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CHAPTER 146

Management of Hypertension in Chronic Kidney Disease

Mritunjay Kumar Singh

Abstract

The relationship between hypertension and chronic kidney disease is phenomenal hypertension (HTN) which is considered as most important modifiable risk factor for chronic kidney disease (CKD). Personalized and individualized HTN therapy using standardized office BP and home BP monitoring hold great promise. Angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), Calcium channel blocker (CCB), appropriate diuretic therapy, dietary salt restriction, and ensuring proper adherence to therapy make up the foundation for the treatment of HTN in CKD.

Introduction

Studies from India and abroad have provided concordant data on high prevalence of chronic kidney disease (CKD) worldwide. Up to 1 in 10 people world wide has CKD. It is a silent killer like other metabolic diseases and engages major human and economical resources. Association of CKD and hypertension (HTN) is bidirectional. There is a cause and effect relationship between them. HTN is considered as most important modifiable risk factor for CKD. Managing HTN effectively not only retards the progression of CKD, but also reduces the cardiovascular risk significantly.

Pathophysiology of HTN in CKD

Pathophysiology of HTN in CKD is multifactorial. It contains components of neural and hormonal pathways. The important mechanisms include:

- Impaired sodium excretion—Guyton and his team have shown that HTN can be generated in partially nephrectomized dog (renal mass reduced to 30%) with salt loading. The elevated blood pressure (BP) in this setting is induced by increased cardiac output (volume expansion) initially, and later on sustained by increased peripheral resistance which is due to autoregulatory peripheral vascular bed vasoconstriction in response to increase peripheral perfusion due to extracellular volume expansion. So sodium retention can induce HTN in two ways—at first by volume dependent mechanism (extracellular fluid expansion) and later on mainly through volume independent mechanism like increased peripheral vascular resistance.
- Increased rennin angiotensin aldosterone activity (RAAS)—Hypersecretion of rennin in a sclerosed kidney leads to increased angiotensin II and RAAS activity leading to increased systemic vascular resistance, sodium retention, and high BP.
- Increased activity of systemic nervous system (SNS)—The kidney is richly innervated sensory organ. Several studies from animal and human subjects establish the kidney-brain axis theory. Sensory inputs from kidney transmitted to central nervous system in turn lead to increased activity of SNS leading to vasoconstriction, rennin secretion, sodium retention, and HTN.
- Endothelin dysfunction—CKD is a chronic low-grade inflammatory state and so endothelial dysfunctions are commonly observed in CKD. Endothelial dysfunction leads to impaired nitrous oxide production and
increased endothelin level leading to increased peripheral vasoconstriction and HTN.

- Vascular stiffness—The distensibility of resistance arteries is affected by certain functional and morphological changes. It includes intima hyperplasia, medial calcification, smooth muscle cell hyperplasia, and endothelial dysfunction. These changes are largely contributed by disturbed calcium-phosphorus balance, secondary hyperparathyroidism and other neurohumoral components discussed above. Vascular stiffness leads to increased systolic BP and wide pulse pressure, which is a strong predictor of cardiovascular mortality in CKD.

- The erythropoietin induced HTN and obstructive sleep apnea (OSA) are important causes of HTN in CKD, especially in dialysis population. The erythropoietin or erythropoietin-stimulating agents used for treatment of anemia in CKD can induce HTN or require change in antihypertensive regimen in approximately 30% of the cases. Besides rapid and over correction of anemia, HTN in this subset is thought to be caused by vasoconstrictor effect of erythropoietin, which is independent of hemoglobin. OSA is common in advanced CKD population. Chronic intermittent nocturnal hypoxemia provoke sympathetic nervous system activity, RAAS activity, and increases nocturnal BP.

- Medications like over-the-counter nonsteroidal anti-inflammatory drugs, herbal supplements, steroids, and decongestants can provoke HTN in the CKD population.

- The worsening of HTN has been reported in CKD patients with the use of potent anti-tuberculosis drug rifampicin. Rifampicin is a potent enzyme inducer and decreases the level of commonly used antihypertensive drugs—amlodipine, metoprolol, and prazosin. So it is advisable to monitor HTN in CKD patients, once they have been put on rifampicin.

- The HTN is the most common complication of CKD as well as major factor responsible for progression of CKD. Renal autoregulatory mechanism protects renal vasculatures from elevated BP. Maintenance of afferent arteriole tone in response to elevated systemic pressure and increased sodium chloride delivery to macula densa are part of this autoregulatory mechanism. However, it is impaired in patients with diabetes and non-diabetics CKD, thus leads to progressive renal damage with even moderate elevation of BP.

**Measurement of BP in CKD**

The proper BP measurement is the first step toward the effective BP management in CKD. BP measurement can vary depending on the setting (e.g., casual office, standardized office, or home) and type of device used (e.g., aneroid or Oscillometric). Standardized office BP (SOBP) is 5–10 mm Hg lower than casual office BP. Most of the recent trials on optimum BP goals have used SOBP as a method of measurement. For standardized office BP measurement certain preparations are required—(e.g., 5 minutes of quite rest/no nicotine, caffeine, and exercise 30 minutes prior to measurement/well validated and periodically calibrated device/correct cuff size/middle of the cuff should be placed at the level of right atrium/average of more than two readings obtained on two occasions) as laid down by 2017 ACC/AHA high BP guidelines.

The out of office BP measurement (ambulatory BP and home BP monitoring) is required to diagnose white coat HTN (defined as elevated office BP with controlled out of office BP, prevalence in CKD ranges from 2% to 41%) and masked HTN (defined as controlled office BP and elevated out of office BP, prevalence in CKD ranges from 6% to 51%). Additionally 24 hour ambulatory BP gives clue about the nocturnal BP. Physiological nocturnal dipping is absent in 14–75% of the CKD population. Thus in CKD out of office BP accurately define the clinical problem and predicts more accurately about the cardiovascular and renal outcomes than office BP.

KDOQI (kidney disease outcome quality initiative) US commentary on the 2017 ACC/AHA HTN guideline commented that home BP monitoring can accurately predict target organ damage and better placed than ambulatory BP monitoring and office BP monitoring. HBPM can also help to overcome the therapeutic inertia.

In our limited resource setting we should prefer standardized office BP, because it requires nothing but our little patience (pre-measurement preparation as mentioned above).

**Target BP in CKD**

The management of HTN in CKD is a dynamic process, as estimated glomerular filtration rate, comorbidities...
and risk changes with time. Due to presence of vascular stiffness and wide pulse pressure in CKD, achieving a BP target rapidly may lead to postural hypotension. So a cautious and gradual approach is required to reach a desired BP target.

From 1994 till 2010, there were four landmark trials compared the standard versus intensive BP control in patients with CKD. These were:
- MDRD (modification of diet in renal disease), year 1994
- AASK (African American study of kidney disease and hypertension), year 2002
- REIN-2 (Ramipril efficacy in nephropathy-2), year 2005
- ACCORD (Action to control cardiovascular risk in diabetes), year 2010

Results of all these trials favored standard BP control rather than intensive control in most of the CKD patients, exceptions are patients with proteinuria more than 1 g/day, which were benefited from intensive control of BP. On the basis of these trials, KDIGO (kidney disease initiative global outcome) 2012 suggested a lower BP for significant proteinuria.
- Albuminuria (<30 mg/24 hr): ≤140/90 (1B)
- Albuminuria (>30 mg/24 hr): ≤130/80 (2D)

Till year 2015, it was thought that controlling BP to less than 140/90 mm Hg is likely to be beneficial in CKD population. But with the advent of SPRINT (systolic BP intervention trial) study in 2015, intensive control of systolic BP (<120 mm Hg) has gained momentum. SPRINT has included data from 9,361 adults age 50 or older with systolic BP of 130 mm Hg or higher and at least one additional cardiovascular disease risk factor. Around 28% of participants had CKD without significant proteinuria. The highlights of SPRINT study are:
- intensive reduction in SBP reduces cardiovascular events
- intensive reduction in SBP has mortality benefit in CKD population
- the subgroup analysis of older patients with CKD in SPRINT has also favorable outcome
- with adoption of SBP <120 mm Hg in all CKD population, separate BP target for proteinuria is not required

However, it should be noted that more than 50% of participants in intensive arm of SPRINT had not achieved SBP target after 1 year. So targeting and achieving a lower SBP is a big challenge. Additionally the benefit of lower BP is less certain in diabetic CKD and advanced CKD population. The 2017 American College of Cardiology (ACC) has adopted the result of SPRINT and suggested more intensive BP control in CKD population. In light of SPRINT and other newer studies KDIGO controversies conference 2017 has also suggested for revision in BP diagnosis threshold and BP treatment target.

In our setting, we should target lower BP:
- If SBP/HBPM is the method used for measurement of BP
- If patient is tolerating the target BP well without postural hypotension or other adverse effect
- If patient is having non-diabetic CKD

Secondary HTN in CKD
Secondary causes of HTN are potentially treatable and should be searched in following conditions:
- If the onset of elevated BP occurred before puberty and preceded the development of CKD.
- Severe or malignant HTN that is out of proportion to the degree of CKD is present.
- Acute worsening of BP control occurs in a previously hypertensive patient with good BP control, or resistant HTN is present.
- Persistent hypokalemia off diuretic treatment (primary aldosteronism).
- Development of tremor and palpitation (pheochromocytoma).
- Flash pulmonary edema (renal artery stenosis).

Non-pharmacological Therapy
Early institution of non-pharmacological therapy in the form of dietary modification and life style modification is the first step to the treatment of HTN in CKD.
- Dietary salt restriction (sodium intake <1.5 g/day)—Reduce BP and proteinuria; potentiate the action of ACEI/ARB.
- DASH (Dietary approach to stop HTN) Diet—Diet rich in fruits and vegetables, low in saturated and unsaturated fat can lead to modest reduction in BP. But it is not appropriate to use DASH Diet in advanced CKD because of the potential for hyperkalemia.
- Modest physical activity of 150 minutes duration/week is useful for CKD population. It can be modified...
depending on the cardiorespiratory fitness status and physical limitation of the individual.

- Other lifestyle interventions include weight loss in obese people, limiting alcohol intake, and avoidance of over-the-counter medications such as non-steroidal anti-inflammatory drugs.

**Choosing Antihypertensive Drugs in CKD**

Most of the CKD patients require multiple antihypertensives for adequate control of HTN. Certain classes of antihypertensives are preferred because of their renoprotective, cardioprotective, and diuretics actions apart from antihypertensive effects. Before choosing antihypertensive agents in CKD we should look for comorbidities, risk benefit ratio of individual drug, volume status, and age of the patient.

- Angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)—
  - ACEI/ARB are the agent of choice to treat HTN in diabetic CKD with severely increased proteinuria (>300 mg/day). But the superiority of ACEI/ARB over other agents (calcium channel blockers, diuretics) is questionable in non-proteinuric CKD. However, as majority of CKD patients require multiple agents to achieve adequate control of HTN, it is reasonable to include ACEI/ARB as add on therapy in non-proteinuric CKD patients.
  - The common side effect of ACEI/ARB is hyperkalemia particularly in advanced CKD hence limiting their use despite their proven benefit. Novel potassium binding agents (patiromer and sodium zirconium cyclosilicate) in combination with ACEI/ARB could change the way of pharmacotherapy in HTN in CKD. But further research is required before their routine clinical use.
  - Another potential problem with the use of ACEI/ARB is acute kidney injury. Recent guidelines suggest that up to 30% increase in serum creatinine in first few weeks and later on stabilization is an acceptable physiological change which confers long-term renoprotection.
  - Combination therapy (ACEI+ARB) has failed to show any cardioprotection and renoprotection in major studies. Additionally this combination is associated with increase risk of hyperkalemia, acute kidney injury, and hypotension.

- Calcium channel blockers (CCB)—dihydropyridine (DHP)-CCB (amlodipine) are frequently prescribed antihypertensives in CKD because:
  - they are the potent antihypertensive agents,
  - can work synergistically with ACEI/ARB,
  - work well in volume expanded states, and
  - minimal side effect (pedal edema).

- Diuretics—
  - Sodium retention and volume overload are the main concerns of the majority of CKD patients. Diuretics act by natriuresis (promote sodium excretion through kidney), thus reduce extracellular volume and has been shown to improve left ventricular mass index (LVMi) and arterial stiffness in CKD patients. Diuretics also enhance the BP lowering effect of ACEI/ARB. Thiazide diuretics (hydrochlorothiazide and chlorothalidone) are less effective at lower glomerular filtration rate so switching to loop diuretics (furosemide and torsemide) with frequent dosing is done in advanced CKD. Some times loop diuretics can be combined with thiazide diuretics to treat refractory edema in advanced CKD.
  - Diuretics should be avoided in end stage renal disease with no residual function and polycystic kidney disease as they can lead to accelerated cyst growth and decreased renal function. The major adverse effects of diuretics are volume depletion and electrolyte imbalance.
  - Mineralocorticoid receptor antagonists (MRA) are effective drugs for resistant HTN but may cause hyperkalemia in patients with low-estimated glomerular filtration rate, so better to avoid at estimated glomerular filtration rate below 45 mL/min/m².

- Beta blockers—
  - Although beta blockers has lost credential in treatment of primary HTN in general population, but still they are found to be useful adjunctive therapy in CKD population because they decrease sympathetic over activity and are cardioprotective. A recent trial named HDPAL (HTN in hemodialysis patients treated with atenolol or lisinopril) has concluded that atenolol arm has less cardiovascular
events and better BP control than lisinopril arm in hemodialysis patients.
- Other antihypertensive agents for patients with CKD include direct vasodilator (minoxidil and hydralazine), centrally acting alpha adrenergic agonist (clonidine), alpha blockers (prazosin), and direct rennin inhibitors (aliskiren).

- Resistant and refractory HTN in CKD\(^1,3,16\):
  - The prevalence is up to 40% as shown in CRIC Study. It has got poor prognosis—increases the risk of death by 30% and the risk of heart failure by 59%. The selection of complementary medications and ensuring drug adherence often resolve treatment resistance. Thiazide and thiazide-like diuretics in combination with ACE/ARB or MRA can be very effective in treatment of CKD populations with apparent drug resistant HTN.

### Adherence\(^2,9\)

Adherence to therapy is poor due to frequent dosing of pills, pill burden, drug interaction, and adverse effects. Strategies to improve adherence include:
- Patients should be communicated regarding treatment and its importance.
- Use of combination pill and whenever possible long acting, once a day medication to be used.

### Nocturnal Therapy\(^2,17,18\)

Non-dipping is detected more frequently in later stages of CKD and associated with significant CV death. Multiple clinical trials have shown an improvement in nocturnal dipping of BP by dosing at least one antihypertensive medication at bedtime.

### Management of HTN in Patients on Dialysis\(^2,3,19,20\)

The relationship between BP and CVD in this group is more complex. There is U-shaped relationship between 24-hour ambulatory SBP and all cause mortality as noted by Mayer et al. So BP treatment should be individualized in this group keeping in mind of comorbid conditions. Besides pharmacotherapy, these are the novel measures to treat HTN in dialysis patients:
- Dry weight reduction (DRIP trial)
- Dietary sodium restriction
- Dialysate sodium restriction
- Adequate time on dialysis
- Consideration of frequent dialysis

### Managing HTN Following Kidney Transplantation\(^1-3\)

HTN is common in post-transplant period. It has been reported that HTN is prevalent in more than 90% of calcineurin inhibitors treated kidney transplant recipient. The higher BP is associated with poor graft survival, increased CVD risk, and most common cause of death post-transplant. KDIGO and the ACC/AHA guidelines currently recommend a BP target <130/80 mm Hg. Some useful tips to manage HTN following kidney transplants are:
- Weight control
- Steroid and CNI dose optimization
- During 1st year after transplant, CCB (DHP) is the preferred antihypertensive agent over ACEI/ARB
- In patient with mild graft dysfunction with proteinuria, ARB are the preferred drug
- In case of post-transplant hyperuricemia losartan is the preferred drug

### Future Perspective\(^21-25\)

In recent years, the underlying mechanism and unmet therapeutic needs to halt the progression of CKD and CVD have been better understood. Due to this few promising therapeutic measures have emerged. They are:
- Sodium glucose transport 2 inhibitor (SGLT-2I): Interest in molecules of this group has intensified following the result of EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) trials, which demonstrated significant slowing of CKD progression and a reduction in the composite outcome of death from CVD. Combining ACEI/ARB with SGLT2I may further reduce intraglomerular pressure by their synergistic effects.
- The DUET (Dual Endothelin Receptor and Angiotensin Receptor Blocker) trials with sparsentan and irbesartan have shown promising results in control of HTN and proteinuria in IgA nephropathy and focal segmental glomerulosclerosis (FSGS).
### Renal denervation therapy (RDN): After initial hiccups this radio frequency energy based therapy for ablation of the networks of nerves around renal arteries has shown promising results in newer trials. However, this strategy is still in experimental stage.

### Conclusion

The Prevalence of HTN in CKD is very high, but HTN control rate is far from optimal. When CKD and HTN coexist, CV morbidity and mortality is substantially increased. Personalized and individualized HTN therapy using standardized office BP and home BP monitoring holds great promise. ACEI or ARB, CCB, appropriate diuretic therapy, dietary salt restriction, and ensuring proper adherence to therapy make up the foundation for the treatment of HTN in CKD.

### References

Abstract

Chronic kidney disease (CKD) afflicts approximately 7–10% of adult population of India. It is a silent killer due to its far reaching ill effects on the cardiovascular system. The manifestations of CKD are varied and can mimic a variety of medical and surgical conditions. Early recognition is of paramount importance since preventive strategies are successful only if applied before irreversible renal fibrosis sets in. This article gives an overview of recent evidences. Dietary protein restriction should be applied to meat based diets and not for vegetable proteins. Plant-based protein intake has been shown to be renoprotective due to its alkaline nature and fiber content. RAS blocker therapy, and antihypertensive therapy are the inseparable duo of prevention. A dose escalating strategy of RAS blockade aiming for proteinuria reduction has been successfully applied in the Indian context. However, it requires close serum creatinine and potassium monitoring to prevent harm. Based on well conducted large trials, SGLT2-inhibitors have provided substantial benefits in terms of renal, cardiac, and all cause mortality. Their use is recommended for both diabetic and non-diabetic renal diseases. Sodium bicarbonate and statin usage have shown benefits. However, uric acid lowering therapy has failed to provide beneficial effects in recent trials.

Introduction

Chronic kidney disease (CKD) is a silent killer, which afflicts approximately 7–10% of world’s adult population. It means that India which makes up 17% of world population carries a large burden of the disease. It is commonly mistaken for a number of conditions such as nutritional anemia, nutritional rickets, peptic ulcer disease, dysfunctional uterine bleeding, etc. In the absence of a National Registry, the exact prevalence of the disease is open to conjecture. A population based study showed incidence of End Stage Renal Disease (ESRD) to be 159 per million population. Once a patient reaches ESRD the treatment is not only prohibitively expensive but survival rates are worse than advanced malignancy. Thus every physician should update himself with current practice guidelines for optimal prevention of progression of CKD.

Contributors to Accelerated GFR Loss

The glomerular filtration rate (GFR) falls at a rate of approximately 0.5 mL/min/year in the normal adult population. Patients with progressive CKD the loss of GFR may be as steep as 5–15 mL/min/year. In addition to non-alterable factors such as age, gender, and genetics a number of factors which are potentially treatable contribute to the risk of progression. A recent work showed genetic polymorphisms involving intracellular antioxidant systems can accelerate the progression and mortality dramatically. Dietary factors, lack of exercise, albuminuria, hypertension, hyperglycemia, lipids, morbid obesity, and metabolic acidosis, mini AKIs, and gut dysbiosis are some of the modifiable risk factors.
**Lifestyle Modifications**

**Diet**

Earlier view—Restricting all forms of proteins in the diet retards the progression of CKD.

Current view—Plant based proteins are renal friendly and should be promoted.

In a community-based study of adults without CKD, higher adherence to a healthy plant-based diet or a provegetarian diet was associated with lower KD risk. Higher consumption of healthy plant foods (fruits, vegetables, whole grains, nuts, legumes, coffee, tea) was associated with a lower risk and slower decline in GFR. Dietary red meat contains cardiotoxic metabolites from lecithin and carnitine such as trimethylamines. Plant-based proteins are recommended for a variety of reasons such as higher fiber content, lesser diet acid load, less phosphorus and uric acid generation, enhanced vitamin K (reduction of coronary calcium scores), and promotion of healthy gut microbiome. Dals, lentils, and Soya beans can be substituted for dietary animal proteins such as meat and dairy products. Daily intake of locally available fruits and vegetables are recommended in CKD Stages 3–4. Compensatory potassium excretion from the colon increases when dietary fiber intake is liberalized. Vegetable diet also inhibits the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 in the distal convoluted tubule cells which increase the cortisol induced K excretion in addition to aldosterone effect.

**Physical Exercise**

Physical deconditioning sets in during progressive CKD, which results in muscle energy dysmetabolism. A reduction in mitochondrial activity develops even in earlier stages of CKD, which is progressive. Oxidative stress, inflammation, erythropoietin, vitamin D, and testosterone deficiencies are possible reasons. The symptoms include easy fatigability and proximal muscle weakness. Later, muscle atrophy sets in. As in general population, the cardiovascular benefits of exercise cannot be ignored in CKD patients. Regular moderate intensity exercises involving all the major core groups of muscles are recommended. Both endurance and weight bearing exercises are indicated in Stage 3 CKD.

**Albuminuria**

Earlier view—Albuminuria is a marker of severity of renal disease.

Current view—It is both a marker and maker of progression of renal disease.

Albuminuria is both a marker and maker of glomerular injury. A direct quantitative relationship exists between the higher proteinuric CKD and faster progression. Filtered albumin is taken up by the proximal convoluted tubule cells where it is toxic and inflammatory. Tubulointerstitial fibrosis sets in faster when the rates of proteinuria are higher. RAS blockers have shown to reduce proteinuria and prevent progression of renal disease. Highest tolerable doses of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors are recommended to provide optimal renoprotection. Higher doses are accompanied by hyperkalemia. An important advance has been the clinical entry of New K binding agents like zirconium and patiromer, which permit continued and safe use of RAS blockade in the face of hyperkalemia. In the OPAL-HK study involving CKD patients with hyperkalemia, treatment with patiromer reduced the serum potassium levels and enabled significantly more patients to continue RAS blockers without interruption than placebo. The drug was well tolerated.

**Hypertension**

Earlier target—BP reduction below 130/80.

Current view—More intensive BP reduction below 120–125/<80 in proteinuric CKD.

Long-term follow-up of 15 years in MDRD and AASK trials highlighted that intensive BP control reduced both overall mortality and progression to ESRD. The recently released SPRINT trial data showed that in CKD subgroup the all cause mortality was lower in the intensive arm. However, the incidence of ESRD or a 50% decline in GFR was not altered in the intensive arm. A note of caution is that diastolic BP reduction below 70 mm Hg is not recommended in older adults with atheromatous central arteries, which can lead onto coronary insufficiency.

ARBs and ACE inhibitors are the preferred first-line agents. Maximally tolerated doses of these drugs should be given. As an example losartan is started on 50 mg OD and titrated up depending on proteinuria reduction and BP reduction to 50 mg BID. Supra pharmacological doses
can be prescribed with a close, watch on serum K and BP. The dose required to optimize GFR reduction was 150±88 mg/day in an Indian Study. Although combinations of ACEi and ARBs are prohibited by most of the guidelines, individualization of therapy can result in better outcomes.

Since multiple drugs are required in CKD, calcium channel blockers, diuretics (Thiazides in Stage 3 and loop diuretics in Stage 4), are added in a stepwise fashion. Dietary sodium restriction to below 2–3 gm/day is an important adjunct to improve BP control. Due to concerns about hyperkalemia, there is reluctance to start spironolactone therapy in those with resistant hypertension. Recently published AMBER study showed that when patiromer is added to spironolactone more patients could continue the latter drug without developing hyperkalemia.

Canrenone and Finerenone are novel non-steroidal aldosterone receptor antagonists with low risk of hyperkalemia. Current prospective trials are testing their efficacy and safety in CKD patients.

Glucose Control

Earlier view—Insulin therapy for Stage 3 CKD onward.

Recent view—SGLT2 inhibitors are strongly recommended to prevent progression of CKD and reduce cardiovascular morbidity and mortality.

CREDENCE trial on canagliflozin versus placebo on CKD patients has shown remarkable renal and cardiovascular benefits for patients with diabetic nephropathy. All the patients had an estimated GFR of 30 to less than 90 mL/minute and albuminuria and were treated with renin-angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease, or a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Over a 2.6-year period, the relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group (hazard ratio, 0.70). The relative risk of the renal-specific composite of end-stage kidney disease, or a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66) and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68). Cardiovascular events were also significantly less in the treatment arm. Risk of amputations or fractures were not significantly elevated in the treatment arm. Sodium reabsorption is inhibited in the proximal convoluted tubule cells following SGLT2 inhibitor therapy. This results in more sodium ions reaching the DCT and thereby producing afferent arteriolar vasoconstriction. This ultimately results in renal preservation since intraglomerular pressure is lessened.

GLP1 analogs (liraglutide) have also shown both renal and cardiovascular benefits in trials. In the LEADER trial involving liraglutide new onset of persistent macroalbuminuria, occurred in significantly fewer participants in the liraglutide group than in the placebo group (hazard ratio, 0.74). The reduction in GFR in the placebo arm was ~5 mL/min/year, which reduced to ~0.3 mL/min/year in the treatment group. In contrast, DPP4 inhibitors have not shown reno- or cardioprotective benefits in trials. But they are still useful agents since the incidence of hypoglycemia is less, which enhances the acceptability of the drug in CKD population.

The recommended target HbA1C level for the prevention of progression of CKD is between 6.5–7%. However, in those with higher comorbidities who are prone for complications of hypoglycemia, one can opt for a compromised target of 7.5–8%.

Acidosis Correction

Recent view—Sodium bicarbonate therapy is nephroprotective.

The serum bicarbonate levels are ideally maintained above 22 meq/L in patients with CKD. Acidosis correction improves bone health and retards progression of renal disease. The latter is due to reduced ammonia generation, which is linked to inflammation by stimulation of alternate complement pathway. A condition called normobicarbonatemic acidosis develops in CKD, which is characterized by reduced urinary excretion of citrate. This can be addressed by providing fruits and vegetables, which are a rich source of citrate.

Sodium bicarbonate is commonly given by oral route in tablet or capsule forms. Adult dose is between 1.5–2.5 gm/day depending on the degree of acidosis. Each gram contains 12 mEq of base. The potential side effects include gastric distension and metabolic alkalosis. Aggravation of hypertension is uncommon. It decreases the absorption of ranitidine and increases the propensity of quinolones for crystalluria. It is contraindicated in hypocalcemia and hypokalemia.
Management of Hyperlipidemia

Earlier view—Statin therapy is beneficial at the earlier stages of CKD. No new data have emerged recently.

Observational studies among apparently healthy individuals or in patients with preexisting cardiovascular disease (CVD) have shown a roughly linear relationship between risk of cardiovascular-related death and serum total and low-density lipoprotein (LDL) cholesterol. Among patients with CKD, however, this relationship is much less obvious. The cardiovascular abnormalities in Stage 4–5 CKD are progressive medial vessel wall calcification, left ventricular hypertrophy (LVH) and diastolic dysfunction. These are poorly responsive to statin therapy. There are no new evidences in the last decade in this field in the aftermath of SHARP trial, which showed a significant, 17% reduction in major atherosclerosis events and a 15% reduction in major cardiovascular events in the entire cohort of 9,000 patients. The earlier the statin therapy is initiated, the better were the cardiovascular protection benefits.

Prevention of AKI

Earlier view—Recovered AKI patients regain normal renal function.

Current view—Up to 30% of patients with comorbidities who develop AKI may progress to CKD.

In CKD patients multiple episodes of AKI are the cause of accelerated decline in GFR.

The downtrending of GFR slope from above 90 mL/min to 10 mL/min does not occur in a straight line if plotted against time. There are periods of flattening interspersed with periods of acute reduction. These “Mini AKIs” due to volume depletion, cardiac failure, UTI, hypotension, and NSAID drug toxicity result in incomplete recovery to original levels. It is critically important that these events are aggressively managed.

Intestinal Microbial Flora

Recent view—It is beneficial to alter the dysbiosis, which is prevalent in CKD patients.

Human gastrointestinal (GI) tract is home to trillions of bacteria, which undergo both a qualitative and quantitative alterations in CKD. Products of bacterial metabolism are linked to inflammation, uremic syndrome, and cardiovascular disease. Oral ingestion of probiotics has been shown to reduce the serum levels of products of protein metabolism like p-cresol and indoxyl sulfate, which induce cardiovascular toxicity.

Obesity

Earlier view—Weight loss should be routinely advised in CKD patients.

Recent view—Mildly overweight category of patients show best survival.

The association between body mass index (BMI) and mortality has shown some surprising findings. In a large observational study from US veterans found that best survival of Stage 3–4 CKD was seen in those with BMI between 25 and 35 kg/m². In morbidly obese patients, when bariatric surgery was undertaken, both proteinuria and GFR reduction are attenuated.

Uric Acid

Earlier view—Treatment of hyperuricemia is reno-protective.

Recent view—Hyperuricemia correction does not result in renal benefits.

Uric acid produces inflammation and proliferation of afferent arterioles in mouse models of CKD. Extracellular precipitation in the form of microscopic crystals and macroscopic urate stones can cause structural damage. Intracellular mechanisms show its propensity to precipitate injury relating to its oxidative properties. Humans and other primates are prone to hyperuricemia because enzyme uricase was lost in evolutionary mutation. To lower uric acid levels, xanthine oxidase inhibitors (XOIs) such as allopurinol and febuxostat are commonly used in clinical arena.

Does Reduction of Uric Acid Produce Renal Benefits?

The short answer seems to be no. Based on many observational studies which reported that higher serum uric acid levels heightened the risk for new-onset CKD as well hastened its progression, a commonly held view was that a level above 7 mg% required intervention for renal benefits. However, two large, high-quality trials, which were published recently refuted a causal relationship and revealed that urate-lowering therapy neither prevents CKD nor slows down its progression.
PERL trial randomized over 500 adults with type 1 diabetes and early-to-moderate diabetic kidney disease, with allopurinol versus placebo. At 3 years treatment with allopurinol had no effect on the change in measured GFR compared with placebo; worryingly, allopurinol increased albuminuria, and nonsignificantly increased the rate of fatal or nonfatal cardiovascular events. In the CKD-FIX study of over 350 adults with more advanced CKD, the rate of decline of estimated GFR at 2 years was the same with allopurinol and placebo.

Anemia correction and correction of calcium phosphorus dysmetabolism have not been shown to have any effect on the progression of CKD, and hence they are not discussed at length. But they have to be addressed all the same since cardiovascular and skeletal health are inseparable sufferers from renal dysfunction.

Thus a multipronged strategy implemented with attention to minutiae will be needed. Though the task looks daunting, it is achievable if pursued with dedication as shown by Prof. M. K. Mani at Chennai.

**Conclusion**

CKD can be termed as An Orphan Disease since awareness levels are low even amongst the physicians. The four most effective strategies for its prevention are RAS Blockade, SGLT2 inhibitor therapy, Hypertension control, and Blood Glucose control. In the years to come personalized medicine looking at the genetic makeup of the patient may become an added tool to decide the therapeutic options.

**References**

CHAPTER 148
Lupus Nephritis—Current Understanding and Management

Krishan Lal Gupta, Joyita Bharati

Abstract
Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, and lupus nephritis (LN) is associated with increased morbidity and mortality. Kidney biopsy is essential and the “gold standard” for diagnosing LN. Extra-glomerular involvement is seen in up to two-thirds of patients with LN and is associated with poor outcomes. The revised 2018 International Society of Nephrology/Renal Pathology Society classification for LN has changed parameters for activity index and redefined few pathological parameters. Repeat kidney biopsy is done for resistant disease or during flare, usually when atypical features are present. Protocol biopsy is a promising tool to monitor patients with LN and decide maintenance therapy. Newer therapies like multi-targeted therapy and biological agents such as obinutuzumab have shown promise in treating LN.

Introduction
Lupus nephritis (LN) is seen in 25–50% of patients at the outset of systemic lupus erythematosus (SLE) and about 60% of the patients are affected during the disease course, which varies with race and ethnicity. The probability of a new renal flare is 20–30% per patient-year of follow-up. Patients with LN, particularly those with proliferative histology, are at 2.28 times higher risk of mortality as compared to those without LN and up to one-third of them progress to end stage renal disease (ESRD) within 15 years. The prevalence of SLE and the chances of developing LN vary considerably between different regions of the world, with higher rates in Africans and Hispanics. Most often, LN occurs early (within 5 years) in the disease course of SLE. SLE is more prevalent in women than men across all age groups and populations; the female-to-male ratio is highest at reproductive age, ranging between 8:1 and 15:1, and is lowest in prepubertal children at about 4:3.

Pathology of Lupus Nephritis
LN is initiated by deposition of circulating immune complexes and by binding of autoantibodies to antigens in the glomerulus and vessel walls. This interaction activates complement mediated cytotoxicity, macrophage, and natural killer cell-induced cell cytotoxicity along with Fc receptor-based T-cell mediated cell damage. Anti-phospholipid antibodies can result in thrombotic lesions in the glomerulus and in the vessels. In 20–30% of patients with LN, anti-neutrophil cytoplasmic antibody can be positive and may contribute to the development of vasculitic lesions.

Value of Renal Biopsy
Treatment of LN is guided by the histological patterns described in the classification system 2003 International society of Nephrology/Renal Pathology Society (ISN/RPS) classification. Clinical severity does not always correlate with histological severity and is shown in Table 1.
Therefore, renal biopsy remains indispensable and the “gold standard” to correctly classify LN. The Kidney Disease Initiative Global Outcomes (KDIGO), American College of Rheumatology (ACR), and European League Against Rheumatism/European Renal Association-European Dialysis and Transplantation Association (EULAR/ERA-EDTA) guidelines recommend that a renal biopsy should be performed to confirm and classify LN in cases of SLE with clinical manifestation of proteinuria (>500 mg/day), urinary red blood cells (>5 per high power field) or cellular casts (any), or unexplained renal dysfunction.

**Classification of LN:** The classification of LN (based on histology) has been in place for over five decades with the latest modification in 2018.

2003: ISN/RPS proposed a new classification system that would provide better clinical correlation, uniformity in reporting and reproducibility. The classification schema is based on glomerular pathology, which includes assessment by light microscopy (LM) and immunofluorescence (IF). Class IV LN is the commonest pattern seen worldwide. In a study from our center, of total 232 patients, Class II was seen in 21, Class III in 36, Class IV in 130, and Class V in 30 patients.17

2018: Changes in the 2018 ISN/RPS revision were: the distinction between class IV-S and IV-G was not evidence based and hence, has been removed; the threshold for defining crescent is lowered and various types of crescents are defined in addition; activity and chronicity scores are modified and are required to be mentioned instead of A (activity) or C (chronicity).

**Extraglomerular Involvement**

Tubular atrophy and interstitial fibrosis (IFTA) are one of the strongest predictors of renal failure. Various studies reported vascular involvement in LN to indicate increased risk for progression to renal failure. In a study from our center, of total 197 patients, thrombotic microangiopathy (TMA) was found in 25.4% with 10% having concomitant APS. Patients of LN with TMA had significantly higher rates of oliguria (p=0.035), advanced renal injury, that is, serum creatinine more than 3 mg/dL (p=0.002), fibrocellular and fibrous crescents (p=0.01), and tubular atrophy (0.001) compared to non-TMA patients. They also had higher rates of treatment failure (p=0.02) compared to the group without TMA. Another study (unpublished data) from our center included 241 patients with LN with 60% having tubulointerstitial involvement, 32.3% having vascular involvement. Those with tubulointerstitial and vascular involvement had lower rates of remission.

**Role of Repeat Biopsy**

Repeat biopsy is done during renal flare for refractory LN or as a protocol after induction and/or maintenance therapy for LN. Repeat biopsy is useful as histological transformations are common and may affect treatment decisions. It has also been shown to be predictive of long-term outcomes. Protocol re-biopsies can guide therapeutic decision as 20–50% of patients in clinical complete response after therapy were shown to have histological activity on the biopsy. Furthermore, protocol biopsy after prolonged clinical remission can help in deciding safe withdrawal of maintenance therapy, as

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### Table 1

<table>
<thead>
<tr>
<th>Lupus nephritis class (ISN/RPS)</th>
<th>Proteinuria</th>
<th>Active urine sediment</th>
<th>Increased serum creatinine</th>
<th>Active lupus serology</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>–*</td>
<td>–</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
</tr>
<tr>
<td>Class II</td>
<td>+/- *</td>
<td>–</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
</tr>
<tr>
<td>Class III</td>
<td>++ (NS: 30%)</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Class IV</td>
<td>+++ (NS: 50%)</td>
<td>++</td>
<td>+/-</td>
<td>++/–</td>
<td>++/–</td>
</tr>
<tr>
<td>Class V</td>
<td>+++ (NS: 60%)</td>
<td>++/–</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>Class VI</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
<td>+/-/–</td>
<td>+/-</td>
</tr>
</tbody>
</table>

(+) represents frequent occurrence of symptom/sign, (–) represents infrequent occurrence of symptom/sign. NS: Nephrotic syndrome; * NS is seen in class I/II LN in presence of podocytopathy.
was shown recently in a prospective study on clinically quiescent LN patients.\(^{20}\) Recently, the **EULAR 2019**\(^{21}\) guideline has recommended repeat biopsy in those with incomplete renal response defined as 24-hour proteinuria more than 0.8–1 g/day with stable/improved renal function despite at least 1 year of immunosuppressive treatment. In a study from our center, which included 62 patients who underwent repeat biopsy for clinical indications, we found histological transformations in 61.3% of the patients.\(^{22}\) Class switch from proliferative to non-proliferative occurred in 13.7% and 18.2% of patients with non-proliferative histology switched to proliferative classes. On repeat biopsy, endocapillary proliferation and fibrinoid necrosis decreased whereas glomerulosclerosis and IFTA increased (P<0.001). Presence of IFTA more than 30% and TMA on the second biopsy correlated with worse long-term outcome.\(^{22}\)

**Management of Lupus Nephritis**

Treatment of LN involves use of aggressive immunosuppressive therapy in the induction phase to achieve rapid control of inflammation in the kidneys followed by less intense immunosuppression to maintain remission. The initial phase for induction is for a duration of 3–6 months followed by a maintenance phase of 3–5 years usually.

**Induction Agents**

*Corticosteroids:* Steroids form the backbone of induction therapy of active LN. However, there is an increasing concern about the side-effects with high and prolonged doses of steroids. Many newer trials have investigated this by trying to compare regimens, which include introduction of lesser toxic novel agents to allow reduction of steroid dose versus the standard induction therapy. Based on these concerns and the existing literature, the 2019 **EULAR-ERA/EDTA guideline**\(^{23}\) for LN has recommended the use of methylprednisolone pulse (at doses between 500–2,500 mg) followed by oral prednisolone of 0.3–0.5 mg/kg/day and a rapid taper to reach less than 7.5 mg/day by 3–6 months.

*Cyclophosphamide:* Intravenous cyclophosphamide (CYC) along with corticosteroids became the standard of care for treatment of LN based on randomized control trials conducted by the National institute of health (NIH). The NIH regimen includes monthly intravenous pulses of CYC at a dose of 500–1,000 mg/m\(^2\) for 6 months followed by maintenance with quarterly infusions at same dose for the next 2 years.\(^{24}\) Using this protocol, remission could be achieved in 61% of patients at the end of induction phase and there were no relapses in the 2-year follow-up period. A similar study at our center revealed overall response rate of 70% (Complete + Partial remission) and 30% failure rate (Failure 20% + Death 10%).\(^{25}\) Major side effects associated with CYC such as leukopenia, infections, gonadotoxicity, hemorrhagic cystitis, and risk of malignancies in long-term are associated with cumulative dose received. Fixed low-dose intravenous CYC, that is, six doses of 500 mg every 2 weekly followed by azathioprine (2 mg/kg) as maintenance agent was compared with NIH regimen in the European Lupus Nephritis Trial (ELNT).\(^{26}\) This trial, which included predominantly Caucasians and excluded severe renal involvement, showed no difference in long-term outcomes like patient survival, renal survival, or doubling of serum creatinine in the two arms. Another trial\(^{27}\) done at our center comparing CYC given as ELNT protocol with mycophenolate mofetil (MMF) for induction in patients with LN showed similar renal outcomes in both the arms. A total of 100 patients were equally randomized to receive either CYC or MMF. At 24 weeks, 37 patients in each group achieved the primary end point. The complete remission rate was 50% in CYC and 54% in MMF group.

*Mycophenolate mofetil:* MMF was first used in induction phase in a pilot study conducted in Chinese patients with class IV LN and was shown to be non-inferior to oral CYC.\(^{28}\) Subsequently, a multiethnic study comparing MMF with intravenous CYC, by Ginzler et al.\(^{29}\) showed non-inferiority of MMF as compared to CYC. One of the largest multicentric randomized control trials by Appel et al.,\(^{30}\) Aspreva Lupus Management Study (ALMS) involving 370 patients comparing intravenous monthly CYC with MMF showed similar clinical response rates (53% vs. 56%, respectively) at the end of 6 months in both the arms. MMF had better response rates compared to CYC in Blacks and Hispanics (60% vs. 39%).

Although guidelines for management of LN including ACR, EULAR/ERA-EDTA, and KDIGO recommend CYC or MMF as agents for induction in LN, high dose CYC (NIH regimen) is routinely reserved for severe renal disease (Sr Creatinine >3 mg/dL), crescentic glomerulonephritis, TMA, and in the presence of concomitant extraglomerular
lesions like central nervous system (CNS) lupus or diffuse alveolar hemorrhage.

**Calcineurin inhibitors (CNIs):** CNIs act by inhibiting T-cell activation and, in turn, decreasing B-cell activation and antibody production. Furthermore, it stabilizes the actin cytoskeleton in podocytes, thus contributing to reduction in the degree of proteinuria. However, long-term uses of CNIs are associated with nephrotoxicity and there is a higher chance of relapse once the drug is withdrawn.

**Cyclosporine:** Cyclosporine A and intravenous CYC. Clinical outcomes at the end of induction phase and maintenance phase were similar between two groups; response rates were 52% versus 43% in CYC and Cyclosporine arms, respectively at the end of induction, and they were 38% versus 58% for overall response at the end of maintenance phase. The extended follow-up (median: 7.7 years) of these patients showed similar rates of renal survival, patient survival, and proteinuria in the two arms.

**Tacrolimus:** Comparison of tacrolimus with MMF for induction in active LN patients showed similar rates of complete remission at the end of 6 months. In those with pure membranous LN, tacrolimus resulted in higher response rates of 100% as compared to 75% in MMF group. However, the rates of relapses by the end of 5 years were higher in those who received tacrolimus (62%) than those who received MMF (42%).

**Voclosporin:** Voclosporin is a structural analogue (trans-isomer) of cyclosporine which is fourfold more potent than cyclosporine and is associated with lesser off-target side effects such as cosmetic effects and nephrotoxicity. In addition, it does not require drug level monitoring owing to stable pharmacokinetics. In a recently completed phase 2 trial on patients with LN, voclosporin, added to MMF and low-dose steroid achieved complete renal remission in 32.6% patients with 23.7 mg twice a day dosage regimen as compared to 19.3% in placebo group. The phase III AURA-LV trial evaluating the efficacy and safety of voclosporin in patients with active LN is ongoing, with interim analysis showing promising results.

**Multitargeted therapy:** Combination of tacrolimus (4 mg/day) with MMF (1 g/day) and steroids (intravenous methylprednisolone 500 mg for 3 days followed by 0.6 mg/kg/day of prednisolone), called multitargeted therapy (MTT), as induction therapy was compared with intravenous monthly CYC (0.75 g/m²) in 368 Chinese patients with active LN. MTT was superior to CYC, with complete remission rates being 46% versus 26% at the end of 6 months. However, rates of serious infections were higher in the MTT group.

### Maintenance Therapy

After the induction phase, maintenance immunosuppressive agent is necessary to reduce the risk of flares and further renal damage. NIH trials showed that maintenance with quarterly pulses of intravenous CYC for a period of 2 years had lesser episodes of relapses in comparison to no maintenance. Contreras et al. showed that maintenance with MMF or azathioprine was better than quarterly pulses of CYC in terms of efficacy and side effects.

**MAINTAIN trial:** It included 105 predominantly white patients induced with intravenous CYC by ELNT regimen and were followed up for 5 years. There was no statistical difference between rates of renal flare between MMF (19%) and azathioprine (25%) maintenance, respectively.

**ALMS maintenance trial:** It included 227 patients who achieved remission with MMF induction and were randomized to MMF and azathioprine maintenance. At 36 months, composite outcome which included renal flare, ESRD, doubling of serum creatinine, death, or use of rescue therapy was significantly lesser in the MMF group than the azathioprine group (16.4% vs. 32.4%). The ALMS maintenance trial, which included multiethnic patients, larger number of patients, and had compared composite outcomes, favors use of MMF as maintenance agent over azathioprine. The ACR and KDIGO guidelines recommend use of either MMF or azathioprine as maintenance agent; however, 2019 EULAR/ERA-EDTA guideline recommends MMF maintenance specifically for patients induced with MMF. Duration of maintenance immunosuppression is recommended to be at least 3 years in patients who achieve complete remission at the end of induction therapy. In those with high risk of deterioration of renal function such as failure to achieve complete remission after induction therapy, frequent renal flares, and high disease activity index, prolonged immunosuppression is given usually.
Newer Therapies

Biological Agents

Despite the use of conventional immunosuppressive agents, response rates of LN are only 60–70% at the end of induction therapy. High rates of relapses after achieving remission and reduction of drug toxicity have been unmet needs in the management of LN. Hence, there is need for newer drugs which are safer and more effective. Biological agents with specific targets in the immune system have been used as alternative options for conventional drugs for achieving higher rates of remission, managing refractory disease and as steroid sparing agents.

Rituximab: This is a chimeric monoclonal antibody against CD20 on the B-cell surface. Several nonrandomized studies have shown efficacy of rituximab in managing patients with LN. LUNAR (Lupus nephritis assessment with Rituximab) trial 39 was a placebo-controlled phase 3 RCT. Those in rituximab arm received 1,000 mg of rituximab 2 weeks apart at the start and it was repeated after 6 months. All the patients received three pulses of intravenous methylprednisolone followed by oral steroids along with MMF at a dose of 2–3 g/day. Renal response at the end of 52 weeks was not different between both the arms (57% vs. 46% in rituximab vs. placebo arms).

However, rituximab was shown to be effective in refractory LN. 40 Rituximab has also been proven to be effective as a steroid sparing agent in a pilot trial of 50 patients of active LN who were given two doses of 1 gm/dose rituximab 2 weeks apart along with MMF and single dose of intravenous methyl prednisolone (500 mg). About 86% of patients achieved response (52% complete response and 34% partial response) at the end of 52 weeks. 41 Based on the encouraging results, an open label, multicentric RCT (RITUXILUP) was being carried out using rituximab for steroid sparing effect. Rituximab or any B-cell depleting agent causes B-cell activating factor/B lymphocyte stimulating agent (BAFF/BlyS) to increase, which in turn can lead to early repopulation of remnant B-cells. So, combination of agents to block both would have the maximum effect. To test this hypothesis, CALIBRATE (ClinicalTrials.gov Identifier: NCT02260934) trial was conducted where in patients with resistant active LN were treated with CYC and rituximab followed by belimumab. An interim analysis 42 of data from CALIBRATE shows:

- Anti-BAFF following anti-CD20 for LN did not improve clinical outcome at week 24;
- Anti-BAFF delayed blood B-cell reconstitution following B-cell depletion; and
- Anti-BAFF following anti-CD20 was not associated with hypogammaglobulinemia or an increase in serious infections. Further analyses at 48 weeks and beyond are awaited.

Belimumab: This humanized monoclonal antibody binds to BAFF leading to decreased activation of B-cells. Belimumab is the only biological agent approved for treatment of active SLE. The BLISS-LN (Efficacy and safety of Belimumab in patients with Active Lupus Nephritis) study was recently announced to have favorable findings; although, the results are yet to be published (https://www.clinicaltrialsarena.com/news/gsk-benlysta-sle-phaseiii-data/). It met its primary endpoint demonstrating that a statistically significant greater number of patients achieved Primary Efficacy Renal Response over 2 years when treated with belimumab plus standard therapy compared to placebo plus standard therapy in adults with active LN (43% vs. 32%, odds ratio (95% CI) 1.55 (1.04, 2.32), p=0.0311). Based on the positive post hoc analyses from trials in non LN patients and the benefits of belimumab in observational studies involving LN, it has been suggested to be used as add-on in treating extrarenal flares/disease activity in LN patients by the 2019 EULAR/ERA-EDTA guideline. 23 It can also be used as steroid sparing agent.

Obinutuzumab: NOBILITY trial 43—in patients with proliferative LN, Obinutuzumab (intravenous) in addition to MMF (2–2.5 g/day) and steroids (0.5 mg/kg/day of prednisone followed by taper) versus placebo in addition to MMF and steroids at same doses as intervention arm—overall renal response was higher than placebo arm at 52 weeks. Obinutuzumab was as safe when compared to placebo. From this trial, it becomes apparent that more effective B-cell depletion results in better clinical outcome, unlike the LUNAR trial. More stringent CD19 B-cell depletion could be achieved with Obinutuzumab as compared to Rituximab as Obinutuzumab is a type II monoclonal antibody known to enhance antibody dependent cytotoxicity of B-cells and therefore, better and deeper response.
Other biological agents that were tested or being tested in clinical trials for Lupus Nephritis are:

Trials which failed or were terminated:
- Abatacept (CTLA4-Ig)—(ACCESS trial)—failed to meet the endpoint
- Bortezomib (plasma cell proteasome inhibitor)—trial terminated
- Rituximab (anti-CD20)—failed to meet endpoint
- Ocrelizumab (anti-CD20)—failed to meet endpoint
- Sirukumab (anti-IL6)—failed to meet endpoint
- Tabalumab (anti-BLyS)—failed to meet endpoint

Trials which showed encouraging results or are ongoing:
- Laquinimod—encouraging phase 2 trial results
- Obinutuzumab: humanized anti-CD20 antibody: NOBILITY—phase 2 clinical trial—encouraging results—show better overall renal response than placebo arm
- Belimumab—anti-BLyS/BAFF antibody: BLISS-LN—phase 3 clinical trial—met the primary endpoint
- Rituximab and cyclophosphamide followed by belimumab: CALIBRATE—phase 2 clinical trial
- Anifrolumab—anti-IFN alpha-R antibody: phase 3 clinical trial—TULIP-LN1—ongoing

Conclusion

LN is characterized by flares and about 30–40% of patients do not respond to conventional induction therapy. Protocol repeat biopsy is a promising tool to monitor LN. Less toxic and more effective agents are the unmet needs in the management of LN.

References

Abstract
Nephrotic syndrome is an important presentation of glomerular disease featured by heavy proteinuria, hypoalbuminemia, and edema. The etiology of nephrotic syndrome is more complex and heterogeneous in adults compared to children. The renal function is often normal but can progress to chronic renal failure which depends on the duration and amount of proteinuria. Acute renal failure is rare and mostly caused by a precipitating event. Early recognition is possible through urine protein estimation, but a renal biopsy is often recommended. Current treatment recommendations are mostly based on randomized control trials (RCTs) in children, and there are only small RCTs and a few case series studies in adults. Diuretics are required in large doses due to the low-serum albumin levels. Immunosuppressive treatment is often used with little evidence. Prophylactic treatment to prevent infection or thrombosis is not recommended routinely unless indicated.

Introduction
Nephrotic syndrome is a glomerular disease, defined as a pentad of proteinuria more than 3.5 g/day, hypoalbuminemia less than 3.5 g/dL, edema, hypercholesterolemia, and lipiduria. Patients present with edema, typically periorbital or at dependant sites or as a complication of nephrotic state such as thromboembolism.

Etiology
Nephrotic syndrome may be due to a primary glomerulopathy, secondary to systemic diseases or as a result of genetic mutations. The primary disorders are minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy (MN). Secondary causes are elaborated in Table 1.

Pathophysiology and Clinical Manifestation
Proteinuria
Protein loss is due to glomerular proteinuria. Electrical potential differences generated by transglomerular flow may modulate the passage of macromolecules across the glomerular capillary wall. The podocyte appears to be the major target of injury in idiopathic nephrotic syndrome. Adult-onset primary MN and focal segmental glomerulosclerosis (FSGS) may be due to autoantibodies to podocyte or circulating factor that affect the podocyte.

Hypoalbuminemia
Most of albumin loss is due to urinary excretion leading to reduction in total protein and serum albumin with increased α2-globulin and reduced γ-globulin fraction. Hepatic albumin synthesis is increased in response to the albumin loss mediated by an increase in gene expression and the release of an unidentified circulating factor.

Edema
Two major mechanisms have been thought to be responsible for the development of edema. One is “underfill hypothesis” where secondary sodium retention due to low plasma oncotic pressure causes shifting of fluid into the interstitium leading to underfilling of the
TABLE 1  Secondary causes of nephrotic syndrome

<table>
<thead>
<tr>
<th>MCD</th>
<th>FSGS</th>
<th>MN</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td>• NSAID</td>
<td>• HIV-1</td>
<td>• Class V lupus nephritis</td>
<td>Plasma cell disorder</td>
</tr>
<tr>
<td>• Interferon-α</td>
<td>• Parvovirus B19</td>
<td>• Rheumatoid arthritis</td>
<td>Paraprotein deposit disease</td>
</tr>
<tr>
<td>• Lithium</td>
<td>• Simian virus 40 (SV40)CMV</td>
<td>• Sarcoïdosis</td>
<td>AA amyloidosis</td>
</tr>
<tr>
<td>• Gold</td>
<td></td>
<td>• Sjogren</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>Allergy</td>
<td>Drug induced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pollens</td>
<td>• Heroin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• House dust</td>
<td>• Interferon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insect stings</td>
<td>• Lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Immunizations</td>
<td>• Pamidronate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Poison oak</td>
<td>• Sirolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>• Tyrosine kinase inhibitors</td>
<td></td>
<td></td>
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<tr>
<td>• Hodgkin disease</td>
<td>Hyperfiltration injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mycosis fungoides</td>
<td>Renal agenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CLL</td>
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</tbody>
</table>

Hypercoagulability

Patients with the nephrotic syndrome have an increased incidence of arterial and venous thrombosis, particularly deep vein thrombosis (DVT) and renal vein thrombosis. Thrombotic state occurs mainly due to urinary loss of antithrombin III, plasminogen, protein C and S. Increased platelet activation, thrombocytosis, hyperfibrinogenemia, and inhibition of plasminogen activation also contributes. Renal vein is a common site of thrombosis in nephrotic syndrome, possibly due to stimulation of thrombin production in the glomerular efferent vessels as a result of glomerular injury.

Hyperlipidemia

Hyperlipidemia is triggered by the reduction in plasma oncotic pressure. The severity of the hyperlipidemia is inversely related to the fall in oncotic pressure and resolves with the remission of nephrotic syndrome. Enhanced hepatic synthesis of lipoproteins containing apolipoprotein B and cholesterol and diminished catabolism caused by inhibition of lipoprotein lipase due to elevated levels of sialylated angiopoietin-like-4 (especially triglycerides) is thought to be the mechanism behind this. Lipoprotein glomerulopathy is a rare form of glomerular disease that is associated with dyslipidemia and lipoprotein deposits in the glomeruli.

AKI and CKD in Nephrotic Syndrome

Acute kidney injury (AKI) is less common in nephrotic syndrome. Most cases of nephrotic syndrome have a risk of progression to chronic kidney disease (CKD) except minimal change disease (MCD). Greatest risk factor is the degree of proteinuria (>5 g/day). Table 2 shows various causes for AKI in nephrotic syndrome.

Diagnosis

Urine Analysis

- **Twenty-four hour urine protein estimation:** More than 3.5 g/day is considered nephrotic-range proteinuria.
- **Protein-to-creatinine ratio:** It is only an alternative to the 24-hour urine protein estimation. The total protein-to-creatinine ratio (mg/mmol) on early morning sample of urine is calculated. This ratio correlates closely with daily protein excretion in
g/1.73 m² of body surface area. A value more than 300 mg/mmol is considered nephrotic range. But this method has limitations and 24-hour urine protein estimation is more preferred.

**Serologic Studies**

A number of serologic studies often are obtained in the evaluation of patients with the nephrotic syndrome depending upon clinical setting (Table 3).

**Renal Biopsy**

In adult nephrotic syndrome, biopsy is indicated when the etiology of persistent nephrotic-range proteinuria is in doubt in order to determine management decisions.

Indication for biopsy:
- Adult with nephrotic syndrome
- Children with:
  - age <1 year or >12 years
  - Gross hematuria
  - Marked hypertension
  - Renal failure without severe hypovolemia
  - Low C3 level

**Imaging**

- **Ultrasound**: It must be done routinely before planning renal biopsy to rule out small kidneys or kidneys with severe cortical thinning, as they indicate chronic irreversible disease. These findings can limit renal biopsy and aggressive immunosuppressive therapy.
- **2D Echocardiography**: When infective endocarditis is suspected.
- **Renal Doppler**: Indicated in patients with flank pain, hematuria, and rapid worsening of renal function to rule out renal vein thrombosis.

**Histological Patterns**

See Table 4.

**Management**

Management of nephrotic syndrome consists of general supportive measures, disease-specific therapy for the underlying cause in secondary nephrotic syndrome, and immunosuppression in case of primary nephrotic syndrome.

**General Supportive Treatment**

It includes measures to reduce proteinuria, edema, control blood pressure, and to address other metabolic consequences of nephrotic syndrome.

**Treating Edema**

All patients with nephrotic edema are initially treated with diuretics and dietary sodium and water restriction. It is recommended to restrict salt intake to less than 3 g per day and water intake less than 1.5 liter/day. Most patients respond well to loop diuretics. They are highly protein-bound but this bonding is reduced with hypalbuminemia resulting in a slower rate of delivery to the kidneys. Loop of Henle may be relatively resistant to loop diuretics. Gut edema also limits the oral absorption of diuretics. Thus, the effective diuretic dose is usually higher in patients with nephrotic syndrome. Intravenous infusion can also
be tried as it increases the diuretic efficacy. Furosemide 40 mg orally twice a day or bumetanide 1 mg twice daily is a reasonable starting dose and may be increased up to a dose of 600 mg/day according to need. Patients who do not respond adequately to loop diuretic require the addition of a thiazide diuretic. Alternatively, amiloride or acetazolamide can be combined with loop diuretics in patients with refractory edema. Prior administration of albumin increases the efficacy of diuretics.

**Proteinuria**

Progressive loss of renal function can be reduced if proteinuria can be reduced below 0.5 g/day. It can be controlled by either blocking efferent arteriole vasoconstriction or decreasing the preglomerular pressure (antihypertensives). Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) are the agents of choice. They reduce proteinuria independent of blood pressure and can be safely used in normotensive patients. If proteinuria persists in spite of ACEI/ARB, aldosterone antagonists can be added. They can raise the serum creatinine by 30–40% as glomerular filtration rate (GFR) is reduced, but should not be stopped unless serum creatinine levels are continuously increasing.

**Hypoproteinemia**

Adequate dietary protein intake of 0.8–1 g/kg/day with high carbohydrate to maximize the use of that protein is recommended. In heavy proteinuria, add the amount of urinary protein loss to dietary protein intake. As a last resort, nephrectomy and renal artery embolization can be done if protein loss cannot be managed medically.

**Hypertension**

Hypertension in nephrotic syndrome requires strict control to delay the progression of renal disease and prevent cardiovascular complications. Initially life style modification can be adopted. High dose diuretics and dietary salt restriction are necessary. The KDIGO guideline recommends a target BP <130/80 mm Hg, but recent SPRINT trial suggests a target of 120/80 mm Hg. ACEIs and ARBs are the first choice. DHP-CCBs are not preferred as they increase GFR causing worsening of proteinuria and also add to peripheral edema.

**Hyperlipidemia**

Control of hyperlipidemia is important in preventing cardiovascular complications. Dietary modification alone has only a moderate effect on hyperlipidemia. Statin alone is preferred in patients more than 50 years of age with early stage CKD and in late stages, addition of ezetimibe is recommended. In young adults, consider statin if having significant comorbidity.

**Prophylaxis for Thrombosis**

The decision to prescribe prophylactic anticoagulation must be balanced against the risk of bleeding. If the
bleeding risk is unclear, ATRIA Risk score or HAS-BLED risk can be used to take a decision. Prophylactic low-dose heparin is indicated in cases with high risk for thrombosis, like in pregnancy or an immobilized patient, with a serum albumin less than 2.5 g/dL. If albumin is less than 2 g/dL, full anticoagulation with low-molecular-weight heparin (LMWH) or warfarin should be considered. Patients with MN are at high risk for thrombosis, and if the albumin level is very low and even if the risk of bleeding is intermediate, they may benefit from anticoagulation. Warfarin is preferred over LMWH because of low levels of antithrombin III impeding efficacy.

**Management and Prevention of Infection**

Risk of infection is exacerbated by nephrotic immunodeficiency caused by T-cell transformation dysfunction and urinary loss of immunoglobulins including IgG and alternate pathway complement factors. Patients may develop recurrent respiratory and urinary tract infections, peritonitis, and sepsis; particularly with encapsulated bacteria. Antibiotic with pneumococcal coverage is the mainstay in infections and prophylactic pneumococcal vaccination is recommended. In case of repeated infection, IgG level should be estimated and if low IVIgG should be given to maintain a level above 600 mg/dL.11

**Treating MCD**

**Initial Treatment**

Low dose oral prednisolone (1 mg/kg/day up to maximum 80 mg/day) should be started according to KDIGO guideline and recommends it to be continued up to 6 months. Initial dose should be maintained for a minimum of 4 weeks if full remission achieved or 16 weeks if full remission not achieved. Once remission has been achieved, dose should be tapered at least within 4 weeks of response. Induction with methylprednisolone pulse therapy may lead to rapid response and fewer relapses. If the patient has not achieved remission even after 12–16 weeks of treatment, consider repeating biopsy, as it can be FSGS which might have been missed due to limited number of nephrons in earlier specimen. If MCD presents with non-nephrotic range proteinuria, it can be managed with ACEIs/ARBs and there is no need for starting steroids.

**Steroid Dependent (Table 5), Frequently Relapsing and Resistant MCD**

These patients should be started on second-line therapy. This includes:

- **Cyclophosphamide**: 2–2.5 mg/kg/day orally for 12 weeks is given. Due to risk of infertility, banking of sperm and ova is to be considered before starting therapy.
- **Calcineurin inhibitors**:  
  - **Cyclosporine**: 4–6 mg/kg/day for at least 12 months is given. Nephrologists prefer calcineurin inhibitors over cyclophosphamide in young adults to prevent infertility.
  - **Tacrolimus**: A dose of 2–4 mg twice daily, adjusted to maintain a target level of 5–10 ng/mL is given. It may be considered as a first line or second line in patient with contraindication for or intolerance to high dose corticosteroid.12
- **MMF**: 750–1,000 mg twice daily for 6 months may be used in cyclosporine dependant cases but did not appear as effective as cyclosporine in studies.
- **Rituximab**: It is a B-Lymphocyte depleting agent (anti-CD20) and is used when disease is unresponsive to all

**TABLE 5** Terminologies regarding treatment outcomes of nephrotic syndrome

<table>
<thead>
<tr>
<th>Complete remission</th>
<th>Reduction of proteinuria to ≤0.20 g/day and serum albumin &gt;3.5 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial remission</td>
<td>Reduction of proteinuria to between 0.21 g/day and 3.4 g/day ± decrease in proteinuria of ≥50% from baseline</td>
</tr>
<tr>
<td>No remission</td>
<td>Failure to reduce urine protein excretion by 50% from baseline or persistent excretion uPCR &gt;2000 mg/g (&gt;200 mg/mmol)</td>
</tr>
<tr>
<td>Steroid resistance</td>
<td>Persistence of proteinuria despite prednisolone therapy, 1 mg/kg/day for 16 weeks</td>
</tr>
<tr>
<td>Relapse</td>
<td>Proteinuria ≥3.5 g/day occurring after complete remission obtained for &gt;1 month</td>
</tr>
<tr>
<td>Infrequent relapse</td>
<td>One relapse within 6 month of initial response, or one to three relapses in any 12-month period</td>
</tr>
<tr>
<td>Frequent relapse</td>
<td>Two or more relapses within 6 month of initial response, or four or more relapses in any 12-month period</td>
</tr>
<tr>
<td>Steroid dependence</td>
<td>Two consecutive relapses during corticosteroid therapy, or within 14 days of completing corticosteroid therapy</td>
</tr>
</tbody>
</table>

Reference: Comprehensive Clinical nephrology - 6th edition
other treatments, but RCT have not been performed. Non RCT studies have shown benefit and reduction in relapse in corticosteroid dependant and frequent relapse cases. A dose of 375 mg/m² weekly for 4 weeks.

FSGS
It is very difficult to distinguish between primary and secondary FSGS and most of the times they are treated as primary FSGS. All patients will benefit from good supportive treatment and immunosuppression.

Initial Treatment
It consist of 6 months of continuous corticosteroid (1 mg/kg/day), later tapered over 4–8 weeks.

Steroid Resistant Cases
- Cyclosporine: Low dose of 3–6 mg/kg/day is given for 2–6 months. Recent studies show that combination of cyclosporine and corticosteroids has a higher remission rate.
- Tacrolimus: Used in cases resistant or intolerant to cyclosporine.
- MMF and Dexamethasone: As per KDIGO guidelines, they can be given in corticosteroid resistant cases that are intolerant to calcineurin inhibitors.
- Rituximab: Used when all other treatments fail and this drug has shown promising results in steroid-dependent cases.
- Abatacept (CTLA-4-Ig): An inhibitor of T-cell costimulatory molecule B7-1(CD-80) showed remission in some patients and further studies are in progress.

Secondary FSGS
Patients with primary FSGS typically present with an acute onset nephrotic syndrome, whereas slowly increasing asymptomatic proteinuria and renal insufficiency over a period of time without profound hypoalbuminemia or edema are characteristic of secondary FSGS. Unlike primary FSGS, these patients are less responsive to immunosuppression and the mainstay of the treatment is to correct the primary cause and provide supportive treatment.

Membranous Nephropathy
It is very difficult to treat MN due to its chronic nature, the tendency for spontaneous remission and relapse and the variability in clinical severity. Specific immunosuppressive therapy should not be considered unless the patient has a persistent nephrotic-range proteinuria (>4 g/day) and it has not declined more than 50% from baseline, over a minimum period of 6 months, despite maximum antihypertensive and antiproteinuric therapy. Treatment of secondary MN focuses on cessation of the offending drug or effective treatment of the underlying disease.

Immunosuppression
- Corticosteroids: RCTs showed no significant long-term benefit on proteinuria or rate of disease progression. Therefore, use of oral corticosteroids as a single agent is not recommended.
- Cytotoxic agents with corticosteroids (PONTICELLI REGIMEN): Benefitted in patients at moderate risk for progression. It starts with methylprednisolone pulses 1 g IV for 3 days at the beginning of months 1, 3, and 5 followed by oral methylprednisolone 0.4 mg/kg/day for 27 days, and each cycle followed by 1 month of cytotoxic agent (cyclophosphamide or chlorambucil). Cyclophosphamide-based regimen is preferred because of a better safety profile.
- Calcineurin inhibitors: Given in patients with corticosteroid-resistant MN but has a higher relapse rate.
  - Cyclosporine: It is used along with low-dose corticosteroids. It may reduce proteinuria not only through its immunosuppressive effects but also by direct effects on the podocyte.
  - Tacrolimus: It can be used as monotherapy, but relapse rate was found to be high.
- MMF: Along with steroids, it showed good initial response, but relapse rate was high.
- Rituximab: Used in steroid resistant cases. Decline in anti-PLA2R antibody and proteinuria was achieved, subsequently resulting in a partial or complete remission.

Plasma Exchange
It may be useful in resistant MN, severe nephrotic syndrome, and high anti-PLA2R antibody titer cases. A
study in such type of patients, treated with a "rescue" regimen consisting of four plasma exchanges, 20 g of intravenous (IV) immunoglobulin, and 375 mg/m² of rituximab showed shorter remission time compared to previous regimens.19

Adrenocorticotropic Hormone (ACTH)
ACTH acts via melanocortin 1 receptor expressed on podocytes. Synthetic form of ACTH, 1–2 mg weekly intramuscularly for 1 year showed prolonged remission in the majority of patients with MN.20

Conclusion
Nephrotic syndrome includes a wide spectrum of primary glomerular disorders and secondary diseases. Early recognition through urine protein estimation and bringing out the histological variant through renal biopsy aids in planning treatment properly in order to prevent progression into renal failure. At present, reducing proteinuria and immunosuppression remains the mainstay in most of the cases and larger RCTs are lacking. Many new treatment targets have been identified, which needs further studies. A proper recommendation for management of nephrotic syndrome needs to be postulated.

References
Abstract

Epidemiological data suggests that dietary salt is a modifiable risk factor for hypertension; especially in those with salt consumption in the highest tertile. WHO recommends 5 gm of salt intake per day but we in India are consuming 9–12 gm of salt per day. Besides hypertension, salt is also incriminated for CV mortality, stroke, and obesity. Hence, there is need to restrict salt consumption to check the menace of hypertension. Here we bring the update on association of salt and hypertension.

Introduction

Today over 30% of world’s adult population has hypertension (HT). Over 60% of the cerebrovascular diseases and about half of ischemic heart diseases are attributable to HT. Dietary salt is one of the modifiable culprits in causation of HT. Present commentary is about data on dietary salt and its association with HT.

Historical Perspective

During paleolithic times, hunter gathering man was dependent on raw meat and his dietary salt intake was less than 1 gm a day. Around 5,000 years back, Chinese learnt that food can be preserved with the help of salt and Egyptian used this knowledge for preservation of mummies. Civilizations started developing along the salt routes, which was considered a precious entity. In Libya, salt was exchanged for equivalent amount of gold. French salt tax “gabellee” probably incited French revolution. In India, Britishers did not allow Indians to make their own salt and wanted them to buy expensive salt brought from England. This was the genesis of famous Dandi March, an important event in the freedom struggle of India. Salt (NaCl) crystals are white in color and readily dissolve in water. The molar mass is 58.5 g/mol.

With agricultural revolution our food habits changed, and from 100% animal food, now plant based food formed 50% of our diet; however, salt intake remained less than a gram per day. Earliest comment relating to dietary salt and HT came from Chinese doctor, Huang Ti Nei Ching Su Wen, who wrote in The Yellow Emperor’s Classic of Internal Medicine—“therefore, if large amounts of salt are taken, the pulse will stiffen or harden.” However, over the years with civilization and changing food habits our dietary salt intake has increased and this is being correlated with increasing prevalence of HT. Today average Indian salt intake is 9–12 gm/day against WHO recommendation of 5 gm. In this article we shall review the available data showing correlation between salt intake and HT.

Consumption and Its Source

A study reported by George Institute from India found that average Indian is taking 10.98 gm of salt per day. Salt consumption is higher in south Indians than north Indians. If one looks at the source of consumed salt, there
are three sources: our natural food (cereals, vegetables, fruits, non-vegetables) contains less than a gm of salt and makes 10% of daily intake. Another 2–3 gm (20–30%) is added as cooking salt in our food and vegetables. However, 70% of our consumed salt comes from processed food—snacks, bread and bread products, pizza, French fries, pasta, pickles, sauces, etc. It may be interesting to know that each large slice of bread has 500 mg of salt in it. Twenty-four hour urinary sodium estimation is the best marker of salt consumption.

Data on Salt Studies and Hypertension

- **Epidemiologically:** It is known that areas with low salt consumption have lower incidence of HT. Solomon islanders consume less than 2 gm of salt per day and have an HT prevalence of 1%. Among Yanomamo Indians from Brazilian amazon, 84% have urinary sodium excretion of 1 mmol/24 hours. Their mean BP is 96/60.0 mm Hg (78/37–128/86 mm Hg) and there is no change in BP with age. In tribes with salt intake of 3 gm/day, prevalence of HT is 3%. Interestingly in Newfoundland average salt intake is of 6.7–7.3 gm and HT prevalence is 15%. Its coastal area where salt consumption is of 8.4–8.8 gm/day, HT prevalence is 27%. This data suggests that with increasing salt intake prevalence of BP increases.

- The effect of life style change and migration is exemplified by Yi community living in southwestern China. Those still living in mountainous environment and eating sodium-poor diet had yearly rise of systolic and diastolic BP by 0.13 and 0.23 mm Hg, respectively. In contrast, Yi community who had migrated in urban areas and consumed sodium-rich diet had a yearly rise of 0.33 mm Hg for both systolic and diastolic BP, stressing the importance of life-style change on BP.

- **First good animal study about salt and its correlation with HT came from chimpanzees that are phylogenetically similar to humans. Normally chimpanzees eat diet rich in fruits/vegetables with dietary salt content of 0.5 gm/day. Study was done on 26 chimpanzees.1 To their normal diet ~15 gm of salt was added. BP started rising and after 84 weeks BP rose by 33/10 mm Hg. Again chimpanzees were reverted back to their original diet, without added salt. BP reverted back to normal 6 months later. Study shows the effect of salt on BP in chimpanzees.

- The first double-blind controlled study of moderate salt restriction on human was from MacGregor et al.2 They recruited 19 patients with mild to moderate HT (average supine BP of 156/98 mm Hg). Patients were advised not to take sodium laden food. After 2 weeks of dietary salt restriction, patients entered an 8-week double-blind randomized crossover study. One group was given “Slow Sodium Ciba” (Ciba-10 mmol of sodium per tablet) and other group received “Slow Sodium Placebo.” In fourth week, the mean supine BP was 7.1 mm Hg (6.1%) lower in slow sodium placebo group (p<0.001). Urinary sodium excretion in the fourth week of slow sodium ciba was 162±9 mmol/24 hours and that in the fourth week of slow sodium placebo was 86±9 mmol/24 hours (p<0.001). They suggested that moderate sodium restriction should become part of the management of essential HT and one should avoid sodium-laden foods.

- First large international study on salt and HT was “Intersalt study.”2 The study was conducted in 52 centers from 22 countries; each with sample size of 200 with a total of 10,079 participants. Four of these 52 centers, were tribal belts with very low salt consumption. Data from 48 centers showed an insignificant trend but pooled data from 52 centers showed that higher salt consumption was associated with age-related rise in BP. This study prompted lot of debate whether to reduce salt consumption or not. A revisit of study inferred that 100 mmol of extra salt intake (70 mmol vs. 170 mmol) was associated with higher BP by 5–7/2–4 mm, stressing the need to reduce salt intake.

- A community trial was done to study the effect of salt on HT in Portugal. Two communities with 800 persons each were selected. Both had salt intake of 21 gm/day and HT prevalence of 30%. In one of the two communities with extensive health education, salt intake could be reduced to 12 gm/day. By the end of second year BP dropped in intervention community by 13/6 mm Hg. BP drop was across all age groups and in both normotensives and hypertensives alike. Those with greatest fall in salt excretion had the largest fall in BP.

- **Trials of hypertension prevention (TOHP I & II):** TOHP I was conducted over 18 months’ duration and TOHP II for over 36 months. Lower salt intake (lower by 44 mmol and 33 mmol/day) in intervention group was
associated with 25% lower CV events. So, besides lowering BP, lower salt intake is associated with lower CV events also. A meta-analysis of 13 studies, with 177,025 participants (FU 3.5–19 years) showed that higher salt intake was associated with greater risk of stroke (RR 1.23) and cardiovascular disease (RR 1.14). A Finnish study on impact of salt and CV events, comprising of 1,173 men and 1,263 women found that increased sodium intake by 100 mmol/day increased the hazard ratio for coronary artery disease, CV disease, and all-cause mortality by 50% (HR of 1.51).

- **INTERMAP study:** A recent study (Hypertension 2018;71:631-37) included 4,680 persons from China, Japan, UK, and the USA. This study addressed the effect of dietary salt intake on BP and its possible modulation with other dietary factors. Study found that group with two SD higher sodium excretion was associated with rise in BP by 3.5/1.7 mm Hg (p<0.001) and most other 26 micro- or macronutrients in diet had only a modest countervailing effects on Na-BP relationship. The study again emphasized the need for salt restriction as other micro- or macronutrients did not make much difference.

- **Prospective urban rural epidemiology (PURE) study (Mente et al., 2018)** was conducted in 18 countries on a population of 1,68,000, in the age group of 35–70 years. The 664 communities from low, middle, and high income countries were selected. A 24-hour sodium excretion was divided into three tertiles: low—4.04, middle—4.70, and high tertile—5.75 gm. The study found that mean systolic BP increased by 2.86 mm Hg per 1 gm increase in salt intake. Sodium intake was also associated with cardiovascular disease and strokes. This association was however significant only in those falling in highest tertile of salt intake (p<0.0001). Study suggested that those in highest tertile of salt consumption had significant detrimental effect.

- **Dietary approaches to stop hypertension (DASH):** In this study 412 normotensive and hypertensive participants were assigned to eat either typical American diet (control diet) or DASH diet. DASH diet is rich in fruits, vegetables, and has low-fat dairy products. Aim of the study was to test if DASH diet reduced BP and if salt reduction in patients on DASH diet had an additional advantage. Study population was divided in three groups:
  - high salt intake—150,
  - intermediate salt intake—100, and
  - low salt intake—50 mmol/day.

In control group, reduction of sodium intake from the "high to the intermediate level" over 30 days, resulted in reduction of systolic BP by 2.1 mm Hg (p<0.001) and in the “from intermediate to the low level” by 4.6 mm Hg (p<0.001). In DASH group salt reduction resulted in drop of BP by 1.3 mm Hg (p=0.03) and 1.7 mm Hg (p<0.01) “from high to intermediate” and “intermediate to low salt” group respectively. Benefit of salt reduction was observed in both sexes, all races and in normotensives also. The study inferred that participants in DASH diet had a significantly lower systolic BP at each sodium level. If one compares control diet group with high salt intake and DASH diet group with low salt intake, there is a BP difference of 7.1 mm Hg in normotensives and 11.5 mm Hg in hypertensives.

Few important points emerge from these studies:

- Epidemiological data clearly shows low prevalence of HT in areas with low salt intake.
- Animal and human trials show drop in BP with reducing salt intake and increase in BP with increased salt intake.
- Cardiovascular mortality also increases with increase in salt intake.

An important inference is that prevalence of HT and risk of CV mortality is prominent and significant in group with highest tertile of salt intake.

- **Salt intake and obesity:** It has been observed that excessive salt intake is associated with obesity. As small as 1 gm of extra salt consumption per day by children and adolescents has been found to be associated with consumption of 27 gm of sugar-sweetened soft drink. There has been controversy, if obesity is due to consumption of extra sugar or processed food or due to extra salt. However, increasing evidence suggests that there is direct link between salt intake and obesity independent of total energy intake. Even after adjusting variables like ethnic group, social status, energy intake, educational status, smoking, alcohol consumption, etc., 1 gram a day of extra salt increases the risk of obesity by 28% (p=0.0002) in children and 26% (p<0.0001) in adults.

- **Is very low salt intake detrimental:** In the “Framingham Offspring study” —a 16-year follow-up data, of 2,632
men and women between 30–64 years, showed that very low intake of salt (<2.5 gm) is associated with increased BP. This is in line with many workers who feel that there is J-shaped curve between salt consumption and hypertension (Fig. 1).

Salt Sensitive Hypertension

An important and debatable issue is that should salt restriction advise be universal or only for those having inappropriately high consumption/salt sensitive population. Luft et al studied 14 subjects (7 white and 7 black) and gave them increasing doses of salt, 10-1500 meq/day. He found mean rise in blood pressure in both groups but rise in blood pressure was higher in blacks (Fig. 2); showing the racial difference. Salt sensitivity can be studied by giving high and then low salt—1 week of 200 mmol and another week of 30 mmol of salt and then seeing the BP response. A 24-hour urinary sodium is collected on last day of the week to see compliance. However, long 29 days compliance for this test is an issue, so an abbreviated version (7 day test) has been suggested. Rise and drop in BP by 5–10% is taken as positive test. Castiglioni et
al." suggested that ambulatory BP monitoring (ABPM) is a better option and more practical. It is assumed that patients who are salt sensitive retain salt and water with resultant loss of circadian nocturnal dip of BP and higher mean heart rate. No salt restriction is required in this test. Based on these two parameters indices have been devised and patients have been divided into mild, moderate, or highly salt sensitive. Most workers believe that 25% of general population and 50% of hypertensive population is salt sensitive. Salt sensitivity is largely genetic.

**Conclusion**

In India, average salt intake is between 9–12 gm/day, against recommended 5 gm by WHO. Most of the epidemiological animal and human data show that high sodium intake in both normotensive and hypertensive individuals is associated with age related HT. Excessive salt intake is also associated with increased cardiovascular mortality and obesity. Reduction of salt intake reduces BP and CV mortality. Some limited data also suggests that very low salt intake (<3 gm) may be detrimental. It is recommended to consume salt in moderation (approx. 5 gm per day). Maximum benefit of salt restriction occurs in population consuming high/very high amount of salt.

**References**

Abstract
Anemia remains one of the challenging aspects in the management of chronic kidney disease (CKD) till date. Oral/intravenous iron and erythropoietin stimulating agents (ESAs) remain the key modalities in the management of anemia in CKD. Traditional forms of oral iron therapy are limited by poor oral tolerance and insufficient absorption from the gut in dialysis population. Newer forms of oral iron such as sucrosomial iron and ferric citrate offer advantages such as alternate mechanism of absorption from the gut, relatively better oral tolerance, and additional properties such as phosphorous binding. Newer forms of intravenous iron preparations have the advantage of higher stability, lesser risk of infusion reactions, and bolus dosing. ESAs are being used for the treatment of anemia in dialysis patients since the 1980s. Although they are effective, higher doses, and higher hemoglobin targets are associated with significant risk of adverse cardiovascular events such as myocardial infarction and stroke. Studies have shown that though anemia predisposes to a poor quality of life and high cardiovascular risk in CKD, correction of anemia does not reduce the cardiovascular risk in these patients. This could be because of the limited options of therapeutic agents available at present and higher doses of both intravenous iron and ESAs have been shown to predispose to higher cardiovascular risk. Thus, there is a need for agents which can not only correct anemia but also not contribute to the pre-existing cardiovascular risk in CKD patients. Hypoxia inducible factor (HIF) stabilizers are one of the newer agents being studied at present in various trials. Studies have shown that these agents can not only reduce the dosages of intravenous iron and ESAs needed to maintain hemoglobin levels in dialysis patients but can also reduce cardiovascular risk. They also have beneficial effect on iron profile such as reduction of hepcidin levels, thus enabling better iron absorption. Thus, research for newer modalities of anemia management in CKD aims to address not only the hemoglobin levels but also improving the quality of life and longevity of CKD patients.

Introduction
Anemia in Chronic Kidney Disease (CKD) predisposes to low quality of life, increased mortality, and cardiovascular disease risk. The incidence of iron deficiency anemia increases with the progression of CKD. Cornerstone of anemia management in CKD so far has been iron therapy and use of erythropoietin stimulating agents (ESAs). Traditional oral iron therapy is limited by poor tolerability, gastrointestinal adverse event, and poor absorption in dialysis dependent patients. Intravenous iron although rapidly restores iron stores is limited by infusion reactions, infections, oxidative stress, iron overload, and increased cardiovascular risk. ESAs, though they reduce the need for blood transfusions, are associated with increased cardiovascular risk when hemoglobin levels exceed 13 g/dL. Thus, at present, search is ongoing for agents which not only increase hemoglobin levels, but also reduces the risk of adverse cardiovascular events seen with the present agents.
Erythropoietin-stimulating Agents

Traditionally used ESAs include epoetin alfa (half-life, $t_{1/2}$ 6.8–19.4 hours, 50–100 u/kg/week dosing), darbepoetin alfa ($t_{1/2}$ 25.3–48.8 hours, 0.45 µg/kg per week to every 2–4 weeks dosing), and methoxypolyethylene glycol-epoetin beta ($t_{1/2}$ 130 hours, 0.6 µg/kg every 2–4 weeks). Longer half-live are achieved through subcutaneous route for epoetin and darbepoetin preparations. Dose escalations beyond double the initial weight based dose are discouraged by KDIGO due to risk of adverse cardiovascular events as observed from the TREAT study. Recently the MIRCERA PASS trial, a multicentre randomized non-inferiority trial, randomized 2818 CKD patients to methoxypolyethylene glycol-epoetin beta (MIRCERA) and reference erythropoiesis stimulating agents. The primary outcome of the study was composite of time to occurrence of death, non-fatal myocardial infarction, or nonfatal stroke. This occurred in 45.4% in the MIRCERA group and 45.7% in the reference group. Higher dose of ESAs was associated with higher risk of primary outcome.

Iron Deficiency Anemia in Chronic Kidney Disease

Iron deficiency is one of the important causes of anemia in CKD. The NHANES (National Health and Nutrition Examination Survey) 1988 to 2004 data of non-dialysis dependent CKD showed that low iron stores defined as TSAT less than 20% or serum ferritin less than 100 ng/mL were present in 57.8–58.8% of men and 69.9–72.8% of women. Causes of iron deficiency in CKD include gastrointestinal bleeding, retention of blood in dialyzers and blood lines, repeated sampling, surgical procedures such as arteriovenous fistula creation, drugs such as proton pump inhibitors and phosphate binders and reduced absorption.

Transferrin saturation (TSAT) and serum ferritin are widely used as indicators of iron status in CKD population. KDOQI 2006 guidelines recommend maintaining serum ferritin more than 200 ng/mL with TSAT more than 20% in dialysis dependent CKD population and serum ferritin more than 100 ng/mL and TSAT more than 20% in non-dialysis dependent CKD population. ERBP (European renal best practice) and NICE guidelines recommend iron therapy when serum ferritin is less than 100 ng/mL and TSAT less than 20%. KDIGO 2012 guidelines recommend iron therapy if TSAT less than or equal to 30% and serum ferritin is less than or equal to 500 ng/mL.

However, TSAT is not an ideal marker of iron status. Levels can increase in the setting of inflammation and decrease in the setting of malnutrition predisposing to low and high TSAT respectively if the circulating iron levels are constant. Transferrin levels also exhibit diurnal variation. Serum ferritin being an acute phase reactant can be increased in later stages of CKD because of systemic inflammation and by itself may not reflect true iron status at high levels. As a result of these variations NICE guidelines in 2015 recommend not to use TSAT or ferritin levels alone to assess iron deficiency status in CKD. The guidelines recommend the use of percentage of hypochromic red cells (<6%) and reticulocyte hemoglobin content (CHr, <29 pg), if possible, in the place of TSAT and ferritin levels.

Newer Forms of Oral Iron Therapy

KDIGO 2012 guidelines recommend that 1–3 months trial of oral iron therapy can be considered in non-dialysis dependent CKD population with anemia and TSAT less than or equal to 30% and serum ferritin less than or equal to 500 ng/mL. Elemental iron (200 mg) per day is the recommended daily dosage for these patients. In a normal individual 1–2 mg of dietary iron is absorbed per day and with oral iron supplementation. The maximum absorption of iron per day during oral iron supplementation is around 25–30 mg/day. This is impaired in patients with uremia due to rising hepcidin levels, hence oral iron therapy is not very effective in dialysis dependent CKD population.

Oral iron supplementation comes in ferric and ferrous forms. The bioavailability of ferrous form is 10–15% whereas that of ferric forms of iron is three to four times lower due to reduced solubility of ferric iron in the alkaline media of the gut. Several forms of oral iron are available with wide variations in their extent of absorption and adverse effects (Table 1).

The most common forms of side effects with oral iron therapy are gastrointestinal like nausea, heartburn, pain, constipation, and diarrhea. This is seen in 30–70% of the cases. Among all the oral iron formulations, this risk is highest with ferrous fumarate.

Ferric Citrate

Ferric citrate is ferric iron preparation, which was approved as a phosphate binder by US FDA in 2014 for
dialysis dependent CKD patients. The formation of ferric citrate coordination inhibits the precipitation of ferric iron and enables better absorption. Formation of oligomeric complexes in acidic pH enables phosphate binding and monomeric complex formation in alkaline pH of duodenum enables ferric iron absorption. Ferric citrate is always administered with meals.

### Non-Dialysis Dependent CKD (ND-CKD) Population

Phase 3 multicenter double-blind randomized placebo-controlled trial with primary end point as change in serum phosphate showed significant reduction of serum phosphate and FGF23 level and significant increase in serum iron, ferritin, and TSAT compared to placebo. Placebo controlled phase 2 (n=149) and phase 3 (n=233) trials with primary end point as mean change in TSAT/phosphorous and more than or equal to 1 g/dL hemoglobin rise showed positive results for patients in ferric citrate arm with similar rate of adverse events between the two groups. Median daily dose was 1680 mg of elemental iron per day. Similar results were shown in 2019 by the ASTRIO study which compared ferric citrate with non-iron based phosphate binders in 93 hemodialysis dependent patients.

### Ferric Maltol

Ferric maltol is novel preparation consisting of ferric iron complexed with maltol (3-hydroxy-2-methyl-4-pyrone). Its hydrophilic and lipophilic properties enable higher bioavailability and better absorption of ferric iron. Since it is not a salt-based formulation, iron is directly absorbed from the complex, and the adverse effects due to free iron seen in salt-based formulations are reduced. Although this compound was described as early as 1980s, it was approved by US FDA for the treatment of iron deficiency anemia in CKD in 2019.

### Sucrosomial Iron

Sucrosomial iron consists of a ferric pyrophosphate core surrounded by a phospholipid bilayer consisting of lecithin and sucrose matrix. Ingredients such as starch and tricalcium phosphate further the coat the structure forming the sucrose. The phospholipids allow the iron to be absorbed in a vesicular form through transcellular and paracellular routes. The absorption is mediated by ‘M’ cells of the Peyer patches. Thus, bioavailability of iron is high with less free iron mediated gastrointestinal adverse effects. Cell culture studies using the Caco-2 cell lines showed threefold higher absorption rates for sucrosomial iron when compared to ferrous sulfate. Animal studies with iron deficient mice have shown that increase in hepcidin that is seen with other oral iron formulations is not seen with sucrosomial iron. An open label randomized control of 99 ND-CKD patients compared sucrosomial iron (30 mg/day for 3 months) and IV ferrous acetate. The trial showed ferric citrate significantly raised hemoglobin levels, TSAT, and serum ferritin and had a comparable phosphate binding ability when compared with active control. Those in ferric citrate arm received less intravenous iron and dose of erythropoietin also significantly reduced with similar adverse events between the two groups. Median daily dose was 1680 mg of elemental iron per day. Similar results were shown in 2019 by the ASTRIO study which compared ferric citrate with non-iron based phosphate binders in 93 hemodialysis dependent patients.

### Table 1: Different forms of available oral iron preparations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Elemental iron per tablet</th>
<th>Salt content per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric sulfate</td>
<td>65 mg</td>
<td>325 mg</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>106 mg</td>
<td>325 mg</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>37.5 mg</td>
<td>325 mg</td>
</tr>
<tr>
<td>Ferric citrate</td>
<td>210 mg</td>
<td>1 g</td>
</tr>
<tr>
<td>Ferric citrate hydrate</td>
<td>45 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>Liposomal iron</td>
<td>30 mg</td>
<td>30 mg</td>
</tr>
</tbody>
</table>
gluconate (1 g) in a 2:1 ratio. The study found that at the end of 1 month, greater number of patients in the IV iron group had increase in hemoglobin, but this difference was absent at the end of 3 months. On discontinuation, hemoglobin levels were stable in IV iron group whereas it fell to baseline in sucrosomial iron group. Adverse events such as hypotension, headache, and infusion reaction were more common in IV iron group. Only 5% of patients experienced gastrointestinal side effects in the sucrosomial group. Thus, although sucrosomial iron is a safer formulation and high bioavailability, iron stores repletion may be slower when compared to conventional iron formulations.

**Dialysate Iron (Ferric Pyrophosphate Citrate)**

This water-soluble preparation consists of ferric iron tightly complexed to citrate and pyrophosphate to reduce the amount of free iron released into the circulation. This form of iron is administered via the bicarbonate component of the dialysate. On entering the circulation, the iron component is directly transferred thus raising TSAT levels. The advantage of this preparation is that it reduces risk of iron overload. For an individual patient 5 mL (5.44 mg/mL) is added to 9.46 liters of bicarbonate concentrate, which gives a concentration 110 µg/L of iron in the dialysate. The drug is administered in each HD session with TSAT and ferritin levels being done every 3 months. Doses are held if TSAT more than 50% or serum ferritin more than 1000 ng/mL. PRIME,30 a phase 2 prospective randomized double blind trial with primary end point as change in ESA dose showed that dialysate iron significantly reduced the need for IV iron and increase in ESA dose. Phase 3 CRUISE 1 and 2 studies31 showed that dialysate iron significantly raised hemoglobin when compared to placebo. The study had three stages: Stage 1—run in period, Stage 2—randomization without change in ESA dose (no IV iron), and Stage 3—open label. Hypotension, headache, and muscle spasms were commonly reported side effects.

**Intravenous Iron**

Intravenous iron preparations contain an iron hydroxide core surrounded by a carbohydrate shell.10 The stability of this determines how much iron is released into the circulation at a time. In older preparations such as iron sucrose, adverse effects like infusion reactions and oxidative stress frequent due to low stability of the core and higher release of free iron. Newer preparations (Table 2) have a more stable core and thus relatively fewer adverse effects.10 Table 2 shows the different intravenous iron preparations used over the years.

KDIGO guidelines 2012 suggests that a trial of intravenous iron may be considered in adult CKD patients with anemia and TSAT less than or equal to 30% and serum ferritin less than or equal to 500 ng/mL, who are not on ESAs or in those who are on ESA and increase in hemoglobin or reduction in ESA dose is desired.6 The guidelines were based on short-term studies with small number of patients and there were very few trials which looked at the safety of giving IV iron in patients with TSAT more than 30% and ferritin more than 500 ng/mL. In 2007, DRIVE33 study randomized 134 hemodialysis patients

### Table 2: Properties of different intravenous iron preparations

<table>
<thead>
<tr>
<th></th>
<th>Iron gluconate</th>
<th>Iron sucrose</th>
<th>Low molecular weight dextran</th>
<th>Iron isomaltoside</th>
<th>Iron carboxymaltose</th>
<th>Ferumoxytol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate shell</td>
<td>Gluconate</td>
<td>Sucrose</td>
<td>Dextran polysaccharide</td>
<td>Isomaltoside</td>
<td>Carboxymaltose</td>
<td>Polyglucose sorbitol carboxymethylether</td>
</tr>
<tr>
<td>Stability of complex</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Labile iron release</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Plasma half-life (hrs)</td>
<td>1</td>
<td>6</td>
<td>5–20</td>
<td>20</td>
<td>7–12</td>
<td>15</td>
</tr>
<tr>
<td>Maximum single dose</td>
<td>125 mg</td>
<td>200 mg</td>
<td>20 mg/kg</td>
<td>20 mg/kg</td>
<td>1000 mg</td>
<td>510 mg</td>
</tr>
<tr>
<td>Minimum infusion time (min)</td>
<td>30–60</td>
<td>60</td>
<td>60</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>
### TABLE 3
HIF alpha stabilizers and their related trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage used in studies</th>
<th>Trials</th>
<th>Primary end point</th>
<th>Results</th>
<th>Other observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roxadustat</td>
<td>20–250 mg</td>
<td>• Phase 3(^{1}) (n=154) multicentre, double blind trial comparing roxadustat with placebo in non-dialysis dependent CKD</td>
<td>Mean change in hemoglobin over week 7 through 9. Mean change in hemoglobin level from baseline during weeks 23–27</td>
<td>1.9±1.2 g/dL raise in hemoglobin in roxadustat group (p&lt;0.001) Greater mean change in hemoglobin in roxadustat group</td>
<td>• Significant reduction in hepcidin and cholesterol levels in roxadustat group. Hyperkalemia and metabolic acidosis seen more in roxadustat group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Phase 3(^{2}) (n=305) study comparing roxadustat and epoetin alfa in dialysis dependent CKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molidustat</td>
<td>25–200 mg</td>
<td>• Phase 2b trial(^{3}) (16 weeks)</td>
<td>Change in hemoglobin level between baseline and the mean value from the last 4 weeks of the treatment period Change in hemoglobin from baseline to each post-baseline visit</td>
<td>DIALOGUE 1: Significant number of patients achieved the estimated mean hemoglobin in the molidustat group DIALOGUE 2: Mean hemoglobin was maintained in the target range for each dose in molidustat group DIALOGUE 3: Mean hemoglobin levels were maintained for 75 mg–150 mg daily as a starting dose Mean hemoglobin concentration during study were 11.10±0.508 g/dL in molidustat group and 10.98±0.571 g/dL in darbepoetin group Mean hemoglobin concentration during study were 10.37±0.56 g/dL in molidustat group and 10.52±0.47 g/dL in epoetin group</td>
<td>Estimated difference in mean change in hemoglobin between molidustat and darbepoetin was 0.6 g/dL. Lower starting doses were associated with a fall below target range in hemoglobin in the first week. Small increase in hemoglobin was seen with starting dose of 150 mg/day. Side effects: Adverse effects were comparable between both the groups and were mild to moderate in intensity in all three trials. Numerically more number of patients had hypertension and nasopharyngitis in molidustat group Mean hemoglobin levels were maintained from baseline and throughout the study period in both the groups. Similar percentage of adverse events in both the groups (85.6% vs. 85.7%). 21% discontinued drug in molidustat arm when compared to 10% in darbepoetin arm. Mean hemoglobin levels were maintained from baseline and throughout the study period in both the groups. Similar percentage of adverse events in both the groups (91.25% vs. 92.2%). More number of patients experienced severe adverse events in molidustat arm (51% vs. 37%). More number of patients discontinued in molidustat arm (23% vs. 7%).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DIALOGUE 1 (n=121): randomized double-blind control trial comparing molidustat and placebo for patients not in dialysis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• DIALOGUE 2 (n=124): open label molidustat in previously darbepoetin treated patients versus continuing darbepoetin for patients not on dialysis</td>
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<tr>
<td></td>
<td></td>
<td>• DIALOGUE 3 (n=199): open label molidustat in previously epoetin alfa or beta treated patients versus continuing epoetin for patients on dialysis</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>• DIALOGUE EXTENSION STUDIES:</td>
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<tr>
<td></td>
<td></td>
<td>– DIALOGUE 4(^{4}) (&lt;36 months): all patients from DIALOGUE 1 and 2 who achieved their mean Hb targets were made to continue their respective treatment for 36 months</td>
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<tr>
<td></td>
<td></td>
<td>– DIALOGUE 5(^{5}): patients from DIALOGUE 4 who achieved mean Hb targets were continued on their treatment for 36 months</td>
<td></td>
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<tr>
<td>Drug</td>
<td>Dosage used in studies</td>
<td>Trials</td>
<td>Primary end point</td>
<td>Results</td>
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</table>
| Vadadustat | 450–600 mg 300 mg OD, 450 mg OD and 450 mg thrice weekly                                | 1) Phase 2b study (non-dialysis dependent CKD, n=210)<sup>46</sup> 2) Open label phase 2 trial (n=94)<sup>46</sup> comparing vadadustat and epoetin alfa | Percentage of patients who in the last 2 weeks achieved Hb ≥11 g/dL or an increase in Hb ≥1.2 g/dL over the predose average | Mean change in hemoglobin concentration                                                        | 54.9% patients in vadadustat arm achieved primary endpoint compared to 10.3% in placebo  
No statistically significant change in hemoglobin from pre-baseline average was observed for all three doses  
More number of patients had serious adverse events in the vadadustat arm compared to placebo (23.9% vs. 15.3%). Three deaths occurred in vadadustat arm  
Nausea, diarrhea, and vomiting were the common adverse effects noted in the vadadustat group. No serious adverse event was noted in the same |
| Daprodustat| 10, 25, 50, and 100 mg 0.5, 2, and 5 mg                                                 | 1) Multicenter, single blind, placebo-controlled study (n=70, NDD-CKD and 37, DD-CKD)<sup>47</sup> 2) Phase 2a placebo-controlled study (n=73, NDD-CKD and n=83, DD-CKD)<sup>48</sup> | Increase and response rates in achieving target hemoglobin, plasma EPO concentrations and reticulocyte count  
Change in hemoglobin over 4 weeks of treatment                                               | Both non dialysis and dialysis dependent population showed a dose dependent increase in hemoglobin, plasma EPO concentrations and reticulocyte count compared to placebo  
NDD-CKD group: Dose dependent increase in hemoglobin  
DD-CKD group: 5 mg once daily dose maintained mean hemoglobin levels after switch from erythropoietin | Treatment was discontinued in 33% in the ND-CKD group and 22% in DD-CKD group due to high rate of hemoglobin rise (≥1 g/dL in any 2 week period) or high absolute Hb value (≥13 g/dL). Hepcidin level decreased and TIBC and unsaturated iron binding capacity increased significantly in the daprodustat group  
Hemoglobin rise occurred with concurrent rise in endogenous erythropoietin levels in daprodustat group. The drug was well tolerated |
| Enarodustat| 2, 4, and 6 mg                                                                          | 1) Phase 2 study placebo controlled randomized trial in nondialysis dependent CKD (n=94, ESA naïve group and n=103, who previously received ESA)<sup>49</sup> | Rate of rise in hemoglobin per week in ESA naïve group and proportion of patients who maintained change in hemoglobin in previously ESA treated group | ESA naïve group: Dose dependent increase in hemoglobin in enarodustat group  
Previously ESA treated group: 70% of subjects in enarodustat arm maintained their hemoglobin levels over 24 weeks | Ferritin and hepcidin levels decreased  
TIBC increased in enarodustat group |
with ferritin 500–1200 ng/mL and TSAT less than or equal to 25% to intravenous ferric gluconate and no iron. The study found that hemoglobin increased significantly in the IV iron group with similar side effects between both the groups. FIND-CKD study in 2014 found that hemoglobin rise was significant in ND-CKD patients randomized to high ferritin targets (400–600 µg/L) when compared to lower targets. REVOKE trial in 2015 which randomized patients to oral ferrous sulfate and IV iron sucrose found similar results but with increased serious adverse events in the Intraavenous group. PIVOTAL, an open label multicenter trial in 2019 randomized 2141 patients on maintenance hemodialysis less than 1 year to IV iron sucrose in a proactive fashion (400 mg monthly, unless TSAT ≥40% or ferritin ≥700 µg/L) or reactive fashion (400 mg if ferritin ≤200µg/L or TSAT <20%). The primary end point was composite of nonfatal MI, stroke, death, and hospitalization for heart failure. The study found that hemoglobin rise was rapid, blood transfusion, and ESA dosage was reduced in the proactive group. Adverse effects were similar between the groups and the most common adverse event was infection. Thus, higher ferritin targets than that proposed by 2012 KDIGO guidelines, may reduce the need for blood transfusion and higher ESA exposure.

**HIF Stabilizers**

Hypoxia inducible factors (HIFs) are transcription factors made of α (1α, 2α, and 3α) and β subunits. HIF 1α is widely expressed across all normal tissues whereas HIF 2α expression is restricted to endothelium, selected cells in the kidney, gut, lung, liver, and carotid body. During normoxia, the enzyme prolyl hydroxylase (PHD1, PHD2, and PHD3) hydroxylate prolyl residues in the alpha subunit of HIF. Hydroxylation leads to recognition by von Hippel Lindau (VHL) ubiquitin E3 ligase and subsequent proteosomal degradation of HIF. During hypoxic conditions, the PHDs are inactive and this leads to dimerization of α and β subunits of HIF and target gene expression. HIF 2α regulates erythropoiesis. HIF 2 binds to hypoxia response elements of genes encoding proteins such as duodenal cytochrome B and ferroportin and enables iron absorption. HIF 2α also suppresses hepcidin levels which are elevated in chronic inflammatory states such as ESRD. HIF alpha stabilizers which are currently under study are mentioned in **Table 3**.

Most of the trials related to HIF stabilizers are phase 2 in nature (**Table 3**). Phase 3 studies are ongoing. So far, phase 2 studies have shown that these drugs are well tolerated in both dialysis dependent and dialysis independent CKD population. Apart from correction of anemia, other effects such as reduction in cholesterol levels have been documented in studies. Preliminary data from phase 3 trials (DOLOMITES study, NCT02021318) of Roxadustat has shown that it reduces major adverse cardiac events by 30%. Despite their beneficial effects shown in the studies, other proposed harmful effects such as promotion of tumor growth by increasing VEGF levels are yet to be studied. Long-term studies with large numbers of patients are required to enable safe introduction of these drugs into clinical practice.

### Other Upcoming Therapeutic Strategies

**Lexaptepid pegol** is a pegylated L-oligo-ribonucleotide, which inactivated hepcidin. Phase 1 studies of the compound have shown good safety profile and dose dependent reduction of hepcidin levels in healthy volunteers and in hemodialysis patients. Activins are dimmers, which belong to transforming growth factor beta (TGF-β) family which influence erythropoiesis. **Sotatercept** is a fusion protein of Fc domain of human IgG1 and activin receptor Ia. Phase 2 studies in hemodialysis patients have shown acceptable safety profiles, stable hemoglobin levels, and lower rates of rescue with ESAs.

### Conclusion

Newer modalities of management of anemia in CKD patients are aimed at development of agents, which can reduce the need for blood transfusion, need for escalation of dose of ESAs and maintain stable hemoglobin levels for prolonged periods of time without increasing the risk for adverse cardiovascular events associated with the current available agents.

### References


**Abstract**

Sodium Glucose co-transporter-2 (SGLT2) inhibitors are a class antihyperglycemic agents, which act by selectively inhibiting SGLT2 present in the proximal tubules in the kidney, causing glucosuria and to some extent natriuresis. Though originally invented as one of the oral hypoglycemic agent (OHA), many randomized controlled trials have confirmed their role far beyond this, in cardiovascular (CV) and renoprotection. This is in sharp contrast to other OHAs which were associated with either mild CV benefits or rather harm. The benefit possibly extends to nondiabetic population as well.

Though SGLT2 inhibitors act mainly by causing glucosuria, natriuresis, and by inhibiting tubuloglomerular feedback (TGF), these effects are insufficient to explain the impressive CV and renal outcomes. In this review we aim to explain the possible mechanisms of cardiorenal protection of SGLT2 inhibitors.

**Introduction**

Sodium Glucose co-transporter-2 (SGLT2) inhibitors (-gliflozins) are a class antihyperglycemic agents, which act by selectively inhibiting SGLT2 present in the proximal tubules in the kidney, leading to increased glucosuria and thereby decreasing blood glucose levels. Though initially approved in 2013 as one of the oral antihyperglycemic agents for type 2 diabetes, the outcomes in EMPA-REG OUTCOME trial opened a window to its role far beyond glycemic control. This study established a remarkable and unexpected cardiovascular (CV) and renal benefits of empagliflozin in patients with type 2 diabetes with clinical cardiovascular disease (CVD). Later many studies supported and strengthened their role in wide class of patients, including those without established CVD proving their beneficial effects in diabetes mellitus as primary as well as secondary prevention for CV & renal endpoints.²-⁷

Table 1 summarizes the CV and renal outcomes in major trials. These trials have established SGLT2 inhibitors as a paradigm shift in the management of CV and renal complications of type 2 diabetic patients²⁸ and may be in nondiabetic CKD patients as well.⁶

**Basic Mechanism of Action of SGLT2 Inhibitors⁹**

Approximately 90% filtered glucose reabsorption is mediated by SGLT2 channels located on S1 segment of proximal convoluted tubules (PCT). These channels are also responsible for 5–14% of Sodium reabsorption depending upon the glycemic status. Thus, the physiological effects of SGLT2 inhibitors are a consequence of both glucosuria and natriuresis.

Before going in detail, let's concentrate on the glucose absorption in diabetes mellitus and effects of SGLT2 inhibitors on tubuloglomerular feedback (TGF)—an important mechanism for glomerular hemodynamic alteration of in type 2 diabetes and diabetic nephropathy (Fig. 1).
In hyperglycemic state, filtered glucose load is increased. To handle that load, there is increased expression of SGLT2 on PCT. Along with glucose, sodium reabsorption also increases. This increased work of Na and glucose reabsorption leads to increased cortical oxygen consumption and also tubular hypertrophy, resulting in renal cortical ischemia, which promotes interstitial fibrosis. As more glucose and sodium are absorbed in PCT, less sodium will be delivered to distal convoluted tubules (DCT), which is sensed by macula densa. This causes increase in single nephron glomerular filtration rate (SNGFR) via TGF. Due to the decreased sodium in DCT (TGF), there is afferent arteriolar dilatation and efferent arteriolar vasoconstriction due to increase in renin secretion and increased renin–angiotensin–aldosterone system (RAAS) activation. High SNGFR further increases the work of reabsorption continuing this vicious cycle. Hyperfiltration and increase in intraglomerular pressure also causes proteinuria which is nephrotoxic and contributes to progression of diabetic nephropathy.

SGLT2 inhibitors interfere with these essential pathophysiological effects in a diabetic kidney (Fig. 2). By inhibiting SGLT2 channels, hyper-reabsorption of Na and glucose reabsorption is inhibited thus decreasing the tubular workload and oxygen consumption avoiding cortical ischemia. Because of the inhibited Na and glucose reabsorption, filtered glucose load decreases to normal levels.

### TABLE 1

Cardiovascular and renal outcomes of SGLT2 inhibitors in trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Cardiac end point hazard ratio (confidence interval)</th>
<th>Renal end points hazard ratio (confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME1</td>
<td>T2D+CVD eGFR&gt;30</td>
<td>3-point MACE* 0.86 (0.74–0.99)</td>
<td>Doubling of serum creatinine with eGFR&lt;45, initiation of RRT or kidney-related death 0.54 (0.40–0.75)</td>
</tr>
<tr>
<td>CANVAS program2 n=10,142</td>
<td>T2D+CVD (if/&gt;30 yrs) or &gt;2 CV risk factors if &gt;/50 yrs</td>
<td>3-point MACE* 0.86 (0.75–0.97)</td>
<td>Progression of albuminuria 0.73 (0.67–0.79) 40% reduction in eGFR, RRT, or renal-related death 0.60 (0.47–0.77)</td>
</tr>
<tr>
<td>DECLARE-TIMI588 N=17,160</td>
<td>T2D+CVD/&gt;2 CV risk factors</td>
<td>3-point MACE* 0.93 (0.84–1.03) non-significant.</td>
<td>&gt;40% decrease in eGFR to &lt;60, ESRD or renal-related death 0.53 (0.43–0.66)</td>
</tr>
<tr>
<td>CREDENCE3 N=4401</td>
<td>T2D+ eGFRof 30 to &lt;90, albuminuria and on stable dose of ACEi/ARBs for &gt;/4 weeks 3</td>
<td>Composites of CV death or HHF 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95) HHF 0.61 (0.47–0.80)</td>
<td>Relative risk of the primary outcome composite of ESRD, doubling of the serum creatinine level from baseline or death from renal or cardiovascular disease. Was 30% lower (hazard ratio, 0.70 (0.59–0.82))</td>
</tr>
<tr>
<td>DAPA-HF3 N=4744</td>
<td>Heart failure and an ejection fraction of 40% or less (irrespective of the diabetes status)</td>
<td>The primary composite outcome of worsening heart failure or CV death 0.74 (0.65–0.85)</td>
<td>A composite of worsening renal function 0.71 (0.44–1.16)</td>
</tr>
</tbody>
</table>
| DAPA-CKD6 N=4304           | Adults with CKD with an eGFR ≥25 but ≤75 mL/min/1.73 m² and a UACR ≥200 mg/g but ≤5000 mg/g on stable dose of ACEi/ARBs for >/4 weeks | The composite of CV death or HHF 0.71 (0.55 to 0.92). | Primary composite endpoint
  - Time to ≥50% eGFR decline from baseline (confirmed by ≥28-day serum creatinine)
  - Time to ESRD defined as eGFR <15 mL/min/1.73 m², need for chronic dialysis (both confirmed after ≥28 days) and renal transplantation
  - Time to renal or cardiovascular death 0.61 (0.51 to 0.72) |

*Primary outcome, §Not significant

3-point MACE, major adverse cardiac events (composite of nonfatal stroke, nonfatal MI, cardiovascular death); ACEi/ARB, angiotensin converting enzyme inhibitors/aldosteron receptor blockers; CKD, chronic kidney disease; CVD-cardiovascular disease; ESRD, end stage renal disease; HHF, hospitalization for heart failure; RRT, renal replacement therapy; T2D, type two diabetes; UACR, urine albumin creatinine ratio.
Fig. 1: Glucose absorption in diabetes mellitus and effects of SGLT2 on tubuloglomerular feedback and in evolution of diabetic nephropathy

JGA, juxtaglomerular apparatus; SNGFR, single nephron glomerular filtration rate; MD, macula densa

Fig. 2: Effect of SGLT2 inhibitors on pathophysiological mechanisms on diabetic nephropathy

Glucose reabsorption in PCT, more is delivered the DCT. This causes afferent arteriolar constriction and decreases SNGFR via TGF mechanism. Also because of increased load of sodium and potassium in DCT, tubular backpressure in the Bowman’s capsule increases, leading to decrease in SNGFR. These effects together lead to decrease in intraglomerular hypertension, glomerular blood flow leading to decrease in proteinuria.

These effects to some extent do explain the renal benefits of SGLT2 inhibitors but may be inadequate to explain the mechanism for CV benefits. Although the glucose lowering efficacy of SGLT2 inhibitors declines at
the lower eGFR range, the CV benefits are persistent across wide spectrum kidney disease (eGFRs of 30–60 mL min⁻¹ [1.73 m]⁻², 60–90 mL min⁻¹ [1.73 m]⁻² and >90 mL min⁻¹ [1.73 m]⁻²).¹⁰ Also, beneficial effects of SGLT2 inhibitors extend to nondiabetic population as well (Table 1).⁶ This implies that many “extrarenal” effects might play a role.

**Metabolic Effects Secondary to Glucosuria**

**Reduction in HbA1c**

Placebo subtracted HbA1c difference in EMPA-REG was mild (0.4%) but it showed impressive 38% reduction in CV death, 35% reduction in heart failure, and 46% risk reduction was seen in composite renal outcome. This is in sharp contrast with other oral hypoglycemic agents (OHAs), which were associated with either mild CV benefits or sometimes even harm.¹¹-¹³ So, mechanisms other than this need to looked into.

It is important to note that SGLT2 inhibitors do not cause hypoglycemia. This is due to intact counter-regulatory mechanisms including upregulation of hepatic gluconeogenesis. Also, SGLT1 downstream prevents glucose excretion during SGLT2 inhibition when the filtered glucose falls below the transport capacity of SGLT1.⁷

**Weight Loss**

SGLT2 inhibitors reduce body weight and fat mass, especially epicardial fat which is important for leptin (a proinflammatory adipokine) secretion. In a 52-week study comparing canagliflozin with glimepiride, canagliflozin reduced serum leptin levels by 25% and increased the levels of the anti-inflammatory adipokine adiponectin by 17%.¹⁴ The antinatriuretic, anti-inflammatory and antifibrotic effects of SGLT2 inhibitors (discussed further) antagonise the deleterious effects of leptin on heart and kidneys.¹⁴

**Decrease in Uric Acid¹⁵**

Though benefit of this effect on CV protection is unclear.

**Hemodynamic Effects Secondary to Natriuresis**

**Blood Pressure Reduction**

Along with SGLT2 inhibition, direct inhibition of the cardiac sodium-hydrogen exchanger (NHE)1 by SGLT2 inhibitors is another pathway hypothesized in natriuresis and reduction in BP.

In EMPA-REG trial, SGLT2 inhibitors reduced systolic/diastolic BP by around 5/2 mm Hg.¹ A recent meta-analysis of 43 randomized controlled trials with 22,528 patients assessed the seated clinic blood pressure effects of SGLT2 inhibitors in patients with type 2 diabetes mellitus. The reduction in blood pressure was over and above the already receiving antihypertensive therapy.¹⁶

**Diuretic Effect**

SGLT2 inhibitors decrease preload by both natriuresis and osmotic diuresis secondary to glucosuria. But those are different from other conventional loop/thiazide diuretics. They do not cause reflex sympathetic activity thus causing no compensatory tachycardia.¹⁷ It is postulated that as opposed to diuretics, SGLT2 inhibitors promote a greater decrease in interstitial fluid relative to blood volume.¹⁸ This may have significant benefits in reducing neurohormonal activation via their effects on RAAS. Also, thiazide/loop diuretics are known to cause hyperuricemia and sometimes hyperglycemia, but these parameters are positively affected by SGLT2 inhibitors.

**Decrease in Intraglomerular Hypertension**

As explained earlier, natriuresis also causes increased delivery of sodium to macula densa which will lead to afferent arteriolar constriction via TGF mechanism. This decreases the intraglomerular hypertension and hyperfiltration occurring in early diabetic nephropathy. This will also decrease proteinuria but at the cost of initial dip in eGFR (around 4–6 mL/min) in initial 3–4 weeks,¹ which is reversible either after stopping medication or sometimes even after continuous prolonged treatment. This suggests that it’s related to a functional change rather than structural changes, similar to angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blockers (ARBs).

Currently, ACEi/ARBs are the standard treatment for this purpose, which dilates efferent arteriole. In EMPA-REG as well as other studies related to SGLT2i, most of the patient population (almost 80%) was already on ACEi/ARBs. Benefits of SGLT2i are additive to current optimal therapy. RAAS blockers are active through neurohormonal pathways of hyperfiltration whereas SGLT2 inhibitors work via tubular pathway.
Though above mentioned hemodynamic and metabolic effects have positive impact on CV outcome, in practice, this impact is unexpectedly strong. Previously it was thought that these CV benefits are because of the effect on atherosclerosis, but benefits are seen as early as 3 months from the start of treatment. It is very unlikely that atherosclerosis-related effect will show impact so early. So, more possible mechanisms have been proposed and are getting tested.

**Cardiac Fuel Energetics**

So to explain these remarkable cardiac and renal benefits, Ferrannini et al. came up with a “Thrifty substrate” hypothesis. Glycosuria lowers insulin levels and raises fasting and post-meal glucagon concentrations. This causes restriction of glucose utilization and increase in lipid mobilization. Increased delivery of free fatty acids (FFAs) to the liver stimulates *ketogenesis*. In conditions of prolonged hyperketonemia, b-hydroxybutyrate is freely taken up by the heart and oxidized in preference to fatty acids. The benefit of preferential fuel selection was demonstrated in a study of 3-hydroxybutyrate versus placebo in humans with chronic HF in which ketone infusion increased stroke volume, cardiac output, and LVEF in a dose responsive fashion. This fuel selection improves work efficiency with respect to oxygen consumption especially, in failing heart and also in kidneys. But recently this theory has been challenged. Animal studies to prove this change in cardiac energetics have been inconclusive. Also, the stressed heart already preferentially utilizes ketone bodies, and the diabetic kidney is a ketogenic organ so what difference does SGLT2 inhibitors do? It needs to be delineated and explored further.

**Hemoconcentration/Erythropoietin Activation**

SGLT2 inhibitors may not only deceive cells into believing that they are fasting but also that they are hypoxic, which activate hypoxia-inducible factor-2α (HIF-2α) via this SIRT1/AMPK pathway. Also, decreased reabsorption in early PCT causes compensatory increased transport work in late PCT and medullary thick ascending loop. This leads to relative medullary hypoxia and stimulation of HIF 1&2 which cause increase in erythropoietin secretion. Elevated hematocrit is also a surrogate marker of reduced plasma volume as well as of recovery of tubulointerstitial function associated with SGLT2 inhibitor therapy. In mediation analysis of EMPA-REG, changes in hematocrit contributed 51.8% of the effect of empagliflozin versus placebo on the risk of CV death, maximum of all the effect of SGLT2 inhibitors.

**Direct Effect on LV Mass**

Along with decreasing preload and afterload, it is possible that SGLT2 inhibitors have direct beneficial impact of cardiac remodeling. The EMPA-Heart trial which included patients with T2D and coronary artery disease demonstrated a reduction in LV mass indexed to body surface area in patients treated with empagliflozin. This was thought to be in part due to a reduction in wall stress.

**Effect on NLRP3 Inflammasome**

Activation of the NLR family, pyrin domain-containing 3 (NLRP3) inflammasome in the innate immune cells and
subsequent interleukin (IL)-1β release has been proposed as one of the pathogenic mechanisms in diabetes, atherosclerosis, and heart failure. SGLT2 inhibitors have been shown to inhibit this effect with respect to sulfonylureas.26

**Effect on Arterial Stiffness**

A post-hoc analysis of trials and study comparing dapagliflozin with hydrochlorothiazide demonstrated that empagliflozin was associated with not only decreased BP, but showed positive effects on markers of arterial stiffness and vascular resistance, that is, aortic pulse wave velocity, brachial flow mediated dilation, and shear rates.27,28

In addition to these mechanisms, many others are being considered and getting investigated in animal/human-inhibition of sodium-hydrogen exchanger 1 on cardiac myocytes,29 increase in Circulating Pro-Vascular Progenitor Cells.30

**Conclusion**

To conclude, though the exact mechanism of cardiorenal protection is still unclear, one thing is clear that we need to expand the horizon of SGLT2 inhibitors from a “glucose lowering agent” to “organ protective” agent. Studies are underway trying to find its use in nondiabetic population (DAPA CKD, EMPA-KIDNEY, TRANSLATE). Results of DAPA-HF trial have shown positive results in nondiabetic heart failure patients.3 There were initial safety concerns with respect to acute kidney injury, diabetic ketoacidosis, amputations, urinary and genital tract infections, bladder cancer, and bone fractures. However, recent trials have downplayed these risks, and benefits are found to outweigh risks.

**References**

Abstract

The global burden of chronic kidney disease (CKD) is increasing particularly among elderly. Aging itself increases vulnerability for poor renal health. High cost of management and poor outcomes of CKD necessitate optimization of renal care to be started early in the course of the disease. Collaborative involvement of patient, caregiver, primary care provider and multidisciplinary clinics is required to achieve optimal conservative care and renal replacement modality. Dietary changes, lifestyle modification, managing the pill-burden, appropriate nutrient supplementation, and vaccination to take care of risks and complications of CKD are key steps as per latest evidences available. For those progressing to end-stage renal disease (ESRD), an approach, taking into consideration of patient’s perspectives and functional and cognitive status, to decide appropriateness of renal replacement therapy (RRT) or end-of-life care is a very essential particularly for elderly patients. There is need of progressive work for optimizing various facets of renal care in elderly patients particularly in economically constrained regions where most of the CKD patients fail to receive appropriate care.

Introduction

The global burden of kidney disease, which has been rising consistently, poses a major challenge to the primary care physician. Recent GBD reported that out of 697.5 million worldwide CKD patients, India harbored 115.1 million.¹ As per latest census in India (2011), around 104 million people were 60 years or above and by 2021 this number is predicted to reach 133.32 million. So, the likely CKD burden among elderly is expected to rise proportionately. Indian CKD registry² reported that diabetic nephropathy was most common cause (31%) for CKD and mean age of CKD patient was 50 years. Prevalence of CKD and its risk factors like diabetes, hypertension, obesity, and cardiovascular disease increases with age. Age-related changes in kidney include structural changes like macrostructure changes (decrease in cortical volume, increase in surface roughness, and size of simple renal cysts), microstructure changes (nephrosclerosis-arteriosclerosis, glomerulosclerosis, interstitial fibrosis, tubular atrophy), and functional decline in total-kidney GFR due to decrease in total nephron count.³ Optimal care of CKD risk factors can delay or even prevent this progression of healthy aging of kidneys into CKD. Elderly population needs special attention to their physical and functional deficits including multiple co-morbidities (hypertension, diabetes), cognitive impairment, frailty and progressive sensory impairment. Owing to high cost and poor outcomes of CKD management, there is a definitive need for optimization of care in elderly CKD patients on individual basis. Optimal care goals include best outcomes at individual, population and society levels for betterment of survival and quality of life. The management of advanced CKD in the elderly can be challenging in regards to prediction of disease progression to ESRD, selection of RRT modality, and choice of optimal vascular access (VA) for hemodialysis (HD). There is a
need for collaborative efforts between patient, caregiver, primary care provider, and interaction of multidisciplinary clinics. Current review will focus on optimizing renal care including conservative medical management and selection of RRT modalities such as HD, peritoneal dialysis (PD) and kidney transplant (KT) for elderly to maximize functional status and minimize treatment-associated morbidity.

**Pre-RRT Phase: Elderly Focused Conservative Care**

In India, a country with 1.3 billion people and around two thousand nephrologists, practices that promote renal health and prevent renal disease progression are important. Optimal care for elderly involves mix of pharmacological and non-pharmacological interventions. Diet may be important in deciding course of CKD before dialysis. Moderate intake of protein, especially dietary strategies that increase plant protein, low sodium, dietary fiber, vitamin D, and reduction in obesity may limit worsening of CKD. Renoprotective effects of maintaining muscle health, especially among elderly who have high prevalence of sarcopenia, are documented and they must be stressed upon in routine care. Life style changes can be recommended based on specific comorbidity of CKD patients, for example, increasing the aerobic exercise capacity in those with cardiovascular disease, high dietary fiber and moderate intensity exercise for patients with chronic lung disease or rheumatoid arthritis and weight reduction for diabetic patients. CKD patients are likely to encounter polypharmacy risks, potential drug-drug interactions (pDDI) and inappropriate prescriptions. Incorporating procedures and pharmacists to determine pDDI into the kidney care model could help dealing these challenges. Non-adherence is a possible outcome of multiple pill burden among CKD patients. Whenever possible during clinical management, tapering thereafter deprescription strategies should be planned. Recommendations have been made on approach to deprescribe PPIs, statins and oral hypoglycemic agents in CKD patients to reduce pill burden. Practices involving identification and avoidance of agents like nephrotoxic antimicrobials, radio-contrast exposure, combining ACEI and ARBs, NSAIDs and diuretics that might precipitate AKI should be promoted.

Providing recommended vaccinations—hepatitis B, pneumococcal, influenza, and other routine vaccines are essential for optimum care of CKD patients. Focus should be laid upon patient’s values and perspectives about the disease, as deficiency about health literacy is widespread in CKD population. Information should be provided using simple terms and techniques like “teach back” to ensure attention and understanding. Routine screening for anxiety, depression, and cognitive impairment may be important because CKD is associated with increased risk for dementia in elderly and poor functional status (including poor overall cognition, language, and memory). Various mediators accounted for cognitive derangement like anemia, increased oxidative stress, inflammatory markers, and changes in lipid and homocysteine metabolism are found in CKD patients. Identifying functional changes is important in order to optimize the management outcome, as studies have shown association of cognitive impairment with negative outcome and increased risk of 1-year mortality among elderly severe CKD patients who were in-hospital. The conservative pharmacological management is sometimes the only choice in elderly patients who are declining or not fit for RRT (Flowchart 1).

**Risks and Complications of CKD**

CKD, due to any cause, can progress through I to V stages. Complications and their management begin usually by stage III onward, and by stage IV aim is to prepare the patient for dialysis with suitable measures like VA to be needed during stage V. Appropriate timely management is required, particularly in elderly patients who may have multiple modifiable risk factors that could prevent or delay this progression.

**Diabetes Mellitus**

Diabetes mellitus is the most common cause of CKD and this holds true for both the developed and the developing world. Diabetic glomerulopathy might be contributing to over half of the ESRD cases. Bringing down of blood glucose levels (to preserve average HbA1c 7%) reflects as delay in urinary albumin excretion, GFR decline, and requirement for dialysis. The use of ACEI/ARBs can further prevent kidney damage in normotensive diabetics with proteinuria. In the elderly, frail, and CKD patients,
the consequences of hypoglycemia are very serious including injury, myocardial infarction, stroke, and death. Therefore, a tailored approach for target HbA1c levels should be followed for elderly CKD patients to avoid risk of hypoglycemia. Metformin is usually the first antidiabetic to begin with. For reducing risk of lactic acidosis, a rare event, FDA recommends avoiding its use if creatinine in men >1.5 mg/dL and women >1.4 mg/dL. Sulfonylureas undergo renal clearance; therefore, risk of hypoglycemia is more in advanced CKD patients and their use should be avoided if GFR <30 mL/min/1.73 m². Among meglitinides, repaglinide is safe to use in CKD. Thiazolidinediones are hepatically metabolized so can be used in CKD with caveat that fluid retention and increased risk of fracture rates in women especially with underlying renal osteodystrophy could be concerning. Insulin is safe for all CKD patients and long acting single dose can be used when oral agents fail to obtain target sugar levels. However, more complicated regimens with multiple insulin dosing may increase chances of error and hypoglycemia, especially among elderly with cognitive impairment. Among GLP1 agonists, no dose adjustments are needed for dulaglutide or albiglutide in CKD while exenatide and liraglutide should be avoided with eGFR <30 mL/min/1.73 m² due to poor renal clearance. DPP4 inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin) are well tolerated and have some renal clearance and require dosage adjustment. Cardioprotective and renoprotective effect of SGLT2 inhibitors (Empagliflozin, Canagliflozin, Dapagliflozin) have been demonstrated in diabetic kidney disease.

Hypertension

With regards to CKD, hypertension is related as both the cause and effect. Hypertension is a major risk factor that increases the risk of progression of kidney disease and increase the risk of cardiovascular complications. The KDIGO (2012) guidelines have described the general management strategies for controlling blood pressure in non-dialysis-dependent CKD patients. A combination of lifestyle changes and pharmacological management are the key approach to achieve target BP goal in CKD patient. Gradually lowering of blood pressure should be recommended. Blood pressure readings based upon ambulatory and self-measurements better reflect hypertension compared to office blood pressure readings and allow individualizing of antihypertensive treatment. Blood pressure targets need to be individualized and medical management should be based on the age, presence of illness and end-organ damage (cardiovascular and retinopathy), progression of renal disease, and tolerance to treatment. Vascular stiffness necessitates periodic monitoring for postural hypotension as it causes higher systolic blood pressure whereas the diastolic blood pressure could still decline. Slowing of the progression of kidney disease and reduction in CVD risk are the goals of antihypertensive therapy and target BP, as suggested by KDIGO guidelines for non-dialysis patients, 140/90 mm Hg in nondiabetics/diabetics without proteinuria and 130/80 mm Hg in patients with proteinuria, is a key strategy to prevent further renal function decline. Initial fixed dose RAAS inhibitor (ACEI/ARBs) based combination therapy (coadministration of CCB, diuretic, α-blocker, or β-blocker) is more effective and efficient than sequential monotherapy for achieving target blood pressure and reduces risk of adverse events by allowing use of lower doses of each drug.

Anemia

In the elderly especially frail elderly with CKD, anemia is related to poor function and quality of life, increased frequency and duration of hospital stays and mortality. Normocytic normochromic anemia a common complication seen in CKD patients. A thorough assessment of other causes of anemia starting with
complete blood count, peripheral smear, iron studies, B12 and folate levels should be performed before labeling anemia of CKD. As per KDOQI 2012 guidelines, target hemoglobin between 10–11.5 gm/dL is desired in all CKD patients. Consider ESA in pre-dialysis and dialysis patients with Hb below 10 g/dL and between 9–10 g/dL, respectively. KDOQI Anemia Work Group recommends sufficient iron supplementation to maintain serum ferritin concentration >200 ng/mL in HD patients and >100 ng/mL in non-dialysis or on peritoneal dialysis CKD patients for optimal erythropoiesis.

Vitamin and Electrolyte Abnormality

Vitamins and minerals supplementation is critical for elderly care. For CKD patients who are already deficient (S.vit. D <20 ng/mL) or insufficient (S.vit. D = 20–29 ng/mL) in vitamin D, adequate vitamin D is absolute requirement for preventing secondary hyperparathyroidism (SHPT) and its complications. Supplementation with ergocalciferol or cholecalciferol should be done as per individual needs. However, once SHPT develops, vitamin D receptor agonists and/or calcimimetics are required. Ensuring normal reference levels of electrolytes like calcium and phosphorous is essential for prevention of bone disorders among CKD patients. Dyselectrolytemias including hypo- and hypernatremia and hyperkalemia are well associated with aging kidneys. Caution with use of potassium sparing drugs among CKD patients is required to avoid serious adverse events. Metabolic acidosis in CKD patients is often due to impaired ammonia excretion and its management, for example using sodium bicarbonate, improves nutritional parameters as well as CKD progression.

Renal Replacement Therapy

CKD patients are prone to progress to ESRD. Options of RRT include HD, which can be provided in-center or at home, PD, and KT. Economic constraint limits RRT availability to majority of ESRD patients in India. Elderly patient on HD are physically frail with multiple comorbidities and functional dependencies. Initiation of dialysis in elderly should use multidisciplinary approach taking into account various factors including life expectancy, pros and cons of each dialysis modality, quality of life, and patient and caregiver preferences. Possibility of survival benefit for elderly patients on dialysis as compared to those with no RRT patients cannot be ruled out; however, they tend to spend lot of time around health-care facility and may not get life satisfaction. Assessing HD accessibility for each elderly patient opting for RRT is necessary as caregivers and patients feel overwhelmed and burdensome about frequent multiple visits (at least thrice weekly) to a faraway located dialysis center. The approach of incremental dialysis in elderly may assist them in adjusting to dialysis and sustaining residual kidney function. Suggested incremental dialysis approach involves 1–2 dialysis session weekly, each around 1.5–2.5 hours duration until worsening of renal function necessitates further modification. Home dialysis can be suitable for those able to perform it by themselves or with a family member support. However, it may not be preferred choice for elderly with multiple comorbidity, frailty, and lack of support. Exploration of ideal RRT has led to understanding that diverse modalities are used by patients during the entire course of CKD. A term coined as “Integrated Care” has been popularized. Originally, it suggested starting with PD and then changing to in-center HD (CHD). The centers pursuing this approach had reported survival benefits and cost optimization. PD needs assistance and can be preferred as home based dialysis modality in presence of an assistant. However, PD may not be suitable for elderly having poor functional status and declining vision. PD is relatively contraindicated among those with severe pulmonary disease, irreducible hernias, active inflammatory bowel disease, significant scar from previous abdominal surgery, colostomy, ileostomy, or gastric tubes. Decision about choice of dialysis modality should also match patient’s values with treatment characteristics in order to maximize achievable quality of life in elderly.

Vascular Access

An effective VA is very essential for carrying out HD and comprises of arteriovenous fistula (AVF), arteriovenous graft (AVG), and central venous catheter (CVC). For long, as first choice, AVF has been created in the non-dominant hand. Procedure began at a distal site to safeguard proximal blood vessels for future use, thus radiocephalic fistulas became initial choice. This site also reported to have higher failure rate because of thrombosis and inability to mature, requiring more surgeries and use of tunneled catheter for dialysis. Moreover, preserving a venous
location in a frail elderly may not be prudent due to fixed life anticipation, so, the most appropriate AVF, utilizing the most excellent vessels should be created first.\textsuperscript{35,36} Complications such as stenosis, thrombosis, and distal hypoperfusion ischemic syndrome (DHIS) are concerning and add to heavy cost and morbidity with access. Therefore, varying views arise stating creation of upper arm AVFs in elderly as standard care or preferring AVGs and CVCs as more suitable options depending on individual patient. De Silva et al. found similar survival for elderly aged >80 years using either AVFs or AVGs, though, that could be attributed to lesser number of patients receiving AVG (25.4%) as compared to AVF (43.2%) that were chosen for tunneled dialysis.\textsuperscript{37} Risk of death is more than risk of progression to ESRD in most elderly CKD, especially if age >85 years, so benefits of an invasive procedure should be weighed against associated complication and additional cost arising out of any potential unnecessary procedure.\textsuperscript{37} O’Hare et al. demonstrated that only about 25% and 33% of patients started dialysis within 6 month and 1 year, respectively, after access creation in 85–100 year old patients with eGFR <15 mL/min/1.73 m\textsuperscript{2}.\textsuperscript{38} Therefore, life expectancy and rate of deterioration of disease should form basis for timing and type of access creation in elderly. For example, a tunneled catheter usually not the most appropriate access choice, could be considered for those with a life very limited life expectancy (e.g., <6 months). CVCs are preferred in IJV and femoral vein since subclavian vein has high risk of thrombosis. Infections, as the complication, amount to about 30–60% of HD CVCs removal and also, hospitalization rates are higher with CVCs than AVF.\textsuperscript{39} Active surveillance and monitoring of AVF is recommended. Physical examination of VA is very useful tool to assess inconvenience during cannulation or clot aspiration, bleeding at cannulation sites post dialysis or failure to attain target blood flows while dialysis. If any such sign present, further evaluation with direct flow rate [using Doppler US and magnetic resonance angiography (MRA)], or indirect flow rate measurement modality [UD (Transonic), timed ultrafiltration methods, ionic dialysance, differential conductivity, and glucose infusion] should be considered.\textsuperscript{40} A low-cost method using hemoglobin dilution test was described by Tiranathanagul et al. which can be used in the resource limited areas where ultrasound dilution test (UDT) is costly and unavailable.\textsuperscript{41}

Kidney Transplant—An Option in Elderly?

Although, age itself is not a contraindication to KT, but poor accessibility and associated comorbidities could make elderly ineligible for getting a transplant organ. There is lower 5-year survival probability among KT recipients aged >65 years compared to aged 35–49 years (61% vs. 75% respectively).\textsuperscript{42} Though Kaul et al. reported, in a retrospective study of ESRD patients, that after adjusting for albumin and BMI, KT group had better short-term and long-term survival as compared to PD group.\textsuperscript{43} So, despite increased age, in the absence of other significant factor limiting the life expectancy, KT could be beneficial for elderly.\textsuperscript{44} Factors that reduce KT rate in elderly may be strict selection criteria, health-care providers’ apprehensions and decreased willingness among older patients for kidney transplantation.\textsuperscript{45} Thus, instead of kidney transplantation, most of the elderly with ESRD undergo dialysis.

Social Support and End-of-Life Care

Like most non-communicable diseases, the treatment for CKD is non-curative, thus patient has to learn living with it. This creates functional restrain thereby limiting social involvement and a feeling of being isolated. Increased requirement of assistance for executive functions, dependency for care including dialysis, adjusting to new pattern of daily routine and cognitive changes of ageing may cause a lot of stress, resulting in a feeling of helplessness. Social support including emotional and instrumental is essential for overcoming. Instrumental support helps patient carrying out all routine and financial activities while emotional support enables person to feel loved and cared.\textsuperscript{46} Ultimately, terminal patient-care needs interdisciplinary management. End-of-life care discussion involving patient and family members, taking care of their preferences to reach a consensus regarding accepting any intervention or simply withdrawing dialysis for palliative care and reviewing goals of advance care should be considered. Kirchhoff et al. observed that after intervening with patient-centered advance care planning, a significant percentage of ESRD patients withdrew dialysis as compared to those without intervention.\textsuperscript{47} Informed choice about all available options, including their pros and cons, can augment decision-making especially for patients on HD among whom 9–13% succumb within 1 year.\textsuperscript{48}
**Conclusion**

Optimization of renal care in a developing country, where health-care infrastructure is already struggling, is challenging. Regardless, perpetual efforts for active care, prevention from and preparation for deteriorating CKD stages and befitting RRT are needed. Optimal care of elderly patients with CKD may be rewarding by decelerating fall in renal functioning, better care of complications, and enabling a rational choice of RRT with well-timed carried out VA.

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Abstract

Diabetes mellitus includes a group of metabolic disorders which share the common phenotype of hyperglycemia. Diabetes mellitus is the leading cause of end stage renal disease. With the prevalence of diabetes mellitus increasing enormously in present times, the burden of end stage renal disease caused by diabetes mellitus assumes significance.

Three major pathways are implicated in the development of DKD (Diabetic Kidney Disease) initiated by hyperglycemia. They are Activation of Protein Kinase C and polyol pathways, formation of advanced glycation end products, and glomerular hyperfiltration leading to glomerular hypertension.

Vitamin D is known to prevent beta cell apoptosis, increase insulin synthesis and enhance peripheral insulin sensitivity. Also, it is known to suppress RAS (Renin Angiotensin Aldosterone System), prevent podocyte loss and structural derangement of slit diaphragm, suppress inflammation and prevent glomerulosclerosis.

Hence, addition of Vitamin D supplements to ACE inhibitors/ARBs is proposed as a novel mechanism to prevent and halt the progression of Diabetic Kidney disease.

Introduction

Diabetes mellitus (DM) poses a major global public health problem with ever increasing incidence and prevalence in recent years.

At present, diabetes is the most common cause of end stage renal disease (ESRD).

Increasing burden of diabetic kidney disease (DKD) is secondary to widespread prevalence of diabetes.

According to International Diabetic Federation, the number of diabetics is expected to exceed 435 million by 2030, with more than 90% having type 2 diabetes.

The increased risk of all cause and cardiovascular mortality in patients with diabetes is due to the presence of DKD.

Approximately, 25–40% of type 1 DM patients and 5–40% of patients with type 2 diabetes develop this microvascular complication.

Over 20% of the newly diagnosed T2DM have concurrent DKD and a further 20–40% develop diabetic nephropathy mostly within 10 years of diagnosis.

Several genetic and environmental factors lead to pathogenesis of DN.

Hyperglycemic state of diabetes leads to various hemodynamic, biochemical, metabolic changes in kidneys including inflammation and oxidative stress.

Considering the burden imposed by diabetes and DKD, extensive research is done in search of therapeutic agent, which can reduce or stop the progression of diabetic kidney disease. One such novel therapeutic agent for diabetic nephropathy is vitamin D and its analogues.

Risk Factors Associated with DKD

Multiple factors are responsible for the development of diabetic nephropathy and its progression.
These factors can be categorized as susceptibility factors—which predispose patients to the risk of developing DKD and are considered as non-modifiable factors. Acute kidney injury (AKI), dietary factors, hyperglycemia, and hypertension which initiate kidney damage and worsen the DKD are considered as modifiable factors.6

Hence, the risk factors for DKD are summarized as:
- **Susceptibility factors:** Old age, male sex, African-American race, and significant family history
- **Initiation factors:** Hyperglycemia and AKI
- **Progression factors:** Hypertension, obesity, dietary factors, and smoking7

Among the various risk factors hyperglycemia and hypertension are the most predominant risk factors.

### Natural History of DKD8

The progressive model of the natural history of DKD has been shown in **Figure 1**.

#### Pathogenesis of Diabetic Nephropathy

Hyperglycemia is the necessary factor in the initiation of renal injury. Abnormal intracellular metabolism, involving three major pathways that are associated with the development of diabetic nephropathy shown in **Flowchart 1**.9

- Activation of protein kinase C and polyol pathways
- Advanced glycation end-products formation
- Glomerular hyperfiltration leading to intra-glomerular hypertension

It is also implicated that there is an excessive production of mitochondrial reactive oxygen species. Interactions between metabolic changes induced by hyperglycemia with hemodynamic factors, including vasoactive hormones such as angiotensin II, play a critical role in inducing renal injury. These mechanisms result in cell injury and activate inflammatory cascade which further perpetuates cell injury and results in vicious
cycle of cell injury—inflammation—further cell injury—fibrosis.

The molecules responsible for inflammation in diabetic nephropathy include:
- Transcription factors, NF-κB
- Proinflammatory cytokines & signaling molecules—IL-6, IL-18, IL-1, TNF, JAK2, & STAT 1&3
- Chemokines CCL2 (MCP-1) and CCR2, CXCL12 (stromal-cell-derived factor-1), CX3CL1
- Fractalkine and CX3CR1
- Adhesion molecules: Intercellular adhesion molecule 1 (ICAM1), Vascular cell adhesion protein 1 (VCAM1), E-selectin (SELE); Toll like receptors—(TLR2, TLR4)
- Adipokines: Adiponectin, Leptin; Nuclear receptors—VDR, NR1H4 (FXR) PPARα PPARγ, PPARδ
- TGF-β1 (transforming growth factor-β1) is a well determined molecule for the accumulation of ECM glycoproteins and subsequent glomerulosclerosis

**Pathology of Diabetic Nephropathy**

Diabetic nephropathy was first described as glomerulopathy, mainly affecting mesangial cells; however, with further research it is found that glomerular epithelial cell abnormalities like podocyte dysfunction (angiotensin II mediated reduced expression of Nephrin), apoptosis, ultimately resulting in depletion of podocytes is central to development of proteinuria which is a hallmark feature of diabetic nephropathy. Also identified are the important changes in other sites like tubules, interstitium, medulla, and papilla. Renal function and prognosis correlate better
with structural lesions in tubules and cortical interstitium than with classic glomerular changes.\textsuperscript{11}

The steps resulting in diabetic nephropathy are:\textsuperscript{\textsuperscript{12}}
- Hypertrophy of glomerulus and hyperfiltration
- Glomerular and tubulo-interstitial inflammation
- Decrease in number of cells by apoptosis and accumulation of ECM.

**Vitamin D**

Fat soluble vitamin D exists in two major forms, namely ergocalciferol (D2) and cholecalciferol (D3).

The main source of vitamin D for human body is endogenously biosynthesized in the skin. Vitamin D absorbed from diet and synthesized endogenously is biologically inert. Vitamin D in liver is converted into 25-hydroxyvitamin D (25(OH) D3) by liver enzyme 25-hydroxylase, which can be measured clinically. 25(OH) D3 is further hydroxylated to 1, 25(OH)2 D3 by kidney-derived 1-alpha-hydroxylase which is an active form of Vitamin D.

The activated form of vitamin D (1,25(OH)2D3) further binds with vitamin D receptors (VDRs) and activates various transcription factors. It is now found that, VDRs and 1-alpha-hydroxylase is expressed in tissues like islets of pancreas, hepatocytes, vascular smooth muscle cells, macrophages, mesangial cells, and podocytes. Vitamin D acts in autocrine manner and exerts multiple non-calcemic effects through VDRs. This includes vascular, immunomodulatory, anti-inflammatory effects, suppression of RAS, and control of glucose homeostasis.\textsuperscript{13}

**Role of Vitamin D in Insulin Synthesis and Regulating Insulin Sensitivity**

Hyperglycemia results in endoplasmic reticulum stress, inflammation (lipotoxicity) and loss of insulin sensitivity.

Thus, hyperglycemia plays a key role in causation of resistance to insulin and \(\beta\)-cell failure.\textsuperscript{14-16} Diet induced hypovitaminosis D in animal mice models revealed this hypovitaminosis D is a result of impaired glucose tolerance, decreased islet function related gene transcription, and increased RAS expression.\textsuperscript{17}

The postulated molecular mechanism behind regulation of insulin homeostasis by Vitamin D includes:
- Promoter regions of insulin receptor genes have VDR response elements (VDREs).\textsuperscript{18}
- Calcitriol in liver is known to induce calcium flux and activate calcium/calmodulin dependent protein kinase (CaMkkB), which further activates 5’ AMP (Adenosine monophosphate) activated protein kinase (AMPK). This results in down regulation of Phosphoenol pyruvate carboxy kinase (PEPCK) and Glucose 6 phosphatase (G6Pase) and thus reduce hepatic glucose output. AMPKa activation can also downregulate sterol regulatory element binding protein 1 (SREBP1c),FAS and Acetyl co-A carboxylase (ACC) which further reduces the hepatic triglyceride content shown in Figure 2.
- Increased intracellular ionized calcium and subsequent downstream signaling mediated by vitamin D is known to enhance glucose and arginine mediated insulin release from \(\beta\)-cells of pancreas.\textsuperscript{19}
- Suppress the transcription of renin, angiotensin receptors and serve to inhibit local RAS mediated beta cell injury.
- Hyperglycemia and increased free fatty acids result in endoplasmic reticulum stress and reduced activity of Akt pathway, which ultimately results in \(\beta\)-cell apoptosis.
- Vitamin D helps in beta cell survival and also increases compensatory beta cell growth in insulin resistant states by enhancing activity of Akt pathway.\textsuperscript{20}
- Vitamin D also reduces accumulation of hepatic triglyceride and glucose output through Ca\textsuperscript{2+}/CaM KK/AMPK signaling activation.
- Vitamin D also inhibits VDR mediated PPAR activity thus inhibits adipogenesis.\textsuperscript{21}
**Vitamin D Role in Inflammation**

Activation of NF-kB pathway results in increased transcription and production of proinflammatory cytokines like TNF-α, IL-1, and IL-6. This proinflammatory milieu leads to leukocyte infiltration of pancreas resulting in reduced β-cell mass, reduced insulin synthesis, islet amyloid deposition, altered downstream insulin signaling through IRS/AKT/PI3K resulting in insulin resistance and also affects the maintenance of energy and blood sugar balance in hypothalamus. VDD promotes inflammation through NF-kB pathway as evidenced by animal model, whereas vitamin D supplementation has shown beneficial effects in preventing the same.

**Vitamin D Role in Diabetic Nephropathy**

Diabetic nephropathy is associated with increased incidence of vitamin D deficiency. Probable explanation for the same includes reduced sunlight exposure (e.g., in elderly, sick, dark-skinned people, people wearing veil, losses of vitamin D-binding protein in proteinuric states).

Vitamin D is known to ameliorate the harmful effects of hyperglycemia on kidney by following mechanism:

- Vitamin D inhibits RAS by downregulating renin, angiotensinogen and angiotensin II receptor expression.
- Enhances the expression of nephrin and prevents structural derangement of slit diaphragm.
- Inhibits activation of ERKs, p38-MAPK, Wnt-b catenin pathway, and down regulates proapoptotic signals Bad, Bak, and upregulate anti-apoptotic signal Bcl2 and prevent podocyte apoptosis and podocyte loss.
- Inhibits the expression of Smad 3 protein or by the physical interaction of VDR with Smad 3 protein downregulates the intracellular level of Smad 3 and thus, reduce the expression of TGF-β, and prevent glomerulosclerosis.
- Inhibits the expression of fibronectin and extracellular matrix proteins from mesangial cells and protect against glomerulosclerosis.
- Inhibits the expression of MCP-1 (Monocyte Chemotactic Protein 1) which results in decreased leukocyte recruitment to kidneys and reduces the renal inflammation.

**Evidence from Clinical Studies**

Clinical trial evidence indicates that combined treatment with losartan and paricalcitol completely prevented albuminuria as well as markedly reduced glomerulosclerosis while restoring glomerular filtration barrier structure. The vitamin D receptor activator (paricalcitol) in albuminuria lowering (VITAL) study showed that addition of two micrograms of paricalcitol to RAS inhibitors safely lowers albuminuria in patients with diabetic nephropathy and can be a novel approach to reduce residual renal risk in patients with diabetic nephropathy who are already on treatment with optimal doses of RAS inhibitors.

**Conclusion**

Diabetic nephropathy is a common renal complication of DM and a major cause of ESRD. RAS is the predominant mediator of progressive injury to renal system in DN. Hence, RAS inhibitors are being used as the mainstay of treatment for DN; however, RAS inhibition leads to compensatory rise in the renin due to the disruption of renin feedback inhibition. Vitamin D plays a renal protective role in DM by suppressing rennin expression by negative regulation of RAS. Combination therapy with RAS inhibitors and active vitamin D and its analogue markedly ameliorates renal injury.

However, Vitamin D is currently only recommended in treatment of patients with moderate CKD associated with secondary hyperparathyroidism and vitamin D insufficiency. Hence, further study is required to answer many questions and thereby uncover the potential renoprotective role of vitamin D and its analogues in treatment of patients with CKD.

**References**

Understanding the Role of Vitamin D in Diabetic Nephropathy
