altering the treatment regimen[61].

The optimal timing of administration of medication has not been studied in CKD patients. CKD patients who do not have the normal decrease in BP during sleep (non-dippers and reverse dippers) have worse cardiovascular and kidney outcomes when compared to dippers[62].

Whether the recently reported strategy of evening dosing to produce nocturnal dipping will improve outcomes in CKD patients, as has been described in individuals with essential hypertension, remains to be established[63].

ACE-Is and ARBs are valuable BP-reducing agents in CKD patients, are indicated if urinary albumin excretion is elevated and are safe to combine with most other BP-reducing agents. Clinically significant hyperkalemia and reductions in GFR can occur in patients receiving ACE-Is or ARBs, particularly in those who have renal-artery stenosis or reduced intravascular volume, or when these agents are used together with NSAIDs, COX-2 inhibitors, or potassium-sparing diuretics. The use of these drugs in women of child-bearing age should be balanced with the risk of pregnancy since they are potentially teratogenic[64].

In patients with CKD, aldosterone antagonists have been shown to decrease urine albumin excretion when added to ACE-I or ARB therapy. In the largest relevant RCT available involving CKD patients with elevated urine albumin levels and type 2 diabetes, 177 patients received eplerenone (either 50 or 100 mg daily) and 91 patients received placebo.106 The addition of eplerenone to enalapril (20 mg/day) resulted in a reduction in AERs of 40 to 50% by 12 weeks in the eplerenone groups, but by o10% in the placebo group. The greater reduction in AER in the CKD patients receiving an aldosterone antagonist in addition to an ACE-I or ARB is consistent with the findings of many smaller trials[65].

Direct renin inhibitors. The first clinically available DRI, aliskiren, The usual dose of aliskiren is 150 to 300 mg given once daily. The dose is not modified according to kidney function. It has been reported that cyclosporine administration increases the half-life of aliskiren in healthy subjects[66].

Volume expansion, often in the absence of overt edema, contributes to the elevation in blood pressure

in most forms of chronic kidney disease. As a result, before other medications are added, the dose of diuretics should be increased until the blood pressure is normalized or the patient has attained "dry weight" which, in the presence of persistent hypertension, is defined as the weight at which further fluid loss will lead either to symptoms (fatigue, orthostatic hypotension) or to decreased tissue perfusion as evidenced by an otherwise unexplained elevation in the BUN and plasma creatinineconcentration[67].

Beta-blockers are one of the most extensively investigated class of agents, having been used to treat hypertension and CVD for over 40 years. In patients with CKD, the accumulation of beta-blockers or active metabolites could exacerbate concentration-dependent side effects such as bradycardic arrhythmias. Such accumulation occurs with atenolol and bisoprolol, but not carvedilol, propranolol, or metoprolol[68].

Calcium-channel blockers are valuable BP-lowering agents in CKD patients, but this class of drugs is very heterogeneous in several respects and the choice of the type of agent used should take into account these differences as well as co-morbidities and other medications the patient is taking.The major subclasses are the dihydropyridines (e.g., amlodipine, nifedipine and lercanidipine), the non-dihydropyridinebenzothiazepines (e.g., diltiazem) and the phenylalkylamines (e.g., verapamil)[69].

Calcium-channel blockers also vary in their effects on glomerular arterioles, reflecting differential blockage of Tchannel receptors (on the afferent and efferent arteriole) versus L-channel receptors (predominantly on the afferent arteriole). T-channel blockade leads to a reduction in intraglomerular pressure, and accordingly a fall in urine albumin levels, while an increase in the urine albumin level can occur with blockade of L-channel receptors. In general, dihydropyridine calcium-channel blockers act on L-channel receptors, hence have the effect of increasing urine albumin excretion, whereas non-dihydropyridines tend not be associated with this side effect.130 Later generation dihydropyridines (e.g., manipine, cilnidipine) are less prone to increasing albumin excretion and may even reduce it[70].

It is wise to avoid dihydropyridine calcium channel blockers in CKD patients with already increased urinary albumin excretion, particularly if there is not concomitant use of an ACE-I or ARB[71].

Anemia:
Anemia is an important complication of CKD because it contributes significantly to the heavy symptom burden of CKD. It has a major impact on the lives of people with CKD but it is potentially reversible with appropriate treatment[72].

Correction of iron deficiency with oral or intravenous iron supplementation can reduce the severity of anemia in patients with CKD. Untreated iron deficiency is an important cause of hyporesponsiveness to ESA treatment[73].

The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice in the 1980 s was a major breakthrough in the treatment of the anemia of patients with CKD. The development of rHuEPO was aimed at replacing the insufficient endogenous erythropoietin (EPO) production related to CKD progression. It remains unclear whether the main cause of anemia is a loss of kidney EPO production capacity or a derangement in oxygen sensing, as proposed more recently[74].

Vitamin D:
Emerging data suggest that vitamin D plays a vital role in renal and cardiovascular health. People with CKD have lower vitamin D concentrations than healthy individuals and observational studies have demonstrated that CKD patients treated with vitamin D receptor activators have a survival benefit compared with untreated patients[75].

Several studies have reported that vitamin D receptor activators decrease albuminuria in both diabetic and non-diabetic nephropathy[67,76,77].

The largest study in this respect was the VITAL study. The results showed that paricalcitol in addition to ACEi or ARB therapy appears to reduce albuminuria in a dose-dependent fashion and was well tolerated[78].

Endothelin antagonists:
The endothelin system is chronically activated in patients with nephropathy. Binding of endothelin to the endothelin type A receptor (ETA receptor) elicits pronounced vasoconstriction, sodium retention, and promotes podocyte dysfunction leading to glomerular damage, proteinuria and renal function loss[79].

In contrast, endothelin type B receptor activation causes vasodilatation and sodium excretion. Specific blockade of the ETA receptor, may thus be a promising target to ameliorate renal complications. Intriguingly, endothelin seems to interact with tubular proteins thereby promoting renal fibrosis. It has been shown that exposure of tubular cells to increasing amounts of albumin causes a dose-dependent increase in the generation of endothelin-1. Endothelin-1 mediates secretion of proinflammatory cytokines and growth factors, such as TGF-β, which contribute to interstitial remodelling and scarring[80].

Avosentan, an endothelin receptor blocker, significantly reduced proteinuria in patients with type 2 diabetes and nephropathy. However,a large phase 3 trial, testing the effect of avosentan on hard renal

outcomes (ASCEND),was terminated prematurely because of an excess of congestive heart failure (CHF) and mortality in the avosentan treatment arm[81].

Anti-inflammatory agents:

Bardoxolone-methyl is an anti-oxidative and anti-inflammatory drug which activates the nuclear factor-erythroid-2-related factor (Nrf2)-Keap1 pathway. Nrf2 regulates the induction of multiple antioxidant genes. As such, it exerts anti-oxidative and anti-inflammatory effects and thus serves as a defense factor against kidney injury[82,83].

In a previous non-randomized 8 week trial, treatment with bardoxolone-methyl resulted in a significant increase in eGFR in patients with type 2 diabetes and CKD stage 3 or 4[84].

Pentoxifylline:

The effect of pentoxifylline on the progression of renal function decline is not (yet) established but currently under investigation in the ongoing Pentoxifylline for Renoprotection in Diabetic Nephropathy (PREDIAN) trial[85].

CTP-499:

CTP-499 is an active metabolite of pentoxifylline. CTP-499 is under development based on previous studies showing anti-albuminuric effects of pentoxifylline. CTP-499 is thought to have an improved metabolic profile. Specifically, a pre-clinical study has shown that CTP-499 possesses anti-inflammatory, antifibrotic and anti-oxidant properties[86].

A 24week phase 2 randomized placebo controlled trial is currently ongoing to assess whether CTP-499 exerts anti-albuminuric effects in 170 patients with type 2 diabetes and nephropathy (NCT01487109). Monocyte chemoattractant protein-1 inhibition Monocyte chemoattractant protein-1 (MCP-1), a potent cytokine, plays a key role in initiating and sustaining chronic inflammation in renal tissues. MCP-1 is secreted in response to high glucose concentrations.MCP-1 promotes monocytes and macrophage activation and activates other pro-inflammatory cytokines. Urinary MCP-1 concentrations correlate with the degree of albuminuria in patients with diabetes and interestingly the reduction of albuminuria induced by ACEi correlates with the degree of urinary MCP-1 reduction[87].

These findings support the idea that inhibition of MCP-1 reduces albuminuria and improves long term renal function. A prospective randomized controlled study showed that pharmacological inhibition of MCP-1 synthesis reduced albuminuria on top of ACEI or ARB therapy relative to placebo in subjects with type 2 diabetes and macroalbuminuria but it did not change albuminuria

in subjects with microalbuminuria. To our knowledge no hard renal outcome trials are ongoing[88].

Vitamin B therapy:

Pyridoxamine is a metabolic derivative of vitamin B6 and inhibits the formation of advanced glycation end products (AGE). AGEs are formed in hyperglycaemic milieus through a chemical reaction of a glucose molecule with a NH2 end product of a protein which in turn becomes glycosolated. AGE formation has a direct pathological effect in the kidney resulting in thickening glomerular basement membrane trough expansion of the extracellular matrix. A recent clinical trial was designed to test the hypothesis whether pyridoxamine delayed the progressive renal function loss in patients with type 2 diabetes, nephropathy and marked proteinuria.The results showed no difference in the rate of renal function decline between pyridoxamine and placebo treated patients, although a *post hoc* analysis suggested that pyridoxamine may delay the loss of renal function in subjects with the lowest serum creatinine concentrations at baseline[89].

Other B vitamins have also not been successful in halting the progression of renal disease or reducing urinary albumin excretion rates. In fact, a multicenter clinical trial of high dose vitamin B therapy (vitamin B6, B12 and folic acid) showed a three-fold increase in the rate of renal function loss and a two-fold increase in the risk of cardiovascular disease[90,91].

Summary

CKD is a heterogeneous group of disorders characterized by alterations in kidney structure and function, which manifest in various ways depending upon the underlying cause or causes and the severity of disease.

Risk factors for CKD include genetic or sociodemographic predisposition, or the presence of diseases which can initiate and propagate kidney disease. Kidney failure is the end-stage of CKD and is define a severely reduced kidney function or treatment with dialysis. The term "end-stage renal disease" (ESRD) generally refers to chronic kidney failure treated with either dialysis or transplantation. Acute kidney injury (AKI) may complicate CKD and hasten its progression.

The purpose of CKD staging is to guide management, including stratification of risk for progression and complications of CKD. Risk stratification is used as a guide to inform appropriate treatments and the intensity of monitoring and patient education.

Much epidemiological and clinical evidence has shown a link between several factors and the initiation and the progression of CKD. These can be

classified into two distinct categories: those proven to be causal (risk factors) and those that are associated with CKD in the absence of established causal relations (risk markers).

The progression of established CKD is variable and depends on several risk factors or markers. Non modifiable factors include genetics, race, age, and sex. For instance, there is much evidence that the rate of progression of CKD is faster among patients who are elderly, male, or African-American.

Most notable among the modifiable progression factors is systemic hypertension. Proteinuria is a reliable marker of the severity of CKD and a powerful and independent predictor of its progression. Controversy prevails as to whether proteinuria is a risk factor for the progression of clinical nephropathies. Patients with persistently high rates of urinary protein excretion (>3–5 g in 24 h) in general have a much faster rate of progression than those with mild or moderate proteinuria (<1–3 g in 24 h).

Initial management of chronic kidney disease entails identification of reversible disorders (such as urinary-tract obstruction, infection, or autoimmune disease) that could respond to specific treatment and lead to stabilization or improvement in kidney function. Irrespective of underlying cause, typical goals of management for all patients with chronic kidney disease include prevention of cardiovascular events and reduction of the rate of progression of the disorder (thereby delaying or preventing kidney failure and other complications).

Primary prevention will rely on controlling the global epidemic of obesity and associated type 2 diabetes as well as hypertension. Lifestyle modifications, such as weight reduction, exercise, and dietary manipulations can be effective, as shown in clinical trials in which the incidence of type 2 diabetes in overweight individuals with impaired glucose tolerance was substantially lowered by these means.

A wide range of disorders may develop as a consequence of the loss of renal function. These include disorders of fluid and electrolyte balance, such as volume overload, hyperkalemia, metabolic acidosis, and hyperphosphatemia, as well as abnormalities related to hormonal or systemic dysfunction, such as anorexia, nausea, vomiting, fatigue, hypertension, anemia, malnutrition, hyperlipidemia, and bone disease. Attention needs to be paid to all of these issues.

RAA Splays an important role in progressive organ function loss in CKD patients as highlighted by the results of several randomized controlled trialsandmeta-analyses demonstrating that inhibition of the RAAS with either ACEi or ARB affords renal and cardiovascular protection.

In addition, dual blockade increased the risk for adverse renal outcomes compared with either monotherapy, in spite of better reduction of blood pressure and albuminuria.

Dipeptidylpeptidase inhibitors are a new class of hypoglycaemic drugs.DPP-IV inhibitors inhibit the degradation of glucagon-like peptide -1 (GLP-1). By inhibiting the degradation of GLP-1 these agents enhance insulin secretion in the pancreas and reduces glucagon release, resulting in a reduction in fasting plasma glucose and HbA1c.Various DPP-IV inhibitors are available for clinical use such as sitagliptin, saxagliptin and linagliptin. The HbA1c lowering effects of the various DPP-IV inhibitors seem to be comparable. However, the pharmacokinetic properties vary among the different agents which could render a specific agent particularly useful for a certain subpopulation. For example, linagliptin is mainly metabolized and eliminated by the liver. No dose adjustments are required for patients with impaired kidney function which makes linagliptin particularly attractive for the patient with diabetes and nephropathy. Whether DPP-IV inhibitors delay the progression towards ESRD is unknown but some studies support a potential renoprotective effect. Sitagliptin has been shown to decrease albuminuria by 20% in a prospective observational study.

Emerging data suggest that vitamin D plays a vital role in renal and cardiovascular health. People with CKD have lower vitamin D concentrations than healthy individuals and observational studies have demonstrated that CKD patients treated with vitamin D receptor activators have a survival benefit compared with untreated patients.

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