



PRESCRIBING PATTERNS OF MEDICINES IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Prescription writing pattern studies are done to evaluate quality and care given to the patients in present healthcare system. Proper selection of drug and dose reduces incidence of nephrotoxicity and which will improve better clinical outcomes. In most of the Chronic kidney disease (CKD) patient's metabolic acidosis occurs usually when GFR falls below 30 ml/min which leads to potentiation of renal osteodystrophy. Metabolic acidosis is treated with sodium citrate and treatment should be continued till the bicarbonate concentration should be greater than 22 mmol/L. In CKD cases metabolic acidosis is observed in early stages of renal dysfunction.

KEY WORDS

Chronic kidney disease, Nephrotoxicity, Meabolic acidosis

INTRODUCTION

CKD (chronic kidney disease) is a usually used for many disorders affecting kidney structure and its function. According to the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defined CKD as a damage to the kidney or a decrease in the Glomerular Filtration rate (GFR) of $<60\text{ml/min/1.73m}^2$ for a period of 3months or more. CKD is usually associated with many different comorbidities and complications (1). CKD is progressive loss in kidney function over a period of time (several months to years). Severity of CKD is classified into 5 stages with stage 1 being mild with few symptoms and stage 5 being the severe with poor life expectancy in untreated condition and based on its cause, recent guidelines reclassified CKD into GFR category (G1, G2, G3a, G3b, G4 and G5), and albuminuria category (A1, A2, A3). The usual signs and symptoms include high blood pressure, hyperkalemia, anaemia, oedema, bone disorders, metabolic acidosis, and sexual dysfunction (2).

CLASSIFICATION

CKD is classified by level of kidney function based on GFR (Glomerular Filtration Rate) into stage 1 to stage 5;

each increasing number indicates a more advanced stage of disease (3).

STAGE	GFR(ml/min/1.73m ²)
1	≥ 90
2	60-89
3	30-59
4	15-29
5	<15

STAGES ACCORDING TO GFR: -

STAGE 1: if the GFR is normal or above 90ml/min which is associated with albuminuria, blood abnormalities, and abnormal urine tests.

STAGE 2: if the GFR is slightly reduced that is in kidney damage which can be studied by imaging, abnormality in urine and blood.

STAGE 3: if the GFR is moderately reduced that is in range of 30-59ml/min which is associated with need of screening and physician reference and it is also divided into: -

Stage 3a (moderate reduction in GFR of 45-59ml/min/1.73m²) and Stage 3b (GFR of 30-44ml/min/1.73m²) (4) STAGE 4: if the GFR is highly reduced that is in range of 15-29ml/min which requires the renal replacement therapy. STAGE 5: if the GFR is less than 15ml/min it is considered to be kidney failure

and requires kidney transplantation which is also called End Stage Kidney Disease.

ETIOLOGICAL FACTORS:

Diabetes and Hypertension are the two main causes of CKD (about two-third of the cases) (5). Other conditions include: - Glomerulo-nephritis, polycystic kidney disease, malformations, lupus, obstructions caused by kidney stones, tumour, or an enlarged prostate gland in men, repeated urinary infections.

SYMPTOMS

CKD gets worse slowly and symptoms usually appear once kidneys are usually damaged. Common symptoms usually observed are itching, muscle cramps, nausea and vomiting, not feeling hungry, swelling in the feet and ankle, shortness of breath, and trouble in sleeping (6).

COMPLICATIONS

Anaemia: - Kidneys usually help produce red blood cells and in kidney damage they may not produce enough red blood cells which is a condition called anaemia.

Bone disease and Hyperphosphatemia: - kidneys keep the right amount of calcium and phosphorous in the body and when there is kidney damage, too much phosphorous build up in the body (hyperphosphatemia) which pulls calcium from the body making them weak.

Heart disease: - it is a common cause of death among people on dialysis.

Hyperkalemia: - Kidneys often filter excess potassium and when there is CKD, then kidneys may not be able to filter potassium causing hyperkalemia.

Fluid build-up: - generally kidneys remove extra fluid from the body and when kidney damage is seen, then they do not remove extra fluid which leads to fluid build-up (oedema) (6).

DIAGNOSIS

CKD can be diagnosed with blood and urine tests (7). Regular testing is usually recommended in people with high blood pressure, diabetes, acute kidney injury, and cardiovascular disease, family history of advanced CKD, protein or blood in urine. Blood test: - Measures the

level of creatinine (waste product) and this value is used in calculation of estimated Glomerular Filtration Rate (eGFR).

Urine test: - checks the level of albumin, creatinine, blood or protein in the urine. Other tests include ultrasound scan, MRI scan, CT scan, and a kidney biopsy.

TREATMENT

Generally, treatment is given to treat underlying cause, reduce the risk of complications, and also to slow the progression of the disease (8).

Anaemia: - Patient having haemoglobin levels <6 were given blood transfusions followed by oral iron tablets and patients with haemoglobin levels from 6-10 were given either erythropoietin with IV iron or blood transfusion followed by oral iron tablets (9). But ESA treatment of anaemia to obtain higher haemoglobin targets does not led to differences in HRQOL in CKD patients (10).

Phosphate balance: - Phosphate binders are prescribed and among them calcium carbonate is mostly prescribed drug (11).

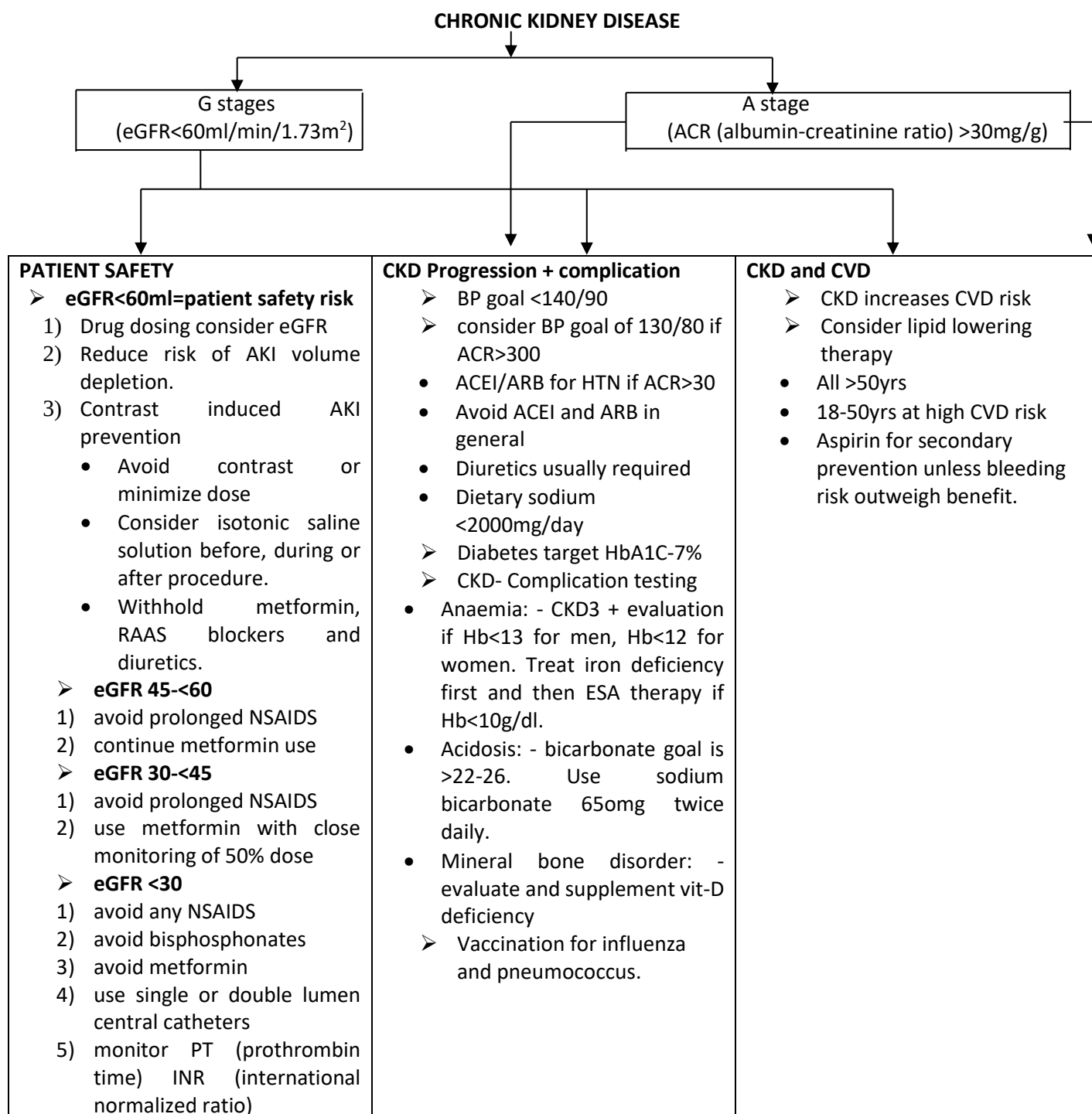
Vitamin-D: - to maintain 25-OHD (20-30ng/ml), vitamin-D supplementation with or without vitamin-D receptor activators (VDRAs) therapy is inexpensive, safe and may have additional health benefits in patients with stage 5 CKD (12).

High blood pressure: - Antihypertensive most commonly prescribed include calcium channel blockers, diuretics, centrally acting sympatholytics, alpha adrenergic blockers, ARBs and beta-adrenergic blockers and alpha plus beta adrenergic blockers (13).

Fluid retention: - As fluid build-up is seen, diuretics are most commonly used (14).

Appropriate selection of drugs to treat CKD is necessary as otherwise, it may lead to unwanted drug effects and also ensures optimal outcome of patients (17). Patients with CKD are at high risk of developing drug related problems as they need complex therapy and even presence of co-morbidities make the situation worse. So, rational drug prescribing is difficult in CKD patients.

Practical Approach to the detection and management of chronic kidney disease Table (16).



Diet: - Dietary intake has an important role in medical management of CKD, and dietary protein is one of the most important parts of dietary intervention in patients with CKD (15). high protein diet may increase the risk of renal hypertrophy, Glomerular hyperfiltration and renal blood flow in healthy subjects. Therefore, a low protein diet is recommended to patients with CKD. They

should also restrict dietary sodium, potassium and phosphorous as excess cannot be excreted (15).

REVIEW OF LITERATURE

1) Various prescribing patterns of drugs in chronic kidney disease

Soumya santra et al., drug utilisation pattern in chronic kidney disease with emphasis on antibiotics. The study

explains about the drug utilisation in chronic kidney disease patients. It states that appropriate selection of the drug and appropriate doses reduces the incidence of nephrotoxicity and better clinical outcomes are seen. So the infections in CKD are managed by prescribing antibiotics and rationalising the use of antibiotics improve quality of life (18). **Pavithra R.Y. et al.**, Drug utilisation pattern of drugs in chronic kidney disease patients in a tertiary care hospital. This study states that the utilisation of antihypertensive drugs like calcium channel blockers, β -blockers, α -blockers combination is most commonly used in non-diabetic patients with hypertension than diabetic patients because β -blockers has known adverse effects like hypoglycaemia. So, it is less commonly used in diabetic patients with hypertension than in non-diabetic with hypertension (19). **Manley HJ et al.**, Medication prescription pattern in ambulatory haemodialysis patients. In this study, they analyzed and compared prescribing pattern of haemodialysis patients in a dialysis centre and concluded that there should be improvement in prescribing patterns (20). **Rajiv A et al.**, Drug utilisation pattern in CKD patients at a tertiary care public teaching hospital. In this study they selected different number of patients and identified different classes of drugs prescribed. They found that cardiovascular drugs are the most prescribed followed by antimicrobials, vit-D and iron supplementations. Most of the patients are prescribed with phosphate binders (21). **Sonikian M et al.**, optimal use of phosphate binders in chronic kidney disease. Hyperphosphatemia is condition seen in CKD patients and treating it is important. Several phosphate binders are available but with variable side effects so there should be optimal use of phosphate binders in CKD patients because the low levels of phosphate in CKD patients have a high impact on cardiovascular diseases (22). **Kiran A et al.**, A study of prescription pattern in the drug therapy of chronic kidney disease. Prescription pattern studies are done to evaluate the quality of care given to the patients in the health care system. Appropriate selection of the drug therapy ensures maximum benefit to the patients and decreases the side effects. A high risk of burden of CKD in Indian population which is leading to morbidity and mortality. Prevalence of CKD was more in men than in women. **Tozawa M et al.**, Analysis of drug prescription in chronic hemo-prescription in chronic hemo-dialysis patients. In hemo-dialysis patients, multiple drug usage was seen. short

term mortality was predicted by number of prescribed drugs and increase in medications were correlated with male sex, diabetes and duplication of drugs (23). **Yoshiyuki M et al.**, medication prescribing patterns of primary care physicians in chronic kidney disease. Antihypertensive drugs were mostly prescribed followed by vitamin-D and sodium bicarbonate and there are certain associations between prescribing pattern and their workplace, speciality and presence of dialysis centre at their workplace (24). **Nobahar M.** Exploration the experiences of haemodialysis patients about drug consumption: A content analysis. Interventions and strategies to promote and improve adherence to medication is needed as there is lack of medication adherence in haemodialysis patients and so appropriate action must be taken on medication adherence by health care authorities (25). **J fasipe Olumuyiwa et al.**, prevalence and pattern of potential drug-drug interactions among chronic kidney disease patients in south western Nigeria. Chronic kidney disease patients require use of multiple drugs due to co-morbid conditions. So, due to use of multiple drugs there are many drug-drug interactions. So physicians, pharmacist must use available interaction checker and reduce occurrence of drug interactions (26). **Smita S et al.**, Evaluation of adherence to therapy in patients of chronic kidney disease. To evaluate the adherence to medication associated with non-adherence to medication in CKD patients. So patients above 18yrs suffering from CKD from six months had interviewed about medication, lifestyle diet by using Morisky medication adherence questionnaire. So they had reported 54% of patients were non-adherent to medication and this non-adherence is due to complex dosing, high cost due to ADRs. 16% of the patients stopped using medications due to high cost. 62% were not known importance of taking medication (27). **Marquito AB et al.**, Identifying potential drug interactions in chronic kidney disease patients. In CKD patients, drug associations are closely related to drug interactions mostly in late stages of the disease (28). **Loqhman-Adham M.** Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. Poor compliance of patients with prescribed medication in many chronic conditions adversely affects the outcome of the treatment. Strategies suggested to improve the compliance of treatment in patients under dialysis and transplant

include simplifying the regimen of the treatment, establishing partnership with patient and by increasing and improving awareness by education and by feedback (29). **Rama M et al.**, Assessment of drug-drug interactions among renal failure patients of nephrology ward in south Indian tertiary care hospital. Polypharmacy is mostly seen in drug prescriptions of CKD patients. In most prescriptions of CKD drug interactions are mostly seen which can lead to severe adverse events and hence there is a need for clinical pharmacist collaboration which is absent in India (30).

2) Various prescribing patterns of drugs in diabetic nephropathy

Devi DP et al., Diabetic nephropathy: prescription trends in tertiary care. Main objective of this study was to evaluate the trends of prescribing in hospitalized patients with diabetic nephropathy. Total 755 drugs were prescribed out of which major classes were GIT plus metabolism (37%) and cardiovascular drugs (28%). Approximately 37% of patients didn't receive medication for diabetes. Insulin prescription (91%) were more than oral hypoglycaemic drugs prescription (9%) (31). **Padmini D et al.**, Diabetic Nephropathy: prescription trends in tertiary care. Drug utilisation studies promote rational use of drugs. Main objective is to evaluate prescribing trends in patients hospitalised with diabetic nephropathy. In this study only 12% of the drugs were prescribed in their generic names. 53% drugs were from WHO essential drugs list. The results of the study showed diabetic nephropathic patients need wide spectrum of drug classes in ATC classification. Mostly prescribed are GIT plus metabolism, CVS drugs, anti-infectives (32).

3) Prevalence, treatment approaches and management of anaemia in chronic kidney disease.

William MC et al., The prevalence of anaemia in patients with chronic kidney disease. This study compared relationship between GFR and anaemia and they observed that with the decline in the GFR there is strong prevalence of anaemia. The percentage of Hb < 12g/dl is increased from 26.7% to 75% when there GFR is decreased from >60ml/min to <15ml/min. so they concluded that prevalence of anaemia increases when there is decreased kidney function (33). **Novak JE et al.**, anaemia management in chronic kidney disease. The study on erythropoietin stimulating agents which are used to treat anaemia in chronic kidney disease patients are observed to increase morbidity and mortality than

increasing haemoglobin and also it states that IV iron is more beneficial and tolerated in CKD patients even if the ferritin levels are more. It also states that erythropoietin stimulating agents are to be targeted when haemoglobin levels are 11-12g/dl but if haemoglobin is less than that level IV iron is beneficial when transferrin is 25% saturated and even if ferritin levels are elevated (500-1200ng/ml) (34). **Bonomini M. et al.**, New Treatment Approaches for the Anaemia of CKD. In CKD normocytic and normochromic type of anaemia is observed. Iron therapy and erythropoietin stimulating agent therapy are mostly preferred in CKD. The erythropoietin introduction into the clinical practice was successful in increasing haemoglobin levels and helps to improve the quality of life and also reduced the burden of repeated blood transfusion but recombinant ESAs are expensive and require parenteral route of administration and there is also a concern that the high doses of ESAs are also leading to significant harm. Several studies are being carried out to discover better drugs to improve erythropoietin level (35).

Lankhorst CE. et al., Anaemia in renal disease: diagnosis and management. Anaemia is a complication mostly associated with widely spread health issue CKD. Anaemia in CKD may be associated with many reasons along with erythropoietin deficiency. The diagnosis and management of anaemia and its cause other than erythropoietin deficiency has to be evaluated. The erythropoietin stimulating agents are used in treatment of anaemia but carry risk and need judicial clearance. Iron deficiency is also seen in CKD patients besides erythropoietin deficiency which is to be treated. The treatment of iron deficiency improve haemoglobin levels and reduce usage of ESAs which leads to improvement in patients condition partially (36). **William M. et al.**, Prevalence and Severity of Chronic Kidney Disease and Anaemia in the Nursing Home Population. Major health concern emerging in older people like nursing home population along with other chronic conditions is chronic kidney disease. The study stated the prevalence of CKD and associated co morbidities in NH population (37). **Samy I et al.**, Prevalence and Associations of Anaemia of CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES). In National Kidney Foundation Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) it was found that the early detection

of anaemia in CKD patients makes the preventive strategies easy and also anaemia prevalence and characteristics were studied (38). **Germain MJ et al.**, Strategies for successfully managing the anaemia of chronic kidney disease in the long-term care setting. The study was conducted on geriatric patients with CKD in management of anaemia and erythropoiesis is also taken as background. This help in increasing the ability of physicians in treating anaemia effectively. The long term treatment of anaemia in CKD should focus on limitations and risk factors associated with current therapies. Generally ESAs are used along with iron supplements but the risk and benefit ratios are taken into consideration (39). **Kalantar-Zadeh K. et al.**, Haemoglobin variability in anaemia of chronic kidney disease. Even though the mean of targeted range of haemoglobin (11-12g/dl) is maintained, the values of haemoglobin remain fluctuating above or below the targeted range. ESAs lead to the fluctuation of the haemoglobin level in cyclic pattern. The maintaining of haemoglobin in recommended levels is very complicated thus patients may have risk of mortality and increased hospitalisation as the cardiovascular events are affected by the ranges of haemoglobin. The adverse effects depends upon the time that haemoglobin levels stayed at high and low values, but it is not proved whether it is due to ESAs or other conditions. Haemoglobin variability is based upon several factors such as drug related, demography related, treatment protocols, pharmacokinetic factors etc. To improve therapeutic outcomes these factors are to be taken into account (40). **Locatelli F. et al.**, An expert opinion on the current treatment of anaemia in patients with kidney disease. The most commonly associated complication with CKD is anaemia which independently affects the cardiovascular outcomes. To treat anaemia nowadays erythropoietin along with iron supplements are used. This study studies about the biosimilars introduction discussion, possible advantages and characteristics in clinical settings. The haemoglobin levels to be targeted are studied, possible treatment options are also studied, to correct anaemia all ESAs are very effective. New drug molecules with pharmacodynamic and pharmacokinetic parameters have been developed. for CKD patients not receiving dialysis, it gives long administrative intervals. Epoetins are cheaper than last generation drugs but to be administered in short time. This study also published

about the Hb(11-12g/dl) level to aim as target (41). **Donald S. et al.**, Intravenous iron supplementation for the treatment of anaemia of moderate to severe Chronic Kidney Disease patients not receiving dialysis. The studies selected 33 CKD patients not receiving any erythropoietin therapy and in them iron as ferric saccharate IV 200mg and elemental iron are administered for 5months. They observed that there is an increase in haemoglobin levels in 22patients as they responded to the IV ferrous saccharate and the remaining patients are non-responders. So, it is concluded that IV ferric saccharate is safe in most anaemic patients with CKD who are not receiving dialysis (42). **Drueke TB et al.**, Does early anaemia correction prevent complication of CKD. Anaemia is one of the major complications of CKD. Over the last years there is use of recombinant human erythropoietin for management of anaemia in CKD patients. So, by using this recombinant erythropoietin in management of anaemia in CKD patients is beneficial and prevent further complication (43). **Avani D et al.**, Utilisation pattern of IV iron and erythropoietin stimulating agents in anaemic chronic kidney disease patients. The study supports that there is an increased utilisation of IV iron supplementation in anaemic CKD patients who are already on erythropoietin stimulating agent therapy. So, by utilization of IV iron supplementation along with ESA there is decrease in therapy duration of ESA. Due to this positive finding the patients who are receiving ESA are supplemented with IV iron (44). **Mario B et al.**, New Treatment Approaches for the Anaemia of CKD. At present, the most leading class of agents seems to be Hypoxia-Inducible Factor (HIF) Stabilizers and is still under development. This class of drug stimulates erythropoiesis by physiologic concentrations of endogenous EPO, which may be a clinical advantage because concerns for ESA safety are higher at the high dose. Sotatercept, traps circulating activin, which is the drug given its potential for not only correcting anaemia but also checking osteoporosis (45). **Philip A et al.**, **A randomized trial of iron iso-maltoside 1000 versus oral iron in non-dialysis depending CKD patients with Anaemia.** Iron iso-maltoside 1000, which is administered intravenously, is more efficacious than oral iron for increase in haemoglobin levels in non-dialysis dependent CKD patients (46).

4) Role of metabolic acidosis in progression of chronic kidney disease.

Ortega et al., Metabolic acidosis and progression of chronic kidney disease: incidence, pathogenesis, and therapeutic options. In CKD patients, metabolic acidosis is seen in early stages of renal dysfunction. Pathogenesis shows the lack of bicarbonate production due to accumulation of acids that leads to the development of tubulo interstitial damage through retention of ammonium and deposition of compliment. This is treated mostly by sodium carbonate. Availability of oral sodium is diverse and is inexpensive (47).

5) Imbalance of sodium and potassium in chronic kidney disease.

Hayes J et al., Association of hypo and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. Mortality in CKD patients is associated with hypo and hyperkalemia. Higher potassium levels are better tolerated in blacks than whites. Race-specific consideration and correction of hypokalemia may slow CKD progression (48). **Checheritha IA et al.,** Potassium level changes-arrhythmia contributing factor in chronic kidney disease patients. Major risk factor for arrhythmia is hypokalemia than hyperkalemia, but any small changes in potassium levels can determine arrhythmias in CKD patients (49). **Kovesdy CP,** significance of hypo and hypernatremia in chronic kidney disease. The most common conditions in hospitalized patients with other co morbid conditions are hypo and hypernatremia. A high prevalence of co morbid conditions are seen in CKD patients that predispose dysnatremias. In CKD patients a substantial incidence, prevalence, and adverse outcomes are seen with dysnatremias (50).

CONCLUSION:

Early recognition with timely initiation of treatment in collaboration with nephrologists will improve the care for CKD patients. Thus, Physicians and nephrologists can play an important role in better outcomes in patients with CKD. So evidence based practice guidelines from NKF and RPA will give care for the CKD patients. So physicians, Clinical pharmacist and pharmacist should be available to check drug interaction and try to reduce the drug interactions.

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