# A Study on the efficacy of Finerenone in Management of Diabetic Nephropathy with Chronic kidney disease: A Prospective

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**ABSTRACT:**

Background: Finerenone is a Non-steroidal Mineralocorticoid Antagonist. Finerenone can significantly reduce clinical manifestations and improve kidney function in patients of diabetic nephropathy with chronic kidney disease and shows its efficacy after its 1st dose. The purpose of the study was to evaluate the efficacy and safety of finerenone in management of diabetic nephropathy with chronic kidney disease. Objective: To evaluate efficacy of finerenone by analyzing patient's urinary protein to creatinine ratio (UPCR) and eGFR in patients with diabetic nephropathy with chronic kidney disease, treated with finerenone for 6 months. Materials and methods: 50 Out-patients of Nephrology department from Asian Institute of Nephrology and Urology hospital were participated in this study are evaluated. Finerenone 10mg once a day orally for 6 months. The primary parameter is each patient's urinary protein to creatinine ratio (UPCR) which is measured at 3 months and at 6 months from baseline. The secondary parameters are estimated GFR, serum potassium level which are measured at 3 months and at 6 months from baseline. Changes in parameters from baseline to follow ups are analyzed by using statistical method that is student's paired t-test. Results: statistically, there is significant improvement in all parameters of our study were observed over 6 months of finerenone use from baseline. Finerenone 10mg once a day orally resulted in mean reduction of UPCR, there is minimal effect on reduction in worsening of decline in eGFR and there is mean increase in serum potassium levels. Conclusion: our study suggests there is anti-proteinuric effect in patients with diabetic nephropathy and chronic kidney disease. We conclude that, after 6 months symptoms are decreased and minimal improvement on kidney function. Statistically significantly it has acceptable safety profile and gradual improvement of efficacy parameters was observed over a period of 6 months.

**Keywords:** Diabetic nephropathy, chronic kidney disease, Finerenone,

## DIABETIC NEPHROPATHY:

Diabetic nephropathy (DN) is also known as diabetic kidney disease (DKD). It is a chronic micro-vascular complication of poorly or uncontrolled diabetes mellitus of type-1 and type-2 which cause damage to blood vessels clusters in the kidneys through which filter waste from the blood. It is evaluated in existence of pathological range of urine albumin excretion (>300 mg/24 hours), diabetic glomerular lesions, UPCR (>0.2) and decline in glomerular filtration rate (GFR). Diabetes mellitus is a most prevalent endocrine disorder, it is a chronic metabolic condition characterized into type 1 and type 2 [1]. Diabetic nephropathy is the most common cause of

mortality in diabetic patients. This progresses from renal disease to end-stage renal disease (ESRD).

Diabetic nephropathy is distinguished by, progressive glomerular basement membrane thickening and mesangial matrix expansion which progresses to glomerular sclerosis. Renal biopsy reveals nodular glomerulosclerosis[2].Anatomical and physiological changes in the kidneys because of diabetes and result in proteinuria and progressive reduction of kidney function is the peculiar feature of diabetic nephropathy.Approximately 20% to 30% of all diabetes which results to nephropathy and greater percentage of diabetic type 1 leading to ESRD [3].The prevalence of DN is mostly in type 2 diabetic patients develop to nephropathy after 20 years of onset of DM and 20% ESRD[4].The major risk factors are Age, obesity, high levels of blood pressure, cholesterol, uncontrolled blood glucose, smoking, family history[5].

The main causes are Hyperglycemia with hypertension results in glomerular hyper-filtration and renal injury, advanced glycation products, and activation of cytokines. Cytokine leads to over-expression of transforming growth factor-β (TGF-β) in the glomeruli and of matrix proteins. TGF-β and vascular endothelial growth factor (VEGF) may contribute to cellular hypertrophy. Protein kinase A enhances collagen synthesis in diabetic nephropathy conditions. Gene polymorphism for angiotensin-converting enzymes results in nephropathy [6,7].

The pathogenesis and progression of diabetic nephropathy are most likely to be as a result of interplay between metabolic and hemodynamic pathways due to poorly controlled or uncontrolled type-1 and type-2 diabetes mellitus results in increase glucose uptake, glucose breakdown in glomerular cells and tubular cells and increase glucose load on kidneys.

Metabolic pathway: Due to increased glucose uptake, glucose breakdown in glomerular cells and tubular cells, advanced glycation end products , activation of protein kinase C pathway, excessive production and accumulation of glycolytic intermediates like sorbitol, hexosamine, succinate stimulate free radical production create oxidative stress. This activates cellular signaling, transcription factors and cytokines (TGF-β-Smad-MAPK, IGF-1). Activated mechanisms will decrease the production of matrix metalloproteinase and aberrant ECM protein expression and accumulation contributes decrease matrix regulation and results in mesangial matrix expansion

**Hemodynamic pathway:**

Due to increased glucose load on kidneys leads to increased proximal tubule reabsorption of Na+ via Na+/glucose co-transporter in turn decreases reabsorption of Nacl in distal tubule. This result in activation of the tubulo-glomerular feedback mechanism at the macula densa attributes to increase intra-renal angiotensin-2. This contribute to increase in oxidative stress via increased NADPH oxidase activity shows increase free radical production and also increases in blood volume, blood pressure, renal perfusion, relative afferent arteriole dilation and efferent arteriole constriction. Due to activation of tubulo-glomerular feedback mechanism and excessive succinate is produced due to increase glucose uptake and accumulated due to glycolysis in glomerular and tubular cells via GPR91 results in activation of RAS and both activations increase renal angiotensin-2 contributes glomerular hyper-filtration there is initial increase in GFR[8-12].

Both, glomerular hyper-filtration and decreased extracellular matrix contributes diabetic nephropathy. Glomerular hyper-filtration causes glomeruli stress, it is pressure induced damage. This damage leads to mesangial matrix expansion and Podocytes injury. Decreasing extracellular matrix also causes mesangial matrix expansion that develops kimmelstiel-wilson lesion due to

accumulation of proteins. Loss /injury of Podocytes which increase glomerular basement membrane permeability to protein like albumin leading to a condition called albuminuria. Inflammation due to endocytosis of protein by tubular cells occurs. Tubular fibrosis mesangial result of matrix expansion and loss/ injury to Podocytes. Tubular fibrosis gives rise to scarred glomeruli that are less able to filter blood effectively leading to decreased GFR results in diabetic nephropathy[13].

**Role of mineralocorticoid receptor:**

Upon the binding of aldosterone to MR, the bound MR translocate into the nucleus and binds to the HRE (Hormone Response Element) of the target gene to initiate transcription. CYP11B2 is manifested in the kidneys, and local aldosterone production occurs in DN, leading to MR over-activation results in increases sodium retention by means of MR mediated Na reabsorption and also due to hypertension will provoke inflammation and fibrosis in the kidneys, blood vessels, and the heart. These processes play an important role in the progression of cardio-renal disease.

Symptoms include edema, nausea, vomiting, itching and diagnosed by UPCR, eGFR, histopathology[14, 15].

**Chronic Kidney Disease (CKD):**

Chronic kidney disease (CKD), it is irreversible, progressive, deterioration of kidney function. CKD is classified into 5 stages based on GFR. They are; stage 1 (>90 ml/min), stage 2 (60-89 ml/min), stage 3 (45-59 ml/min), stage 4 (15-29 ml/min) and stage 5 (< 15 ml/min).There are several factors contributing to onset, such as glomerulonephritis, hypertension, diabetes mellitus. The most significant effects are notified in tubular secretion, selective reabsorption, and glomerular filtration rate. Water reabsorption is severely impaired due to significant decline in GFR and amount of filtrate formed. There is a significant rise in blood urea levels due to renal failure that leads to a condition called uremia that causes symptoms like nausea, vomiting, gastro-intestinal bleeding, anemia and purities. Decrease in GFR results in increase in concentration of metabolic waste like creatinine and urea in blood[16].

**Finerenone:**

Finerenone is a non-steroidal drug that blocks mineralocorticoid receptor (MR) which is primarily located in DCT and collecting duct of nephron. It available in brand name known as Kerendia. The aldo-MR-Rac1triangle facilities nuclear transcription which increases in inflammatory mediates resulting to tubular fibrosis and progression of CKD to ESRD in diabetic nephropathy patients. So, mineralocorticoid receptor antagonists acts as Reno- protective agent reduces UPCR (anti-proteinuria effect), reduce risk of CKD progression and cardiovascular events, and decrease risk of sustain decline in eGFR in patients of diabetic nephropathy.

**Mechanism of action:**

Finerenone is a non- steroidal mineralocorticoid antagonist (nMRA) which blocks mineralocorticoid receptor (MR) which is activated by binding of aldosterone to regulate mineralocorticoid receptor (MR) contributes gene transcription. Finerenone has high potency and selectivity towards only MR and it has no significant affinity or activity towards androgen, Progesterone, estrogen and glucocorticoid receptors because it's Non - steroidal structure. [16]

In diabetic patient when MR over activated CYP11B2 is expressed in renal cortex results in activation aldosterone leads to stimulation SGK1 and induces subsequent inflammation, oxidative stress, apoptosis and fibrotic process promoting inflammatory and fibrotic process in the kidney.Finerenone blocks sodium reabsorption which is MR-mediated and over activation of

MR in kidneys, heart, blood vessels tissues which contribute fibrosis and inflammation of organs. [17] So, finerenone is important for protecting kidney from kidney failure.The action of finerenone reduces inflammation and facilities to decrease inflammatory mediator's release which promotes mesangial cell expansion and Podocytes injury which contribute tubular fibrosis and albuminuria in patients of diabetic nephropathy. As a result, several physiological changes are likely to be influenced like reduce in cardiac fibrosis, myocardial remodeling, heart failure patient hospitalization and endothelial damage.It is indicated in patients with diabetic nephropathy (proteinuria stage A3), CKD stage 3-4, and non-proliferative diabetic retinopathy and heart failure in patients with CKD-DM type 2.

AVAILABLE DOSAGE: 10mg and 20mg tablets.

DOSAGE REGIMEN: Measure serum potassium levels and eGFR before then start the drug.

DOSAGE REGIMEN GIVEN BASED ON eGFR MEASUREMENT:

eGFR ≥60 ml/min/1.73 m2: 20mg once daily orally

eGFR ≥25to <60 ml/min/1.73 m2: 10mg once daily orally

eGFR<25 ml/min/1.73 m2: Don't initiate.

DOSAGE REGIMEN GIVEN BASED ON SERUM POTASSIUM LEVELS:

Serum potassium level ≤ 4.8mmol/L: 20mg once daily orally

Serum potassium level 4.8 to 5.5mmol/L 10mg or 20mg once daily.

Serum potassium level >5.5mmol/L: Stop finerenone and restart with 10mg once orally at serum potassium 5.5mmol/L level.

**Pharmacokinetics of Finerenone:**

It is well absorbed orally with bioavailability of 44%, at peak plasma concentration 160mcg/L. The drug protein binding is 92% and with volume of distribution 52.6L and of half-life of 2-3 hrs. It is primarily metabolized by CYPA4 (90%) and CYP2C8 (10%) in liver to inactive metabolite and excreted 80% in urine and 20% feces.It has drug-drug interactions with drugs like diltizam, doxycycline, tadalafil, labetalol [18].

**Materials and methods:**

50 Out-patients of Nephrology department from Asian Institute of Nephrology and Urology hospital were participated in this study are evaluated. Finerenone 10mg once a day orally for 6 months. The primary parameter is each patient's urinary protein to creatinine ratio (UPCR) which is measured at 3 months and at 6 months from baseline. The secondary parameters are estimated GFR, serum potassium level which are measured at 3 months and at 6 months from baseline. Changes in parameters from baseline to follow ups are analyzed by using statistical method that is student's paired t-test.

**Result and Discussion:**

A total of 50 patients of both genders who have been treated with finerenone 10 mg/ day at the Department of Nephrology department of Asian Institute Of Nephrology and Urology Hospital, Banjara hills, Hyderabad were enrolled in the study. The distribution of the patients based on their age included patients (38%) between 59-68 years, patients (34%) between 39-48 years (14%), between 18-38 years (4%) and patients between 69-78 years (2%). In our study, the majority of patients are under the age of 59-68 years. The age-wise distribution of the patients was mentioned in table-1.Distribution of patients based on their gender included 44 male patients (88%), 06 female patients (12%). The Gender wise distribution of patients was mentioned in table- 2. Distribution of patients based on medication combinations such as use of finerenone with ACEI, ARBs, SGLT2I table-3

**Efficacy of finerenone:**

In our study finerenone had shown its effect by reducing UPCR in 33 patients out of 50 patients in which 66% patients are improved and gained benefit while remaining 34% couldn't be benefited. The main reason is due to lack of medication adherence. In our study finerenone had shown its effect by slowing down the worsening of decline in eGFR in 18 patients out of 50 patients which is 36% are improved while 64% couldn't be benefited.In our study finerenone had increase serum creatinine levels in 34 patients out of 50 patients in which 68% couldn't be benefited while 32% are only benefited.In our study finerenone had shown slight increase in serum potassium ratio in 38 patients out of 50 patients in which only 24% had no change in serum potassium levels.In our study finerenone had shown few adverse effects like body pains and itching in 8 patients out of 50 patients that is 16% stopped drug use and remaining 84% of patients are on medication. Statically efficacy of finerenone is analyzed in table-4

**Table-1: Age wise distribution of patients**

| Age of patients | Number of patients | Percentage (%) |
|---|---|---|
| 18-28 | 1 | 2% |
| 29-38 | 1 | 2% |
| 39-48 | 7 | 14% |
| 49-58 | 17 | 34% |
| 59-68 | 19 | 38% |
| 69-78 | 4 | 8% |
| 79-88 | 1 | 2% |
| TOTAL | 50 | 100% |

**Table-2: Gender wise distribution of patients**

| Gender | Number of patients | Percentage |
|---|---|---|
| Males | 44 | 88% |
| Females | 06 | 12% |

**Table-3: distribution based of combination of ACEIs/ARBs and SGLT2Is with finerenone**

| Combinations | No of patients | Percentage |
|---|---|---|
| ACEI/ARB + finerenone | 50 | 61% |
| SGLTI +ACEI/ARB + finerenone | 32 | 39% |

**Table-4: Mean standard deviation of baseline and follow ups values of parameters:**

| Parameters | Mean | Std. deviation |
|---|---|---|

| | | |
|---|---|---|
| Baseline UPCR value | 1.6 | 0.2262 |
| UPCR after 3 months | 1.352 | 0.1912 |
| UPCR after 6 months | 1.135 | 0.1605 |
| Baseline eGFR level | 30ml/min | 4.242 |
| eGFR after 3 months | 43.4ml/min | 6.1376 |
| eGFR after 6 months | 38.34ml/min | 5.422 |
| Baseline serum creatinine value | 1.6 | 0.226 |
| serum creatinine after 3 months | 2.33 | 0.3295 |
| serum creatinine after 6 months | 2.506 | 0.3544 |
| Baseline serum potassium | 4.2 | 0.5939 |
| serum potassium after 3 months | 4.836 | 0.6873 |
| serum potassium after 6 months | 4.946 | 0.6994 |

In our current study 50 participants with UPCR value≥ 0.2 as considered and observed that there is significant effect of reduction in UPCR in more than half of patients and remaining there is no effect of reduction in UPCR.In our current study, mainly patients of stage 3 of CKD are more benefited by slowing down decline of eGFR by finerenone than patients in stage 4 of CKD.
In our current study patients with high UPCR and mild to moderate stage of CKD are benefited highly by reduction of UPCR and slow down decline in eGFR.Finerenone in combination with ACE inhibitors, Angiotensin receptor blockers and SGLT2 inhibitors show more beneficial effect than finerenone alone. There is very minute increase in the serum potassium levels, than other steroidal mineralocorticoid receptor blockers. Finerenone had an acceptable safety profile in our participants, with improvement in UPCR value with estimated GFR as 30ml/min /1.73$m^2$.
Over all, the current study confirmed the beneficial safety profile of finerenone.

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