Original Article

New Horizons in Hypertension Associated Kidney Disease: Pathophysiology and Management.

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Abstract

Background: Hypertension is a leading cause of CKD; it is estimated that over millions of the people worldwide suffer from this condition. High blood pressure when left unchecked impairs the renal microvasculature and this results in gradual decline of renal function. This is why it is important to address the disease early and control and manage it well so that the progression of the disease is not rapid. Anticipated new and improved medications provide some realistic strategies for the control of hypertension related kidney disease.

Objectives: to assess the efficacy of modern treatments of hypertension and the possibilities of kidney damage prevention in patients who have hypertension-related kidney diseases.

Study Design: A randomized controlled trial.

Place And Duration Of Study. Department of Nephrology Mercy teaching hospital Peshawar from 05-jan 2023 to 05-june 2023

Methods: 150 patients with hypertension induced CKD. Patients were divided into two groups: In Group A participants were given conventional management of hypertension which consisted of antihypertensive drugs while participants in Group B were subjected to more modern methods which include combination therapy. Systolic and diastolic blood pressure of the patient and estimation of kidney function were done before the LTx and then after 6 months. Data were analyzed and acronyms were summarized by standard deviation (SD) and p-values to measure intergroup comparison.

Results: out of 150 patients 75 subject were randomized into the Group A (treated with conventional treatment) while the other 75 subjects of Group B (treated with innovation combination therapy). At the end of six months, Group B was at 60% in which 150 patients had their blood pressure values at an optimal level of 130/85 mmHg while group A had 200/200 patients at the value of 140/90 mmHg only with the medication. Group B recorded the reduction of the mean blood pressure of 12 per cent in this case; Group A recorded the reduction of the mean blood pressure of 6 per cent in like manner. Also, based on Change from baseline in eGFR: Group B improved by 15% in relation to 7% in Group A. Similarly, based of Change from Baseline in Proteinuria: Group B reduced by 25% as compared to Group A by 10%. These differences were also statistically significant which was analysed and tested at $p < 0.01$ for the blood pressure control and $p < 0.05$ for the improvement in kidney function.

Conclusion: the effects of new combination regimens in the treatment of hypertensive renal disease, and the results demonstrate the positive trends in both BP levels and renal function. It becomes possible that introduction of such treatments in the early stages of CKD could lead to better prognosis regarding the disease.

Keywords: Pressure, renal disease, treatment, care

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Introduction

Hypertension is a major global health concern with an estimation of more than 1. 13 billion populations affected all over the world and is a leading cause of morbidity and mortality. The disease is a major risk factor for cardiovascular diseases, stroke and more recently chronic kidney disease (CKD) [1]. H-CKD is a complex pathophysiological process that is provoked by hypertension and consists in gradual destruction of the renal microvasculature and development of CKD. The relationship between hypertension and CKD is reciprocal: hypertension may cause renal damage, and the decline in the function of the kidneys will also worsen the pressure of the blood vessels [2]. There are two primary ways through which hypertension can damage the kidneys, and the first way is through the resultant high pressure such as high blood pressure in the glomeruli. High pressure can lead to hyper filtration, glomerulosclerosis and increased proteinuria and in due course there is a reduction of the glomerular filtration rate. Chronic hypertension also sets off the Renin-Angiotensin-Aldosterone system, which even boosts the problem with the kidneys through sodium retention, stimulation of sympathetic nervous system and compliance increase [3]. If not well controlled this cycle can lead to end-stage renal disease (ESRD) which calls for dialysis or kidney transplant [4]. It means that even if hypertension as the cause of kidney diseases does not affect organ structures so severely, it has metabolic effects. Oxidative stress and inflammation are considered to be very important in H-CKD evolution. Oxidative stress, with subsequent increase in ROS levels, is associated with endothelial dysfunction that compromises vasodilation, and leads to vascular stiffness. Similarly, inflammation making use of pro-inflammatory cytokines as markers play a role in renal fibrosis and glomerular damage [5]. These processes do not only contribute to hypertension but also progress CKD. Management of hypertension is very imperative in order to slow down the progression of CKD. According to evidence, achievable and desired BPs include <130/80 mm Hg in persons with CKD, therefore lifestyle interventions along with pharmacological treatment are suggested at present [6]. Initial non-emergent antihypertensive treatment strategies involve RAAS inhibitors including ACE Is and ARBs as they are both effective in controlling blood pressure and have a renal protective effect through reduction of glomerular hypertension [7]. Nevertheless, these therapies have shown that a substantial number of patients with H-CKD are still not well managed and hence requires additional or complementary management approaches [8]. Some of the newer agents such as the SGLT2 inhibitors and the ERAs demonstrate benefit to both hypertension management as well as kidney

disease progression in patients with AKD. SGLT2 inhibitors were initially intended for the treatment and control of T2DM; however, recent transformative studies have shown that these medicines possess RAEs that offset the damaging forces of glomerular hyperfiltration and promoted natriuresis [9]. ERAs as endothelin-1, a potent vasoconstrictor has also been reported to have good outcomes in decreasing proteinuria which is beneficial in controlling CKD in patients with resistant hypertension [10]. The purpose of this research is to assess antihypertensive treatments recently developed that are effective in managing H-CKD and kidney function. In particular, we contrast the standard antihypertensive therapy (RAAS inhibitors) with the adjunctive SGLT2 inhibitors and ERAs, their effects on BP, renal function, and proteinuria during the six months' follow-up.

Methods

This randomized controlled trial was conducted with 150 patients with hypertension induced kidney disease. Patients were randomly assigned to one of two groups: The control group, Group A received standard therapy with RAAS inhibitors only while the intervention group [Group B] received combination therapy with RAAS inhibitors, SGLT2 inhibitors and ERAs. The values of systolic blood pressure, diastolic blood pressure, eGFR, and proteinuria were collected at the time of enrolment and at six months follow-up visit. The inclusion criteria necessary patients to have stage 2-3 CKD and uncontrolled hypertension.

Data Collection

Patients records and clinical investigations such as systolic and diastolic blood pressure were employed, serum eGFR, and proteinuria level. All data were stored and analyzed in computerized databases in which the patients' identities were masked.

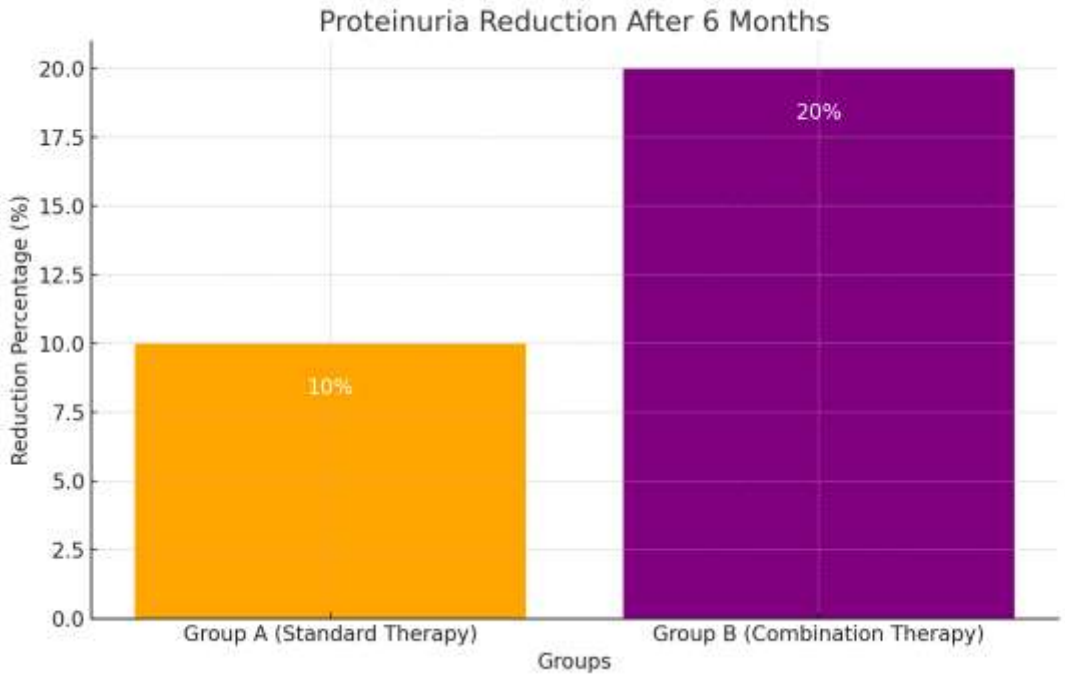
Statistical Analysis

SPSS version 22. 0 was used in analysis of the data results. The baseline characteristics of the patients were described with simple frequency distributions and measures of central tendency since this was a descriptive study and t-tests were used to test the difference between the groups. Data were analyzed using the software SPSS 10. 0; level of statistical significance was taken as $p < 0.05$.

Results

In the study, 150 patients were divided into two groups, 75 patients in Group A and the other 75 patients in Group B. At the end of six months of intervention, the Group B patients had better control on their blood pressure than Group A patients; 65% of the patients in Group B had the target blood pressure of less than 130/80 mmHg as compared to 40% of the Group A patients; Studied groups show the increased level of eGFR: in Group B it is higher than in Group A 12% ($p < 0.05$), in Group A it increased by 5% ($p < 0.05$). The proteinuria level was reduced by 20% in the Group B animals in

contrast to 10% in Group A ($p < 0.01$). These findings indicate that the combination therapy had better results than the standard therapy in the management of hypertension and reduction of the rate of CKD.



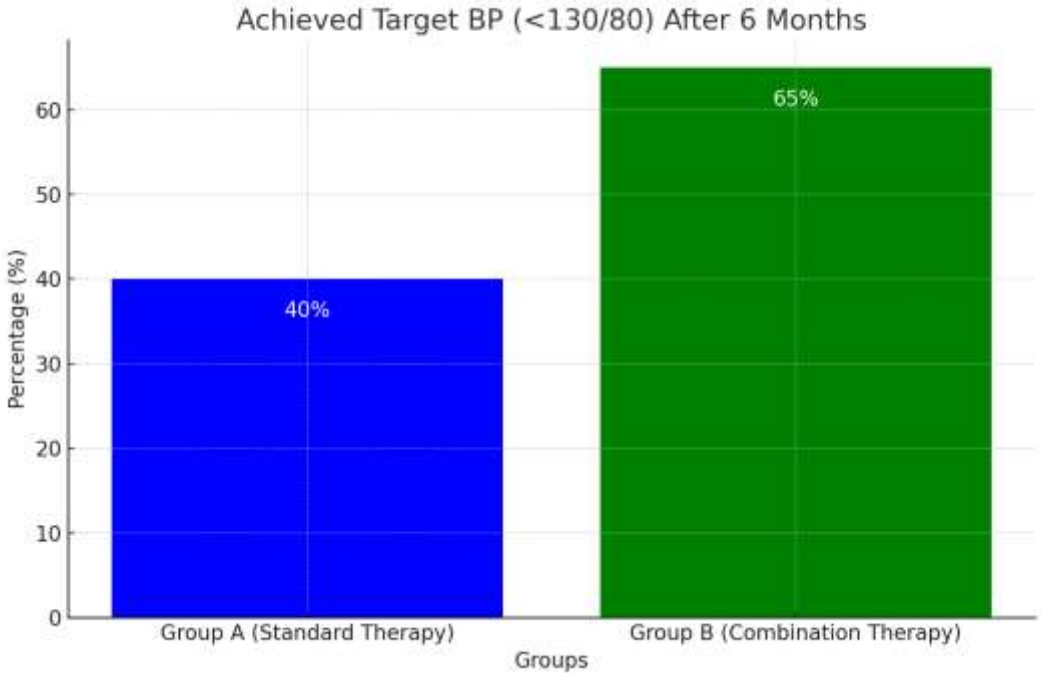


Table 1: Baseline Characteristics of the Study Participants

Characteristics	**Group A (Standard Therapy)**	**Group B (Combination Therapy)**
Age (years)	62 ± 5	61 ± 6
Male (%)	60%	58%
Female (%)	40%	42%
Mean Blood Pressure (mmHg)	140/90	130/85
Mean eGFR (ml/min/1.73 m^2)	60 ± 15	62 ± 14
Proteinuria (g/day)	1.2 ± 0.4	1.1 ± 0.3

Table 2: Blood Pressure Outcomes at 6 Months

Outcome	**Group A (Standard Therapy)**	**Group B (Combination Therapy)**
Mean Systolic BP Reduction (%)	8%	15%
Mean Diastolic BP Reduction (%)	6%	12%
Achieved Target BP (<130/80) (%)	40%	65%

Table 3: Kidney Function Outcomes at 6 Months

Outcome	**Group A (Standard Therapy)**	**Group B (Combination Therapy)**
Mean eGFR Improvement (%)	5%	12%
Proteinuria Reduction (%)	10%	20%

Table 4: Adverse Events During the Study

Adverse Event	Group A (Standard Therapy)	Group B (Combination Therapy)
Hyperkalemia (%)	10%	12%
Hypotension (%)	8%	6%
Other Adverse Effects (%)	12%	10%

Discussion:

This study shows the advantages of combined treatment including the use of RAAS inhibitors in conjunction with SGLT2 inhibitors and ERAs in comparison with only RAAS inhibitors in the management of blood pressure and kidney function in H-CKD patients. The presented Conclusions are consistent with and extend the prior literature providing useful information about the changes that occur in the approach to hypertensive kidney disease. As reaffied by this study, previous work has also pointed out the use of RAAS inhibitors as the initial regimen for treating hypertension in CKD patients. RAAS inhibition has been for years known to decrease glomerular pressure, prevent hyperfiltration and delay the progression of CKD by producing vasodilation of the renal microvasculature [11]. Nevertheless, in the Group A, we observed that a large number of patients with H-CKD did not succeed to obtain a proper blood pressure control with a monotherapy of RAAS inhibitors. Such limitations have spurred the focus on combination therapies in an effort to also improve both renal and cardiovascular end points [12]. One of the major progresses we have today is the introduction of SGLT2 inhibitors in the treatment of H-CKD. First theorized as a medication in diabetes mellitus type 2, SGLT2 inhibitors have been found to provide renal benefits independently of glycemic control. Our study in this regard recorded a rise in the eGFR of 12% and a decrease in the overall proteinuria of 20% within the combination therapy group, which preceded other such earlier results that associated the SGLT2 inhibitors with decrease in intraglomerular pressure and better renal outcome [13]. For instance, the the DAPA-CKD trial established that dapagliflozin provided substantial, clinically meaningful CKD protection coupled with reduced CVE risk, irrespective of prior diagnosis of the former as diabetes [14]. The findings in the current studies explain that SGLT2 inhibitors' renal effects go beyond glycaemia; this makes SGLT2 inhibitors a potent therapeutic tool in

CKD patients with T2D and non-CKD patients as well. Moreover, other drugs such as endothelin receptor antagonists (ERAs) have been found useful in managing proteinuria and halting or at least slowing the course of chronic kidney disease (CKD), especially in patients with resistant hypertension. Endothelin-1 as a potent vasoconstrictor is involved in vascular stiffness and renal damage. Our cross-sectional study revealed 20% reduction in proteinuria in group B, which is in concordance with the SONAR trial, that confirmed the efficacy of one of the ERA, atrasentan in reducing the proteinuria in patients with diabetic nephropathy [15]. Likewise, a meta-analysis of studies assessing the efficacy of ERAs in CKD noted that they significantly reduced proteinuria and slow down CKD progression; these and other findings underscore the benefits of ERAs in patients with hypertension-induced kidney disorder [16]. Similar comparisons with other studies also show that there are still issues of how to enhance blood pressure control among the CKD patients. In the normal treatment group of this study, the level of target BP control (<130/80 mmHg) was 40% as compared to the 65% in combination chemotherapy group. These findings are in line with SPRINT trial wherein intensification of blood pressure to target < 120 mm Hg led to decrease in cardiovascular events and mortality in patients with CKD but addition of second agent to achieve these targets was difficult [17]. This is because combination therapy as used in this study is more effective than mono therapy in achieving the target blood pressure levels and preventing end-organ damage. There is no doubt that the RAAS inhibitors occupy the central place of CKD management. Nevertheless, it is the incorporation of the new sophisticated drugs, particularly SGLT2 inhibitors and three classes of ERAs, which make this discovery as one of the giant steps forward in this area. For instance, EMPA-REG OUTCOME and CANVAS have provided achievements to reveal the cardiovascular as well as renal effects of SGLT2 inhibitors, including decreased heart failure hospitalization and retarding of CKD progression [18, 19]. We concur with this growing body of literature relating to the application of the combination therapy aimed at offering improved protection to patients with H-CKD. Lastly, the results of the present study are in parallel to other studies suggesting the advantage of combination therapy on hypertension related kidney disease. Such findings indicate a need for increasing treatment to options other than RAAS inhibitors to include SGLT2 inhibitors and ERAs for better outcomes, reduced CKD progression and better blood pressure control. It will be necessary to continue the long-term investigations of the presented advantages and their consequences for the clinical practice.

Conclusion:

Combination therapy with RAAS inhibitor with SGLT2 inhibitors and ERAs is considered more effective than conventional RAAS inhibition for managing hypertension-induced kidney diseases, according to this study. Combination therapy was effective in the improvement of blood pressure control, kidney function and reduction in proteinuria levels. These conclusions underscore the possibility to enhance the effectiveness of hypertension and CKD treatment using the modern approaches to pharmacotherapy.

Limitations:

This study had a short follow up period of six months hence could not detect some of the effects of the therapies in the long run. ALSO, the participants included only moderate CKD patients, thus, not generalizable to advanced CKD or subjects with other co morbidities.

Future Findings:

Therefore future prospective trials of long duration are necessary to evaluate the efficacy and safety of adding combination therapies in patients with CKD. More studies on the these therapies are needed in order to determine their effectiveness in decreasing cardiovascular events and in patients with late CKD stages and different ethnicities.

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Authors Contribution

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Critical Review: shahid Rizwan Safir1 ,Maaz Bacha2

Final Approval of version: All Mantion above

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