WORLD JOURNAL OF CLINICAL AND BIOMEDICAL

CSK SCIENTIFIC PRESS

Research Article

Volume 1 | Issue 1

Outcome of Use of A Novel Modulator of Oxidative Phosphorylation on Kidney Function in Patients With Chronic Kidney Disease

Ebima Clifford Okundaye*[1], Ella Egberanmwen Enobakhare[2], Larry Odigie[3], Chiejine Gibson[3], George Oba Okotete[3], Chika Obimah[3], Peter Otuaga, Christina Escamilla[3] Diamondneshay Ward[4]

[1]*University of South Dakota School of Medicine and University of Houston*
[2]*Harvard Medical School*
[3]*Premier Kidney Clinic*
[4]*University of Houston*

***Corresponding Author:** Ebima Clifford Okundaye, University of South Dakota School of Medicine and University of Houston.

Submitted: 01 Mar 2024 **Accepted:** 21 May 2024 **Published:** 28 May 2024

Citation: Okundaye E C*[1], Enobakhare E E[2], Odigie L[3], Gibson C[3], Okotete G O[3], et al.Outcome of Use of A Novel Modulator of Oxidative Phosphorylation on Kidney Function in Patients With Chronic Kidney Disease, Journal of Vaccines, Medicine and Health Care, Research Article. 1(1). 1-10

Abstract

Introduction: *CKD is a contributor to illness and is associated with a diminished quality of life and reduced life expectancy. Several studies have proposed and evaluated therapeutic options of curbing the progression of the disease and decline in kidney function as measured by the glomerular filtration rate. Although these medications have been shown to be helpful in minimizing the rate of decline of CKD progression, currently no therapeutic option is available for patients to restore or repair any already incident loss of glomerular function leading to an improvement in renal function from their baseline. A new pathway targeting NAD+ pathway has been proposed by animal studies. In this article we studied the effect of utilizing a novel drug QRX3, a promoter of NAD/NAD+ oxidative phosphorylation pathway and its effect of glomerular filtrate rate in patients with chronic kidney disease.*

Methodology: *We invited and screened patients presenting for evaluation and follow up at a nephrology outpatient clinic. 45 patients were screened for the study. Diabetes and Hypertension were the causes of CKD in the study population. 17 patients with estimated glomerular filtration rate between 9 and 48 mls/min/1.73m2 and meeting criteria were included in the study and were started on the novel medication in addition to their standard CKD management. The primary outcome was a mean and percentage change in glomerular filtration rate at 3 months and at 6 months.*

Results: *Using analysis of the data for all participants, the mean change in renal function by eGFR was from 29 mls per minute to 35.5 mls per minute at three months (P-0.027 Confidence interval 22.68 to 35.43, DF 16, SE 3.01) ,which was sustained at 35.2 mls per minute at six months (p=0.07 DF 11 Confidence interval 23.1 to 40.05, SE 3.8). This reflected a percentage mean increase of 20.9 % for all the study participants. This effect was similar for percentage increase from the mean eGFR at 3 months for both stage 3 and 4 (P= 0.0086 for CKD 3 and P=0.02 for CKD 4) when compared to CKD stage 5 patients.*

Conclusion: *Among patients with slowly declining chronic kidney disease, the use of a novel drug target of NAD/NAD+ oxidative phosphorylation pathway resulted in a mean improvement in their kidney function above baseline, an effect that was sustained even at 6 months.*

Introduction

Chronic kidney disease is estimated to affect nearly over 800 million people globally today (with roughly 125,000 people ending up annually on dialysis in the United States alone (1-2). CKD is a contributor to illness and is associated with a s diminished quality of life and reduced life expectancy (2 -5). CKD enormous impact on comorbidities and incidence mortality poses a challenging difficulty in addressing this global disease. While other causes are minor incidence aetiology, diabetes and hypertension are two of the most common causes of chronic kidney disease today [6].

Several studies have proposed and evaluated ways of curbing the progression of the disease. Lowering blood pressure and the widespread use of ACEI or ARB to block the endothelial damage via the RAAS system and cause a decrease in intraglomerular pressure has been shown as a means of slowing the progression of the disease es-

pecially with convincing evidence in patients with diabetes [7-10].

The use of bicarbonate supplementation has also been shown to slow the rate of kidney decline (11-13). These along with a more recently discovered sodium glucose cotransporter inhibition (SGLT2) via its natriuresis, and glucose induce osmotic diuresis and subsequent intraglomerular pressure reduction have been helpful in slowing the rate of decline in patients with or without diabetic nephropathy (14-16). Although all these medications have been shown to be helpful in minimizing the rate of decline of CKD progression, but currently no therapeutic option is available for patients to restore or repair any already incident loss of glomerular function.

One study has proposed mechanism of ongoing pathophysiological pathway of the disease with the presence of proteinuria directly from or along with intraglomerular pressure increase having been correlated with a more rapid rate of kidney damage and progressive decline in glomerular function (17).

Another proposed mechanism of renal decline has been proposed to be via intracellular mechanisms including the decrease intracellular Nicotinamide adenine dinucleotide (NAD+) and dysregulation of oxidative processes with secondary inflammatory marker releases suggesting a mitochondrial oxidative phosphorylation changes within the tubular and interstitial cells present in the kidney [18]. Nicotinamide adenine dinucleotide (NAD+) supplies energy for deoxidation and anti-inflammatory reactions fostering the production of adenosine triphosphate (ATP). NAD molecules and their activity in electron transfer in renal tissue has been shown to be low in CKD states. These cascade of oxidative inflammatory cells markers have been shown to contribute to renal fibrosis [19-21]. Mitochondrial dysfunction has also been observed in CKD, and preventing mitochondrial damage reduces fibrogenesis in rat models [22].

An earlier animal study has shown that oral supplementation with Nicotinamide (NAM) a precursor of NAD+ attenuated progression of CKD in rat models [23]. There was significant difference in BUN and serum creatinine changes as well as histological changes of decreased fibrosis in kidney tissues of NAM supplemented rats. Decreased availability or impaired NAD production has been linked to premature renal aging in a few studies [23-26]. These studies strongly suggested NAD+ administration or activity optimization may be a novel therapeutic approach for CKD prevention. However, the target of this NAD+ supplementation did not show any statistical benefit in CKD patients in the COMBINED trial [24].

Thus, there are currently no widely available therapeutic benefits to evaluating intracellular mechanisms that result in the cascade of progressive damage within renal tubular cells. Several treatment options for mitochondrial dysfunction have been suggested. QRX-3 (Eserenate) is a formulated drug designed to supply and optimize NAD+ mitochondrial availability in order to target the loss of nephrons via renal fibrosis and tubular senescence of the kidney cells by enhancing the mitochondrial activity of these cells via the NAD/NAD+ redox pathway as well as reduce the presence of fibro genic intracellular inflammatory markers.

This novel drug therapy stabilized the intracellular oxidative phosphorylation process a pathway mechanism that is dysregulated or abnormal in the ongoing renal tubular cell injury and damage in chronic kidney disease. In this study we evaluate the effect of intervention with this novel drug therapy on a chronic kidney disease CKD population with slowly declining renal function.

Patient Selection

All patients presenting at the clinic for their CKD management were eligible for selection. Patients with a lower eGFR at the time of screening compared to than their previous values indicating a declining renal function were screened for participation in this study

Methodology

Patients presenting in an outpatient chronic kidney disease clinic were used for the study. Patients with slowly progressive renal function with current renal function as assessed by estimated glomerular filtration rate (eGFR) using creatinine by MDRD system were identified. Proteinuria as attained by random urine protein creatinine ratio was also obtained and documented. Patients were continuing on their standard dose of ACEI or ARB as well as use of sodium glucose cotransporter inhibitors without any subsequent change in that dosage during the duration of the study.

All patients were worked up and ruled out for other secondary causes of chronic kidney disease and were removed from the study. Causes of rapid decline in renal function with suspected superimposed acute kidney injuries were also not eligible to participate in the study. Regular follow up and monitoring of labs as well as side effects were documented. Standard dose of QRX-3 was administered. Due to already documented major adverse effects of smell and taste, patients were encouraged to mix QRX3 with any beverage of their choice.

Study Design and Oversight

The study was performed as a single arm nonrandomized study. Patients were recruited from two CKD clinics in the Houston Texas area. Golgotha pharmaceuticals – the sponsoring company, monitored and provided the novel drug QRX-3 also referred to as Eserenate. Patients presenting for care of their chronic kidney disease were interviewed and screened for this study. The study was approved by the Premier Kidney clinic Institution Review board committee, the local clinic IRB; and informed patients consent for the drug use from all the subjects and or their legal guardian was obtained. No minors or illiterates were involved in the study.

The trial was designed to enrol 20-25 patients as a phase II trial. Forty-five patients were screened for the study. An initial 20 patients were initiated on the new drug. Three patients were first included in the study but later removed from analysis resulting in a total of 17 patients. Patients in the study have their demographics and CKD stages collected and tabulated. Their previous eGFR from between 3-6 months before time of screening were collected, to eliminated risk of acute kidney injury, and compared to their current renal function. Patients with more than 20% rate of decline were excluded as well as those with suspected secondary acute or subacute cause of kidney injury. Proteinuria levels by random urine protein creatinine methods were documented and patients meeting

nephrotic range levels as defined by random urine protein/creatinine ratio of 3g/g/day or higher were identified and compared. Follow up data at 3 months and 6 months after start of trial intervention were collected.

Study Participants

All patients have CKD and were being evaluated at the CKD clinic. eGFR between 9 mls/min/1.72m2 and 50 mls/min/1.73m2 was the criteria for being screened for study participation .

Inclusion criteria

- Patient with Chronic kidney disease
- Estimated Glomerular function by MDRD of less than 60mls/min
- Patients with declining renal function (as measured by eGFR by MDRD)
- Rate of decline of eGFR over the last one year of less than 20%
- Negative Serology markers for CKD etiology
- Provider perceived adherence to study follow up

Exclusion criteria

- Rapid rate of decline in kidney function of > 20 % over last one year
- Symptomatic renal failure
- Presence of any suspected Acute renal failure superimposed
- Presence of cast , haematuria, or abnormal urinalysis outside of simple UTI • No known reversible cause of renal decline

Randomization and Intervention

No randomization was done for the study population. All patients have slowly progressive chronic kidney disease with similar or lower renal function at the time of screening compared to their previous data. Intervention was the addition of the novel QRX3 therapy to their already existing management of their CKD. Patients were advised to report any other medication changes. Medications that affect renal function were not allowed during this period . Their dosage or use of ACEI/ARB,SGLT-2 were not altered. Follow up at 1 month, 3 months and 6 months were done. Laboratory studies were done at Quest laboratory facilities .

Study Outcomes

The primary end point was the change in estimated glomerular filtration rate (eGFR) by MDRD for the study participants at 3 months and at 6 months compared to their baseline starting eGFR rate. eGFR was calculated from serum creatinine obtained during each visit. Random urine protein/creatinine ratio was used to determine the presence of significant proteinuria. Safety and tolerability of the drug were obtained as any reported new symptoms or events during each follow up visit and documented.

Statistical Analysis

Analysis of the data was done with a paired two sample T-test. Baseline characteristics were evaluated by mean and standard deviations (SD) as appropriate. The percentage of increase or decrease in eGFR with the intervention at follow-up visits, were calculated from the baseline eGFR values. Mean eGFR at baseline and the percentage of change at 3 months and 6 months were compared. Patients with missing appointments at 3 months but had 4 months follow up data were recorded in the 3 months data bracket. Similarly, patients with data at 7-8 months were also included in the 6 months data bracket. Patients with missing data were analysed only with results of data they had, as we did not use any algorithm to input values for those with missing data statistical analyses were performed with the Stata software 18, 2023 version. A P-value of 0.05 was used as the criteria cut-off for significance.

Results

Findings: Over 45 patients were screened, and 20 patients were initiated on the study. However, follow up data was only available for 17 of these 20 patients. Three patients with already symptomatic CKD stage 5 were initiated on dialysis within one week of starting therapy and were not included in the data analysis. That are from all completed 17 patients were collected and analysis was done.

1. Patient Characteristics

There was no age limit for participation in the trial. the mean age for this study population was 71 years with the mean eGFR of 29.4mls per minute power 1.72-meter square **(Table 1)**.

Table 1: Baseline Demographics of the study population showing age of patients , gender numbers, common diagnoses, and CKD stages.

Demographics of study population (N-17)	
Age	71.1 years
Mean eGFR	29.6mls/min
Male	11
Female	7
DM	12
HTN	17
RAS	1
ACEI/ARB	14
SGLT2	8
Stage-3	8
Stage-4	7
Stage-5	2

Combination of Diabetes and Hypertension were the common causes of the Chronic kidney disease in 12 of the 17 patients. Four patients have pure hypertension as their cause of kidney injury. One single patient has a combination of hypertension and microvascular renal artery stenosis causing their CKD status **(Table 2).**

Table 2- Showing individual patient's data = Age, clinical diagnosis causing CKD and corresponding estimated renal function at baseline

Patient	Age (in years)	Diagnosis	Baseline eGFR (in mls/min/1.72mls/sq2)
1	81	DM/HTN	GFR- 0
2	71	HTN	39
3	75	HTN/DM	44
4	69	DM/HTN	30
5	43	DM/HTN	21
6	74	DM/HTN	57
7	68	HTN	21
8	60	DM/HTN	21
9	83	DM/HTN	39
10	70	DM/HTN	27
11	63	DM/HTN	17
12	74	DM/HTN	40
13	79	DM/HTN	31
14	65	HTN	29
15	77	HTN	39
16	74	DM/HTN	26
17	83	HTN/RAS	9
			14
Mean	71.11765		29.64706

Table showing of study patients with their diagnosis and baseline estimated glomerular filtration rate as measured by MDRD formula. GFR-0 is baseline estimated GFR at time the time of initiation.DM = Diabetes, HTN -Hypertension, DM/HTN- combined diabetes and Hypertension, RAS- Microvascular renal artery stenosis.

Of the total 17 patients all with CKD; 8 patients (47%) were in CKD stage 3. Stage 3 was divided as 3A for eGFR above 45-59mls/min/1.72m2 and stage 3B eGFR between 3044mls/min/1.72m2. 2 were in CKD stage 3A(11.7% of study population), 6 patients with CKD stage 3B (35.3%), 7 patients were in CKD stage 4 (41.1%) and two patients were in asymptomatic CKD stage 5 Status at baseline (11.7%) **(Table 3).**

Table 3- Baseline CKD stages of Participants

CKD stage	Number of Patients	Percentage of sample Population
3A	2	11.7
3B	6	35.3
4	7	41.1
5	2	11.7
Total	**17**	**100%**

Three patients with CKD stage V with eGFR below 15mls/min who were initially thought to be stable but noted to have developed symptoms within two weeks of the start of the therapy were discontinued from the study and initiated on dialysis. Their data was not included in the evaluation analysis. The majority of the patients were on ACEI /ARB (n=14 , 83%) except for two patients in CKD stage 5 and one patient in CKD stage 3 who had recurrent hyperkalaemia resulting in discontinuation of ACEI/ARB therapy.

2. Rate of Change in kidney function

At the time of participation in the trial, the patients had a mean decline in their prior renal function renal function from 33.8ml/min/1.72mls/min from the preceding 3-6 months prior to 32mls/min at the time of study initiation. Of the 17 patients, 7 (41%) patients did not have all eGFR values for the 4 time periods (Pre,-3 months and 6 months) needed for complete analysis. Some patients lacked either the post 3 or post 6 months eGFR values. 4 (23.5%) of them lack the pre-baseline data but were clinically determined to be in a stable renal decline. 10 (58.8%) patients have their completed data and analysis in comparism of the pre-, baseline or 0, 3 months post and 6 months post data were done. All of these patients in the study have their data evaluated**(Table 4).**

Table 4: of patients with completed data for all 4 time periods

GFRPRE3	GFR0	GFR3	GFR6	
43	57	81	81	
44	39	47	44	
34	27	29	31	
21	17	22	29	
42	40	54	48	
35	31	35	35	
31	29	32	31	
44	39	39	35	
11	9	10	10	
33.8	32	38.7	38.2	Mean
11.4	14	20	19.2	SD

Glomerular filtration rate changes with therapy at 3-6 months pre-initiation of study (GFR-Pre), at time of study (GFR0) and at three and six months of intervention (GFR3 and GFR6) respectively.

Table 5: Comparism of renal function by eGFR at baseline (0), Prior eGFR (Pre-), 3 months after start of therapy and 6 months after therapy initiation.

GFRPRE3	GFR0	GFR3	GFR6
45	39	X	41
x	44	52	64
x	30	40	x
X	21	24	x
43	57	81	81
24	21	23	x
32	21	34	x
44	39	47	44
34	27	29	31
21	17	22	29
42	40	54	48
35	31	35	35
31	29	32	31
44	39	39	35
X	26	29	24
11	9	10	10
X	14	14	18

All study participants had an increase in their renal function by use of the QRX drug compared to their baseline. There was a 100% increase in the renal function measured by MDRD eGFR at three months after drug initiation (Figure 1a and b). There was an average increase by 6 mls per minute from 32mls/min at start of study to 38.8 mls/min improvement in renal function at three months. This improvement in renal function was sustained at six months with an average mean eGFR of 38.2 mls per minute P = 0.04, CI 24.8-39.2) **(Table 5).**

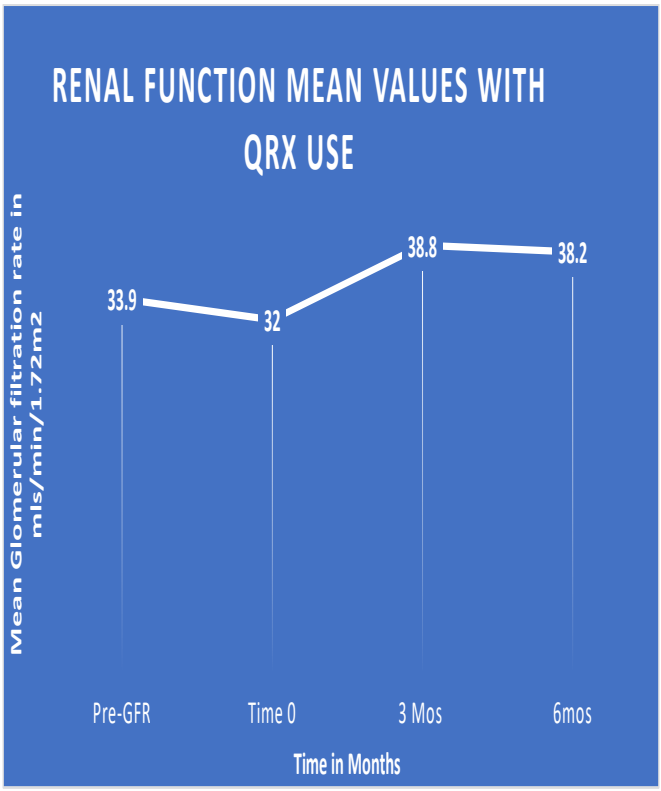

Fig 1a: Showing comparison of mean renal function (by eGFR by MDRD) at different time periods with QRX drug intervention for the same subset of study patients.

Using analysis of the data for all participants, the mean change in renal function by eGFR was from 29 mls per minute to 35.5 mls per minute at three months (P = 0.027 Confidence interval 22.68 to 35.43, DF 16, SE 3.01),which was sustained at 35.2 mls per minute at six months (p=0.07 DF 11 Confidence interval 23.1 to 40.05, SE 3.8). This reflected a percentage mean increase of 20.9 % for all the study participants. As previously mentioned, 5 patients did not have data at 6 months follow-up.

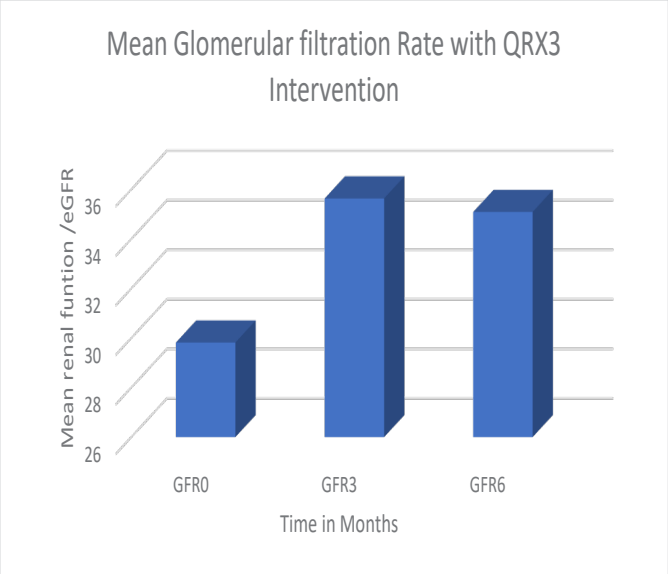

Figure 1b

3. Level of Proteinuria effect: Among patients with significant nephrotic proteinuria there was an average mean increase of 5.8 mls per minute (change of 15.7%) for the nephrotic proteinuria group vs 6.7 mls per minute (change of 23.5%) for those with non-nephrotic proteinuria at the start or during the period of the trial. As the nephrotic range proteinuria was defined as random urine protein creatinine ratio of greater than 3g/g. This translated to a mean percentage increase in renal function of 15.7 percent for the proteinuria group and 23.5% for the non-proteinuria group. (23.5 vs 15.7) P =0.03 CI 4.7-6.9 (Table 6, Figure 2).

Table 6: Showing the impact of baseline proteinuria on mean change (increased percentage above baseline) of renal function after QRX-3 intervention at 6 months.

	Nephrotic Range	Non - Nephrotic
Mean change inGFR	5.8	6.87
Percent Increase	15.5	23.5

Nephrotic range proteinuria was defined as random urine protein creatinine ratio of >3 g/g., mean change in GFR was obtained from average of all the difference between baseline and 6 months values. Their percentage from the baseline values also shown.

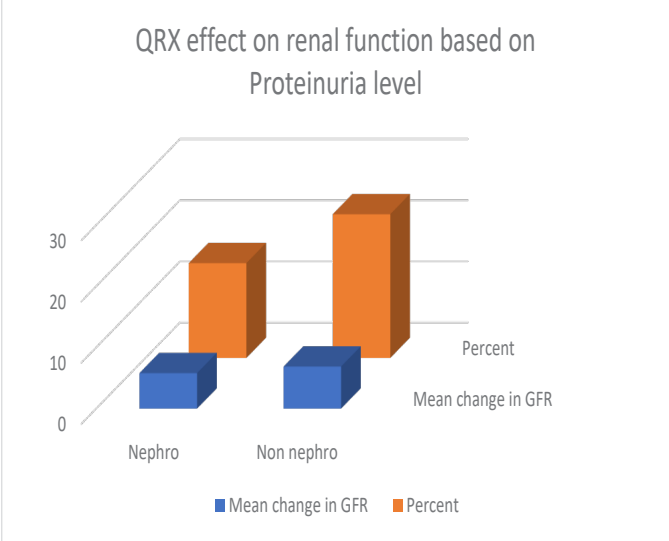

Figure 2 : Graph showing the pattern of mean improvement of eGFR for all CKD stages based on the level of baseline proteinuria (Nephrotic vs non nephrotic) and their percentage mean change

4. Analysis of outcome by CKD stage: When analysed by baseline stage patient CKD stage 3 have an average increase of 23.1% increase in their baseline glomerular filtration function at three months which was sustained at 20.5% above the baseline value at six months. The mean baseline GFR for this body population was 39.8 mls per minute **(figure 3).**

For CKD stage 4, the basically baseline eGFR was 23.1mls/min, and there was a mean average increase of 20.2 % at three months wish for that improved to 20.7% at six months in the overall renal function **(Figure 4).**

For the 2 patients with asymptomatic CKD stage 5 there was an average me increase of glomerular filtration of 0.5 mls per minute at three months which improved to 2.5 mls/minute/1.72m2 at six months corresponding with an average increase of 5.5% at three months and at up to 20 percent at six months. None of the patients has transition to requiring dialysis as at this time **(Figure 5)**.

The level of increase in renal function with QRX 3 drug use was similar in percentage between CKD stage 3 and stage 4 but higher than the improvement in CKD stage 5 (percent increase 23.1% and 20.2% vs 5.5% (P= 0.0086 for CKD 3 and P=0.02 for CKD 4). But at the end of study, there was a similar overall improvement ratio (20.7 vs 20.7 vs 20%) for all CKD stage **(Table 7).**

Table 7: Relationship of CKD stage with resulting level of improvement in renal function by QRX3 drug intervention.

CKD Stage	Meane GFR at baseline	Percentage change at 3 months	Percentage change at 6 months
3	39.8	23.10%	20.50%
4	23.1	20.20%	20.80%
5	11.5	5.50%	20%

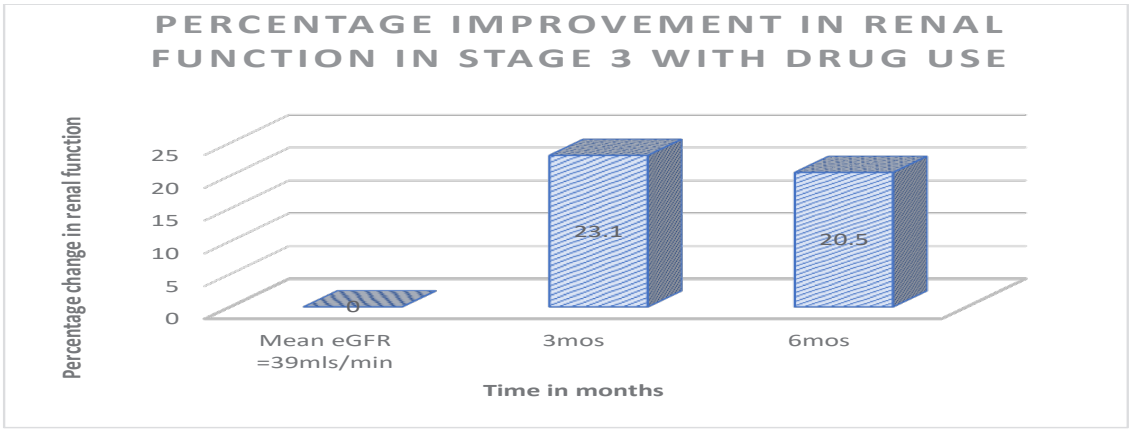

Figure 3: Graph showing the pattern of improvement of eGFR by percentage at 3 and 6 months after intervention when compared to baseline for patients in CKD stage 3.

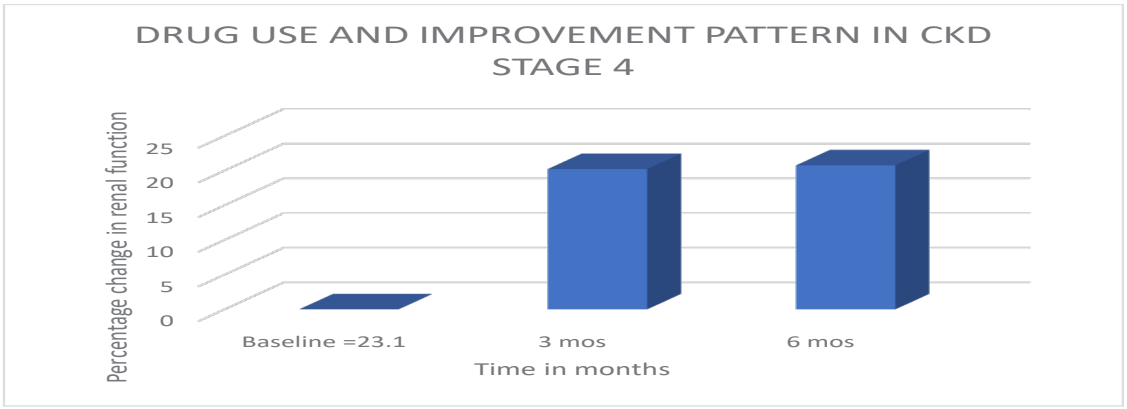

Figure 4: Graph showing the pattern of improvement of eGFR by percentage at 3 and 6 months after intervention when compared to baseline for patients in CKD stage.

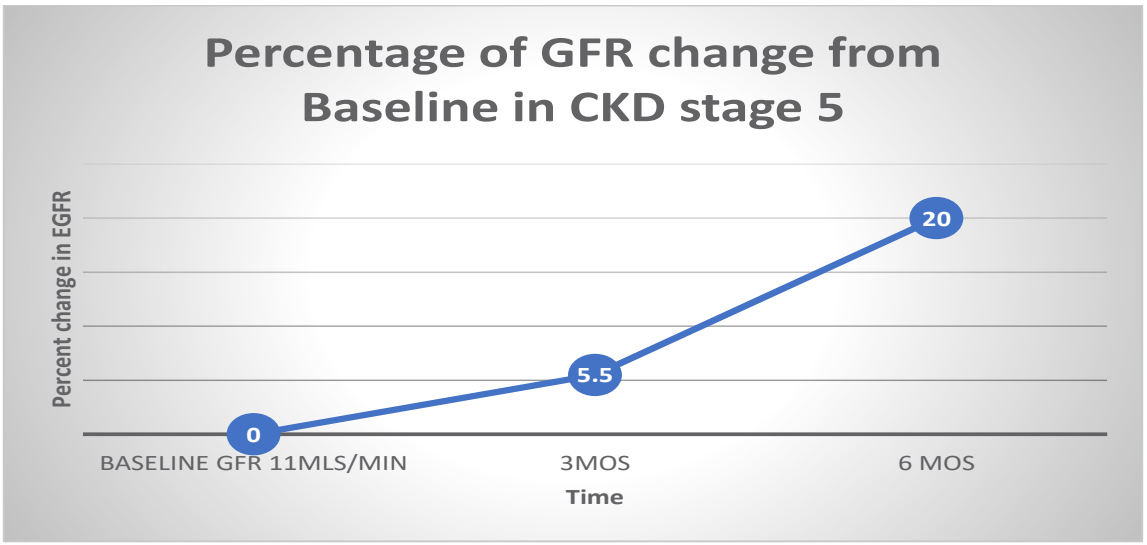

Figure 5: Graph showing the pattern of improvement of eGFR by percentage at 3 and 6 months after intervention when compared to baseline for patients in CKD stage 5.

5. Safety: Adverse effects noted 12 patients (70.5%) reported poor smell and taste of the QRX3 drug that was readily ameliorated by advising mixture of the drug with a beverage. One patient (n=1, 4.7%) developed a rash that improved with removal of the P - component from the drug regime and treatment with steroids. No other major side effect was observed.

Discussion: Our novel drug candidate target of oxidative intracellular redox pathway of injury to renal tubular cells can be an effective way of revising progressive chronic kidney disease injury. Understanding and the pathophysiology off injury focus is on the president of dysregulation of the positive phosphorylation pathway that is primarily in the mitochondria region. The improvement in kidney function as shown by the increase glomerular filtration rate after start of the drug indicate the role of electron transfer in the NAD+ oxidative reduction (redox pathway) for mitochondria oxidative phosphorylation appears to be essential for continued optimal functioning of both the glomerular and the tubular renal cells (18). The COMBINED trial failed to show any benefit of NAD supplementation in CKD patients by supplying oral NAD precursors (23) despite a reported benefit of NAD precursor use in CKD rat model (24).

We remedied the scenario by design of our novel drug that supply and promote the activity of NAD+ as well as having a component that minimizes generation of inflammatory markers. Since NAD has been shown to decrease with age , we targeted a higher age population in this study to show benefit of our therapy in this older and less likely to respond to this modality of therapy population.

QRX3, a drug developed to optimize the oxidative phosphorylation pathway as well as mop up oxidative inflammatory radicals as well as precursors of extracellular matrix formation like adhesive glycoprotein fibronectin (FN) VEGF, ICAM as well as other inflammatory cytokines; has been shown from this study, to not only reduce the rates of declining renal function by preventing tubular senescence, tubulointerstitial fibrosis and collagen matric formation with subsequent endothelial injury as well as stabilize currently dying renal cells and nephrons . But it also resulted in an overall improvement in renal function which continued to be sustained several months after initiation of the drug. This prove the possible continued reactivation of already dying nephrons , to continue to function in tubular creatinine excretion and a possible strong impact of this reduction in oxidative stress on the glomerular cells themselves ,allowing for better glomerular filtration function .This study, although small in sample size, has shown a possible door into the understanding of the unique intracellular dynamics that happened in patients with both hypertensive and diabetic renal injury causing progressive nephropathy.

The minimal improvement or less than expected increase in eGFR noted in patients with nephrotic range proteinuria is consistent with earlier studies showing presence of proteinuria causing a more accelerated and progressive loss of glomerular filtration in the CKD population. Therefore, QRX3 would work better in patients with lower or non-nephrotic range proteinuria. The use of ACEI or ARB to further minimize proteinuria could further enhance the effect of QRX3 therapeutic use in patients with this subset of nephrotic range proteinuria. In this study, the patient selection and the high mean age of the population is beneficial in representing the older population of advanced chronic kidney disease patients. The tendency for older population to have a lower regenerative ability and slow healing of their kidney injuries were targeted to suggest a more impactful outcome of the trial with the QRX3 intervention. Thus, the ability for the QRX3 to even cause a higher-than-expected improvement in this older age population is a testament to the efficacious pathway of this targeted therapy. If extrapolated to a younger age population, we anticipate a much better outcome with a higher mean improvement in the renal function with the intervention.

In this study, the use of the comparison of prior renal function to the GFR status at the time of study eliminated the possibility of acute kidney injury contributing to the study outcome. The decline of average of 1.8mls/min mean eGFR is in line with pattern of a slow gradual progression of ongoing renal injury is typical for this study population. Although a better follow up measures to ensure a perfect collection of all subsequent data for the 3- and 6-months intervention period, would have been ideal but the data collected and available were still adequate to compare the result of the mean change in kidney function after start of intervention to the baseline GFR at time of inclusion in the study. The study has a major limitation of small sample size, but this is typical for a phase 2 trial evaluating the potency of a new drug . We hope to subsequently be able to reproduce this data in a much larger phase 3 study. However, till date, this is the first drug therapy that has shown any promise of reversing decline in glomerular filtration rate in patients with CKD .

Conclusion: In patients with progressive decline in renal function, the use of an innovative drug formulation QRX3 targeted at optimizing oxidative phosphorylation via NAD supplementation and activity enhancement provided a significant improvement in renal function at three months that was sustained at six months.

Availability of data and materials: All data sets generated and analysed in this study are not available publicly due to privacy laws and patient consents, However based on responsible request, some data can be declassified and made available upon request from the corresponding author.

Abbreviations

CKD – chronic kidney disease

NAD – Nicotinamide Adenine Dinucleotide (NAD)

NAD+- Oxidized form of Nicotinamide Adenine Dinucleotide

eGFR – estimated glomerular filtration rate – which in this

study was based on MDRD

DM – diabetes mellitus

HTN – Hypertension

RAS – renal artery stenosis

ACEI – Angiotensin converting enzyme inhibitor

ARB – Angiotensin Receptor blockers

SGLT-2- Sodium glucose co-transporter inhibitors

1. Ethics approval and consent to participate - was obtained and addressed as noted above
2. Consent for publication – provided
3. Competing interest - N/A
4. Funding- no funding provided for conflict of this study, drug was supplied by the sponsor.
5. Author's contributions:

- EO- designed the study as well as preparing the manuscript
- EE – did the statical analysis for the study and manuscript writing
- CE- oversaw participation in the trial as well as retrieval of data from records
- LO- helped in trial design and protocol processes
- DW- helped in data retrieval and manuscript review
- GC- helped in trial design and manuscript writing
- CO- helped in manuscript writing
- GO- helped in protocol processes and manuscript writing

Acknowledgements - special thanks to all the patients and staff of premier kidney clinic.

References

1. Webster AC, Nagler EV, Morton RL, Masson P (2017) Chronic kidney disease. The lancet, 389: 1238-1252.
2. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson, et al. (2016) Global prevalence of chronic kidney disease–a systematic review and meta-analysis. PloS one 11: e0158765.
3. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, et al. (2020) Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine, 383: 1436-1446.
4. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, et al. (2004) Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. Journal of the American Society of Nephrology, 15: 1307-1315.
5. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, et al. (2006) Chronic kidney disease and mortality risk: a systematic review. Journal of the American Society of Nephrology, 17: 2034-2047.
6. Chen TK, Knicely DH, Grams ME (2019) Chronic kidney disease diagnosis and management: a review. Jama, 322: 1294-1304.
7. Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, et al. (2012) Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. The Lancet, 380: 1649-1661.
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. New England Journal of Medicine, 351: 1296-1305.
9. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, et al. (2016) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. The Lancet, 387: 957-967.
10. Qin Y, Chen T, Chen Q, Lv JY, Qi N, et al. (2016) The effect of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use on mortality in patients with chronic kidney disease: a meta-analysis of observational studies. Pharmacoepidemiology and drug safety, 25: 503-511.
11. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM (2009) Bicarbonate supplementation slows progression of CKD and improves nutritional status. Journal of the American Society of Nephrology: JASN, 20: 2075. Doi: 10.1681/ASN.2008111205.
12. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, et al. (2010) Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney international, 78: 303-309. DOI: 10.1038/ki.2010.129.
13. Phisitkul S, Khanna A, Simoni J, Broglio K, Sheather S, et al. (2010) Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. Kidney international, 77: 617-623. DOI: 10.1038/ki.2009.519.
14. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, et al. (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine, 375: 323-334.
15. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher

G, et al. (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. New England Journal of Medicine, 377: 644-657.

16. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, et al. (2019) Dapagliflozin and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine, 380: 347-357.

17. Cravedi P, Remuzzi G (2013) Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease. British journal of clinical pharmacology, 76: 516-523.

18. Morevati M, Fang EF, Mace ML, Kanbay M, Gravesen E, et al. (2022) Roles of NAD+ in Acute and Chronic Kidney Diseases. International Journal of Molecular Sciences 24: 137.

19. Genovese F, Manresa AA, Leeming DJ, Karsdal MA, Boor P (2014) The extracellular matrix in the kidney: a source of novel non-invasive biomarkers of kidney fibrosis?. Fibrogenesis & tissue repair, 7: 1-14.

20. Sparding N, Rasmussen DGK, Genovese F, Karsdal MA, Hornum M, et al. (2022) Circulating Levels of Endotrophin Are Prognostic for Long-Term Mortality after AKI. Kidney360, 3: 809.

21. Humphreys BD (2018) Mechanisms of renal fibrosis. Annual review of physiology, 80: 309-326.

22. Jiang M, Bai M, Lei J, Xie Y, Xu S, et al. (2020) Mitochondrial dysfunction and the AKI-to-CKD transition. American Journal of Physiology-Renal Physiology, 319: 1105-1116.

23. Kumakura S, Sato E, Sekimoto A, Hashizume Y, Yamakage S, et al. (2021) Nicotinamide attenuates the progression of renal failure in a mouse model of adenine-induced chronic kidney disease. Toxins, 13: 50.

24. Chanvillard L, Tammaro A, Sorrentino V (2022) NAD+ Metabolism and Interventions in Premature Renal Aging and Chronic Kidney Disease. Cells, 12: 21. doi: 10.3390/cells12010021. PMID: 36611814; PMCID: PMC9818486.

25. Liu X, Luo D, Huang S, Liu S, Zhang B, et al. (2021) Impaired nicotinamide adenine dinucleotide biosynthesis in the kidney of chronic kidney disease. Frontiers in physiology, 12: 723690. doi:10.3389/fphys.2021.723690. PMID: 34603081; PMCID: PMC8484911.

26. Doke T, Mukherjee S, Mukhi D, Dhillon P, Abedini A, et al. (2023) NAD+ precursor supplementation prevents mtRNA/RIG-I-dependent inflammation during kidney injury. Nature Metabolism 5: 414-430. doi: 10.1038/s42255-023-00761-7. PMID: 36914909; PMCID: PMC10230446.

27. Ix JH, Isakova T, Larive B, Raphael KL, Raj DS, et al. (2019) Effects of nicotinamide and lanthanum carbonate on serum phosphate and fibroblast growth factor-23 in CKD: the COMBINE trial. Journal of the American Society of Nephrology: JASN, 30: 1096.