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Review Article

Conventional Therapy for Chronic Kidney Disease: A Retrospective Review

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ABSTRACT

Chronic Kidney Disease (CKD) is defined as abnormalities in either kidney's morphology or its functional derangement, present for more than three months period time, with multiple health implications. Chronic kidney disease postures a high morbidity and mortality rate in global health criterion as per the disease study performed at 2015. The prevalence is highly associated with hypertension, diabetes, glomerulonephritis, and Human Immuno deficiency Virus (HIV) infected patients. Indian studies reported gender specific CKD prevalence, having higher prevalence of CKD among men (8.1% - 21.0%) than women (16.3% - 19.1%). The diagnosis of CKD is made usually on the levels of serum creatinine and blood urea. The management of CKD aimed at multiple factors associated with progression; there is no cure for CKD. Medical management helps to control the signs and symptoms and reduce the progression of disease. Patient with advanced CKD needs renal replacement therapy. Therefore, early detection and correct conservative medical management is the only way to manage CKD. This multi-factorial views, guidelines, protocols, and practices gives us a thrust to study this pattern treatment and furthermore on CKD in future from our locality. This study shows a various standard treatment guideline followed globally.

1. Introduction

Chronic Kidney Disease (CKD) is defined as abnormalities in either kidney's morphology or its functional derangement, present for more than three months period time, with multiple health implications.[1] Recently, Kidney Disease improving Guidelines Outcomes (KDIGO) 2012, clinical practice guidelines for the evaluation and management of CKD have a different staging of substantiating CKD. They propose that CKD is primarily classified based on the etiology, Glomerular filtration rate levels, and albuminuria category. Glomerular Filtration Rate (GFR) categories are classified as G1, G2, G3a, G3b, G4, and G5 respectively.[2,3]

As per the standardized staging of CKD, it results in the possible outcome of ESRD (End stage Renal Disease) in patients who requires replacement therapies like dialysis or transplantation. It postures a high morbidity and mortality rate in global health criterion as per the disease study performed at 2015 worldwide. The prevalence was highly associated with hypertension, diabetes, glomerulonephritis, and HIV-infected patients.[4-6] It leads to frequent hospitalization, hospital-acquired infectious diseases, other co-morbidities, and a reduced rate of life expectancy.

Coordinated professional health care for the improvement of CKD patients including the management of risk factors, other complications, proper patient education is required to boost the quality of life of them. Their needs complete monitoring on anemia, electrolyte balance, lipid profile, cardiovascular abnormalities, diabetes, and other associated co-morbid conditions. An emerging role of pharmacist is to play a vital role in providing optimized interdisciplinary care to patients and elevate recovery from symptoms.[7, 8] Sustainable development goals (SDG) focuses on promoting social development, notices the components that affect global kidney health to reduce premature mortality.[9]

Chronic Kidney Disease postures an increased level of morbidity and mortality rate in the scenario of global health criterion as per the disease study performed in 2015 worldwide. Yet there is no permanent cure for this CKD. Advanced stage needs dialysis (or) a kidney transplant to maintain,

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prolong and to sustain an increased expectancy of life. Hence early detection and correct conventional medical management becomes the only way to manage the disease throughout their life. In this review we explore and expound the extended therapeutic strategies, based on the preventing criterion for CKD.

2. Prevalence of Chronic Kidney Disease

The CKD prevalence of five stages 13·4%(11·7–15·1%), and stages 3–5 was 10·6%(9·2–12·2%) throughout the world -wide mean (95)percent Cl.[10,11] When compared chronic kidney disease (CKD) is more prevalent in women than in men.[12] CKD has a high global prevalence with a consistent estimated global CKD prevalence of between 11 to 13% with the majority stage 3.[13-19] Over 2/3rd of the cases of CKD are diabetes and hypertension in western countries.[20] In worldwide 2017, 697·5 million (95% UI 649·2 to 752·1) cases of CKD. Almost a third of patients with CKD lived in two countries, China (132·3 million [95% UI 121·8 to 143·7] cases) and India (115·1 million [106·8 to 124·1] cases). Bangladesh, Brazil, Indonesia, Japan, Mexico, Nigeria, Pakistan, Russia, the USA, and Vietnam had more than 10 million cases of CKD each. 79 of 195 countries included in GBD had more than 1 million prevalent cases of CKD.[21] Mortality rate 1.2million uncertainty interval people died from CKD.[22]

The prevalence of CKD as 17.2% with stage 1, 2, 3, 4 and 5 as 7%, 4.3%, 4.3%, 0.8% and 0.8% respectively. 43.1% of their cohort had hypertension, and 18.8% had diabetes. Epidemiological studies we need to formalise few issues,

(i) Creatinine estimation should be standardized, which is not the case so far in India

(ii) In absence of co-morbidities should an aging kidney be categorized as CKD and

(iii) As suggested by the guidelines KDIGO, CKD-EPI equation should be used.

A recent study from India is compared with GFR by Gate's method, plasma clearance method and eGFR by MDRD equation. The minority of CKD patients reach ESKD (0.15–0.20%/year over next 10–25 years), this population is 10–100 times vulnerable for cardiovascular (CV) events.[23]

The overall pooled prevalence of CKD among Indian adults was 10.2%. As per highest prevalence was 17.2% which is found among the participants of SEEK (Screening and Early Evaluation of Kidney Disease) and lowest prevalence was 4.2% found among ≥ 20 years old adult residing in Delhi. Age-specific prevalence: Three studies from India were reported as age-specific prevalence of CKD. In age specific prevalence two studies reported that using MDRD equation and the next one used CKD-EPI equations. Gender specific prevalence: Six Indian studies reported that gender specific CKD prevalence. Higher prevalence of CKD among men is ranged between 8.1% and 21.0%. Therefore, studies reported that the CKD prevalence was higher among female participants ranged between 16.3% and 19.1% than their male counterparts.[24-29]

3. Diagnosis

The diagnosis of CKD is made usually on the levels of serum creatinine and blood urea.[31] Supplemental information is provided by Albuminuria levels.[32] One of the following needs to be present for at least 3 months : Decreased eGFR (<60 mL/min/1.73m²).

Table 1. Guidelines, Recommended & Indicated Tests for CKD

Guidelines	Recommended tests	Indicated tests
Belgisch Centrum Voor Evidence Based Medicine (CEBAM)-2012	eGFR creatinine and albumin-creatinine-ratio and urine protein-creatinine – ratio of urine	Imaging renal ultrasound
Haute Autorite De Sante (HAS)-2013	serum creatinine, eGFR, blood count, serum uric acid, serum electrolytes, serum glucose, lipids, serum calcium ,serum PTH, serum 25-hydroxy – vitamin D, Albuminuria, urine leukocytes, hematuria and imaging renal ultrasound	Serum urea, serum albumin, serum phosphorus, serum electrophoresis, antinuclear antibodies, complement, anti glomerular basement membrane, Anti neutrophil cytoplasmic antibodies. 24hrs urine, bladder ultrasound, renal artery Doppler and kidney biopsy
Kidney Disease Improving Global Outcomes(KDIGO)-2013	Hematuria, serum creatinine and Albuminuria	Serum cystatin C and clearance
Kidney Health Australia-Caring for Australasians with Renal Impairment(KHA-CARI)–2013	Blood pressure, serum creatinine, eGFR creatinine, blood count, serum urea, serum albumin,serum electrolyte, serum glucose, lipids,urine microscopy and imaging renal ultrasound	Serum calcium and serum phosphate
British Columbia Medical Association(BMCA)–2014	eGFR and urine albumin creatinine ratio	-
University of Michigan Health System(UMHS)-2014	eGFR ,Albuminuria	Renal ultrasound and renal artery Doppler
Department of Veteran's Affairs(VA-DOD)- 2014	eGFR, Albuminuria and renal ultrasound	-
National Institute of Health and Care Excellence(NICE)-2015	eGFR creatinine .Unless able to detect microalbuminuria : proteinuria-reagent strips Unclear opportunistic detection : hematuria	eGFR cystatin c, inulin, cr-EDTA, l-iothalamate, iohexol, urine protein creatinine ratio and imaging renal ultrasound

The recommended tests are done as a routine procedure but the indicated tests are to be done when the patient needs it specifically. Normal values = eGFR creatinine = >90 mL/min/1.73m^2, Albumin to creatinine ratio = <30, Protein to creatinine ratio = > 3.5, Serum creatinine = 0.6 to 1.21 mg/dL , Serum uric acid = 0.5 to 1.5 mg/dl, Serum calcium 8.6-10.3 mg/dL, Serum PTH 11-51 pg/mL

Marker of Kidney Damage:

In albuminuria, urinary albumin to creatinine ratio is >30mg/g. Structural abnormalities-imaging, urine sediment abnormalities such as hepatitis, red and white blood cell casts, tubular epithelial cells, electrolyte and other abnormalities due to tubular disorders.[33] Most frequently recommended testings were serum creatinine, eGFR and proteinuria. Detailed testing recommendations are issued by Haute Autorite De Sante (HAS) and Kidney Health Australia-Caring for Australasians with Renal Impairment (KHA-CARI). HAS test should be ordered only if recommended by a nephrologist. The various diagnostic tests for the chronic kidney disease and associated diseases are enumerated in **Table - 1**.[34]

4. Management of CKD:

The management of CKD is focused at multiple factors, related to progression and therapeutic strategies including general lifestyle measures, blood pressure control, interruption of RAAS.[35]

Generally, gradual combination of lifestyle modification and pharmacotherapyshould be utilized in lessening the Blood Pressure (BP). The possibility of tapering blood pressure also decreases the developmentof cardiovascular disease incident and chronic kidney disease (CKD).[36] The treatment used in lowering BP may produce tremendous adverse events which includes; cerebral perfusion (contributing to unsteadiness, disorientation and accidental falls) and acute devastation in renal functioning. The risk and benefits should be taken into consideration particularly for BP agents. The curtailment of blood pressure can be tough in CKD patients with co-morbidities like increased conduit artery stiffness which leads to significant increase in pulse pressure (with high systolic and low diastolic pressures) is not uncommon in CKD and diabetics. The soared up pulse pressure declines the effort to decrease the systolic BP in geriatrics and those with coronary artery disease can leads to reduction of diastolic BP to levels well below the diastolic targets, which may be linked with greater morbidity and mortality.

While consideration in the selection of BP lowering agents, it is obliged to be adjusted to the individual patient's requirement. For instance, Angiotensin converting enzyme receptor blockers (ACE-I's) and angiotensin receptor blockers (ARB's) are potentially detrimental in the presence of renovascular disease or hypovolemia, or when used along with NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) or COX-2 (Cyclooxygenase-2) inhibitors.[37]

Diuretics:

Fluid accumulation is one of the causative factors for hypertension in chronic kidney disease. Patients with CKD require the use of a diuretic, in order to attain the blood pressure goal. Three classes of diuretics are used in the management of elevated blood pressure: thiazide, loop and potassium sparing. Aldosterone antagonists are not used widely.

Thiazide diuretics proveto be effective in treating elevated blood pressure and bringing down the risk of CVD. Loop diuretics are efficacious in reducing extracellular fluid (ECF) volume,also they have been used in combinations with other antihypertensive agents in many CKD patients. It proves to be beneficial for CKD patients and also reported by various evidence based studies. It is preferrable for patients with GFR less than 30ml/min/1.73m^2. Patient whom having loop diuretics resistance may be benefitted in combining a loop diuretic with metolazone, which has the mechanism of action at various sites of renal tubule.

Potassium sparing diuretics like triamterene and amiloride are less productive as mono-therapy in lowering ECF volume than thiazide and loop diuretics. They are more often used as an adjunct to thiazide and loop diuretic for averting and treating diuretics-induced hypokalemia and peripheral edema.[38] Dosage regimen of diuretics for the treatment of hypertension is tabulated below.

Table – 2: Management of **CKD**

Pharmacological Class	Antihypertensive Agent	Usual Dose (mg/day)	frequency
Thiazide Diuretics	Chlorthalidone	12.5-50	q24h
	Hydrochlorothiazide	12.5-50	q24h
	Indapamide	1.25-5	q24h
	Metolazone	0.5-1.0	q24h
	Metolazone	2.5-10	q24h
Loop Diuretics	Bumetanide	0.5-4	q8-12h
	Ethacrynic acid	0.25-100	q8-12h
	Furosemide	40-240	q8-12h
	Torsemide	5-100	q12-24h
K^+-Sparing Diuretics	Amiloride hydrochloride	5-10	q24h
	Triamterene	25-100	q24h

Hypertension:

Antihypertensive therapy should be started in diabetic or non-diabetic CKD patients with ACE inhibitor or an angiotensin 2 receptor blockers.[39]

Guidelines for the Treatment of Hypertension in Patients with CKD:

Patient without diabetes: Patients with proteinuria along with chronic kidney disease (urine ratio of albumin to creatinine ≥ 30mg/mol) : Antihypertensive therapy should incorporate an ACE inhibitor (grade A) or an angiotensin-receptor blocker if intolerant to ACE inhibitors(grade D).

Blood pressure is to be aimed below 130/80mm Hg (grade C).

For patients with non-proteinuric chronic kidney disease (albumin to creatinine ratio <30 mg/mmol),antihypertensive therapy should contain either an ACE inhibitor (grade B), a thiazide diuretic (grade B), a β-blocker (patients aged 60 years or less grade B)or a long acting calcium channel blocker (grade B).

Patients with diabetes: Antihypertensive therapy should consist of either an ACE inhibitor (grade A) or an angiotensin receptor blocker (grade A). Blood pressure goal is to be less than 130mm Hg of systolic (grade C) and less than 80 mm Hg of diastolic (grade B).

Patients with large vessel renal vascular disease: Renovascular hypertension should be managed in the similar manner as non-diabetic, nonproteinuric chronic kidney disease.Caution is advised with the use of an ACE inhibitor or an angiotensin receptor blocker due to the risk of acute renal failure (grade D).[40]

(Grade A- Highly validity, accurate and applicable studies, Grade B and C-Studies of lesser degrees of validity, Grade D- Based on lower rank of evidence and clinicians opinion).

This combined approach of encapsulating the National Kidney Foundation consensus report and American Society of Hypertension Guidelines (49,50); ACE inhibitor,angiotensin receptor blocker (ARB), K^+ sparing diuretics ,calcium channel blocker(CCB). Potassium sparing diuretic drugs like chlorthalidone and indapamide may have the risk of hyperkalemia. Note: Hyperkalemia is evident when serum potassium level exceeds 5.5

meq/L. The therapeutic algorithm of hypertension with diabetes is shown in **Figure** 1.[41]

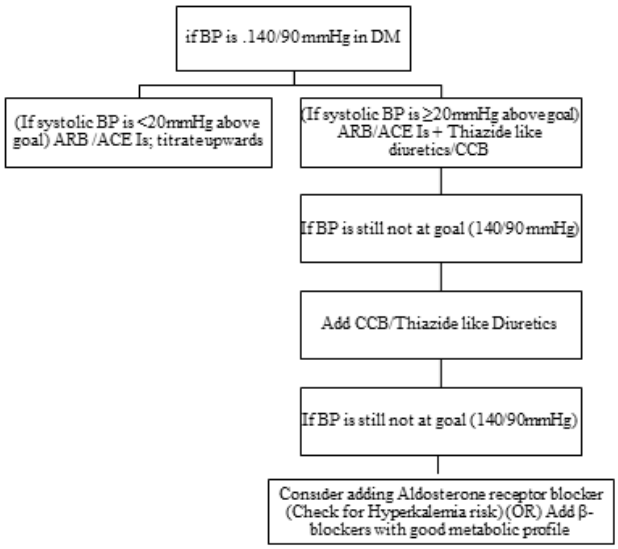

Figure 1. An updated general strategy for attaining BP goals in people with diabetes

The ACE inhibitors and ARB's therapy results in reduced glomerular blood flow, which is revesible; GFR lowers during therapy, if the reduction is < 25% within two months treatment should be carryed on. If the GFR reduced above 25% below the baseline value, the drug should be discontinued and referred for nephrologist opinion.Metformin is used with caution if GFR 30-60mL/min/1.73m^2,and is not advocated if GFR is less than 30mL/min/1.73m^2.Trimethoprim might increase creatinine level but has no effect on GFR[42,43].

Lifestyle Modifications

Management of diet,body weight, and physical activities are the intial strategies of treatment and secondary prevention.[44]Lifestyle intervention involves 4 weeks of group behaviour and lifestyle modification is smoothened up by a dietician and psychologist. This program is aimed at sustainable diet and behavioural changes assisted with weight reduction. The dietician therapy is supported by evidence based practice guidelines for nutritional management of CKD patients with eGFR between 25 and 60ml/min per 1.73 m^2.[45]Restricted intake of salt <6g/day (≤100mmol/day), protein not lower than 0.75g/kg body weight/day & to stabilize serum albumin ≥35g/L[46].

End Stage Renal Disease

Patients having end stage renal disease require renal replacement therapy. The treatment choice for the patients with ESRD includes hemodialysis, peritoneal dialysis, and transplantation.[47]The option of renal replacement therapy (a technique at regular intervals, duration and time gap between sessions,device setting and anticoagulation method) is prescribed normally and followed up according to national guidelines.[48]Renal Supportive Care (RSC) is a initiative that is enclosed in usual renal care along the therapy pathway. RSC includes an interdisciplinary perspective that integrates the expertise of renal medicine and palliative care to aid the CKD patients. This is attained by the management of symptoms and bolstering them in living with terminal illness.[49]

5. Discussion

The chronic kidney disease patients are mostly aimed to maintain the BP below 140/90 mmHg; it can be managed by offering some renin angiotensin system antagonist to them. Before administering renin angiotensin system antagonists, measuring serum potassium concentrations and estimation the GFR should be done. It should be repeated for 1-2 weeks after commencing the course and after every adjustment of (increased) dose. If the serum potassium concentration is more than 6.0 mmol/litre RAAS antagonist dose should be tailored. And if any other drugs that promotes hyperkalemia is being consumed it should be taken out of the prescription immediately.[50]

Hyperkalemia is a condition of increased serum potassium concentration with decreased glomerular filtration levels; it mitigates the renal homeostasis. For CKD patients the potassium level in serum, more than 5.0 mmol/L is considered as pathologic. This altered potassium levels may cause cardiac arrhythmias. A study was performed in Italy and explained about how to normalize the elevated serum potassium level in advanced conditions of CKD by: oral therapy with sodium bicarbonate 3-5g/d can be given followed by a loop diuretic which enhances K^+ excretion, then by therapeutic K^+ binders like calcium polystyrene sulfonate, sodium polystyrene sulphate (not available here).[51-54]

For hypertensive patients, the antihypertensive agents should be selected in accordance with the specific patient individualization. For example, ACE inhibitors and ARBs are not to be recommended in the case of renovascular disease or volume depletion or when used with NSAIDs or COX 2 inhibitors.[37] The common cause of hypertension is fluid retention; these patient's BP can be managed by diuretic agents. The KDOQI clinical practice guideline shows that thiazide and loop diuretic have a effectiveness in decreasing blood pressure, where as potassium sparing diuretics like amiloride are not very efficacious in reduction of ECF volume.[38]

The guidelines have recently amended the management of dietary nutrition among all 1 to 5 staged adult CKD patients. They had explained the micro, macro nutrients and electrolyte balance in patients. It comprises about the electrolytes, energy intake, medical nutrition therapy, micronutrients, nutrition assessment, nutrition supplementation and protein. Nutrition assessment includes determining routine nutrition, energy requirement, laboratory assessment, protein calories intake etc. The adults of stage 1 to 4 CKD are counseled to have more vegetables and fruits to reduce the decline in rate of residual kidney functioning; it also provides positive effect on acid biomarkers.[55-58]

The Canadian Medical Association has defined the guideline for treatment of hypertension with and without diabetes in CKD patients. Patients with diabetes include ACE inhibitor or angiotensin receptor blocker, patients without diabetes are classified into proteinuric and without proteinuric. In patients with proteinuric CKD, hypertension management must contain an ACE inhibitor; for the latter therapy includes ACE inhibitor, thiazide diuretic, β blocker and long acting calcium channel blocker. Patients with large vessel renovascular disease are also treated with the similar techniques as in non-diabetic & non-proteinuric CKD.[40] ACE inhibitors and angiotensin receptor blocker decreases the proteinuria more effectively whereas the non-pharmacological ideas of therapy are considered to be less effective. Similarly another study has compared the effect of ACE inhibitor action with the traditional anti-hypertensive therapy among patients with protein excretion ≥1 gram/day; here former one is more beneficial than the latter.[59-65]

Self management harmonized with prescribed blood pressure medication helps in alleviating hypertension in CKD patients. It includes educating people about their diagnostic plan, and allowing them in decision making

about their care, enabling them to consider their treatment type in severe conditions. National institute for care and excellence (NICE) provide guidelines for health care professionals with evidence based recommendations on existing conditions. The professionals should educate people about the severity of condition, on psychological aspects and conservative management.[66-68]

Likewise, the kidney health of Australia explicates the management of CKD, which shows that ACE inhibitors and ARB causes reversible reduction in glomerular blood flow. That is the level of GFR lowers while starting the treatment, if the reduction is not more than 25% for a couple of months treatment, it can be continued. In conditions like diabetic nephropathy, with type -2 diabetes while prescribing metformin, it can be used with at most care if GFR is 30 - 60mL/min/1.73m^2 and is not recommended if GFR is <30mL/min/1.73m^2.[42,43]

The Non-pharmacological approaches of CKD include lifestyle modifications; initially diet and physical activities are taken care.[44] On diet, limited intake of salt <6g/day (≤100mmol/day), protein not less than 0.75g/kg body weight/day and serum albumin ≥35g/L should be consumed.[45]

If the underlying cause of the disease is known, some types of CKD can be treated. Though, CKD has no cure, conventional medical management usually helps to control the signs and symptoms, and reduce progression of the disease. Patients with advanced CKD need renal replacement therapy or dialysis.[46] Generally the patients on hemodialysis, are affected with depressive thoughts, thus they require antidepressants in addition with cognitive behavioural therapy. It emphasizes a relief in chronic disease patients. So for the patients with ESRD especially psychological comfort is required. A study performed by Grigoriou, Stefania S et al have suggested the group therapy to improve patient's mental health.[69-72] Hence chronic kidney disease patients should be under keen observation, to recuperate them symptomatically. A proper counseling regarding the awareness towards the therapy and compliance required during dialysis in advanced staged conditions should be provided.

6. Conclusion

CKD is a progressive degenerative disease that deteriorates nephron the functional unit of kidney in a while, which leads to functional and morphological deformities of kidney.[1] CKD is a global burden as its prevalence increases not gradually and it is one of the three diseases causing death globally, which makes it more considerable.[73] The management becomes difficult because the symptoms are prominent only after most of the nephrons are damaged.[74] The damage is irreversible so there is no cure in the pharmacological treatment. Though the kidney transplant is available as a choice of treatment, it is not effectively followed in many areas due to the affordability, surgical complications, organ rejection, availability, immune-compromising, co-morbidities, lifestyle (habits and habitats) and other risk factors, etc.[75,76] Despite the permanent cure the disease can be mitigated by pharmacological and non-pharmacological treatments.[35-38] The outcomes of conventional medication therapy is well known and it can help to recuperate from the illness. The advised dietary modifications with simple lifestyle modifications would give more positive outcomes on following up.[55-60] Dialysis is also a treatment option but it is preferred only on ESRD to extend the life expectancy.[47] This multi-factorial views, guidelines, protocols and practices gives us a thrust to study this pattern of treatment and further more on CKD in future from our locality.

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Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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