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ASSESSING THE IMPACT OF ANTIHYPERTENSIVES IN KIDNEY FUNCTION OF PATIENTS WITH DIABETIC NEPHROPATHY

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ABSTRACT

Objective: The objective of the study was to determine the impact of anti-hypertensives (ARB, ACEI, CCB, Beta Blockers and Diuretics) in kidney function (Proteinuria, Serum Creatinine, eGFR) of patients with Diabetic Nephropathy. **Methods:** A prospective observational study conducted on patients with diabetic nephropathy (DN) in tertiary care teaching hospital, kerala, south India. 107 DN patients were enrolled in the study. The baseline serum creatinine and proteinuria were assessed from laboratory data and patient's medical records. eGFR were calculated by MDRD formula. A follow up was conducted on the third month recording the levels of serum creatinine, proteinuria and eGFR. **Results:** Out of 107 patients were enrolled into the study, 46.43% prescribed with ARBs, 7.35% with ACEIs, 19.11% with CCBs, 15.44% with Beta blockers and 11.76% with Diuretics. Most prescribed drug was Telmisartan (39.41%) and ACE Inhibitors were the least prescribed due to its side effects. While comparing the baseline and follow up values of kidney function variables among the selected antihypertensive classes, a decline in proteinuria, the main indicator of DN was only seen with RAAS Inhibitors. But an improvement in other variables like serum creatinine and eGFR were noted with other class of antihypertensives. **Conclusion:** ARB showed the most beneficial impact in reducing proteinuria in type II DN patients and the study concluded that antihypertensives had a significant role in preventing the progression of Diabetic Nephropathy in which ARB are the

best drug of choice.

KEYWORDS: Diabetic nephropathy, Antihypertensives, Proteinuria.

INTRODUCTION

Diabetic nephropathy, which is the leading cause of end stage renal disease, is characterized by persistent albuminuria, elevated creatinine levels or decline in glomerular filtration rate. It also refers to a characteristic set of structural kidney abnormalities, which include hypertrophy of the kidney, increase in glomerular basement membrane thickness, nodular and diffuse glomerulosclerosis, tubular atrophy, and interstitial fibrosis.[1]

Stages of Diabetic Nephropathy

Hyperfiltration characterized by renal enlargement, intra-renal hypertension and high GFR, may be seen early in the course of diabetes.[2]

Silent Phase Very few patients develop microalbuminuria during the first 10 years of their diabetes and usually may remain undiagnosed for many years and present with an advanced disease.

Microalbuminuria The normal rate of excretion of urinary protein is upto 300mg/24hr, of which 10% is albumin. Albumin excretion rate of 20-200mcg/min, which is equivalent to a urine albumin creatinine ratio (ACR) of 10-25mg/mmol, is termed as microalbuminuria.

Overt Nephropathy Albumin excretion rates above 200mcg/ min or 300mg/day is defined as overt nephropathy.

Risk Factors for development and progression of diabetic nephropathy are Family history, Poor glycemic control[3], Racial groups, Gender, Diabetic nephropathy undergoing dialysis, Level of protienuria, smoking, Age[1] etc.

Pathophysiology

Diabetic nephropathy typically affects the micro vasculature in the glomerulus. DN includes with excessive filtration of protein into the urine. Hyperglycemia may directly results in mesangial expansion. Increased mesangial pressure and stretch can stimulate this expansion. TGF-β is important in the mediation of expansion and fibrosis. Glucose binds reversibly and eventually irreversibly to protein in the kidneys and circulation to form AGEs. AGEs form

complex cross links of hyperglycemia and can contribute to renal damage by stimulating fibrotic and growth factors via receptors for AGEs.[4]

MANAGEMENT

Specific Goals in the Prevention of Diabetic Nephropathy

- Avoidance of potential use of nephrotoxic drugs such as aminoglycoside and NSAID.[5]
- Early detection and management of diabetes, especially in setting of family history.[5]
- A strict glycemic control.[6]
- Therapy with the first line drugs in the patients with DN aims to reduce intraglomerular pressure using the inhibition of renin angiotensin system.[7]
- The rate of fall of glomerular filtration rate can be reduced from around the range 12ml/min/year to <5ml/min/year if arterial blood pressure is adequately controlled.[1]
- A full lipid profile should checked at baseline and then yearly or half yearly in patients.[8] It is recommended that a LDL target of less than 70 mg/dl to be more appropriate in patients with nephropathy.[9]
- Cutting excessive alcohol consumption, smoking, and increase in aerobic exercise is the most important lifestyle targets.
- For CKD stage 1 and 2, daily protein intake of 0.8 g/kg is mainly recommended. And in stage 3 and 4, the decline to 0.6 - 0.8 g/kg is recommended.[6]
- In type I and type II DM, patient restriction of dietary salt to less than 100mmol significantly reduces BP.[5]

MATERIALS AND METHODS

Study design

This study was designed as a prospective observational study to assess the impact of anti-hypertensives in kidney function of patients with diabetic nephropathy.

Study population

Patients aged above 40years of age with diabetic nephropathic patients who were taking antihypertensives were selected as study population. The data were collected from December 2017 to may 2018 from KMCT Medical College Hospital, Kozhikode in the out-patient department.

Patients were not eligible if they met the following exclusion criteria: age ≥40 years, patients with type 1 DM, newly diagnosed diabetic nephropathy patients, pregnant and lactating

mothers, patients with end stage kidney failure and special population.

Before entry into the study, eligible patients were informed by the investigator about the scope and conduct of the study and collect their signature of consent. The study was planned and conducted in accordance with the principles of Declaration of Helsinki.

Clinical Evaluation

The study was conducted only after getting approval from the Institutional Ethical Committee (IEC).

107 patients were enrolled in the study according to inclusion criteria. Patients were prescribed with ARBs, ACE Inhibitors, CCBs, Beta blockers and Diuretics. Proteinuria, Serum creatinine and eGFR were selected as variables of kidney function.

The baseline serum creatinine and proteinuria were assessed from laboratory data and patient's medical records. eGFR were calculated by MDRD formula. A follow up was conducted on the third month of first visit. At follow up visit, the levels of serum creatinine, proteinuria and eGFR were recorded.

Baseline and follow up values of kidney function variables were cross checked among each class of antihypertensive drugs in order to find out which antihypertensives give the best impact on kidney function.

Statistical analysis

The data entry and statistical analysis were done using software SPSS version 2.0. A 'p' value of <0.05 was considered to be statistically significant.

RESULT

Out of 107 patients were enrolled into the study, 46.43% prescribed with ARBs, 7.35% with ACEIs, 19.11% with CCBs, 15.44% with Beta blockers and 11.76% with Diuretics. Most prescribed drug was Telmisartan (39.41%) and ACE Inhibitors were the least prescribed due to its side effects.

While comparing the baseline and follow up values of the selected variables the following data were obtained.

A. Impact of Antihypertensives on Urine Protein

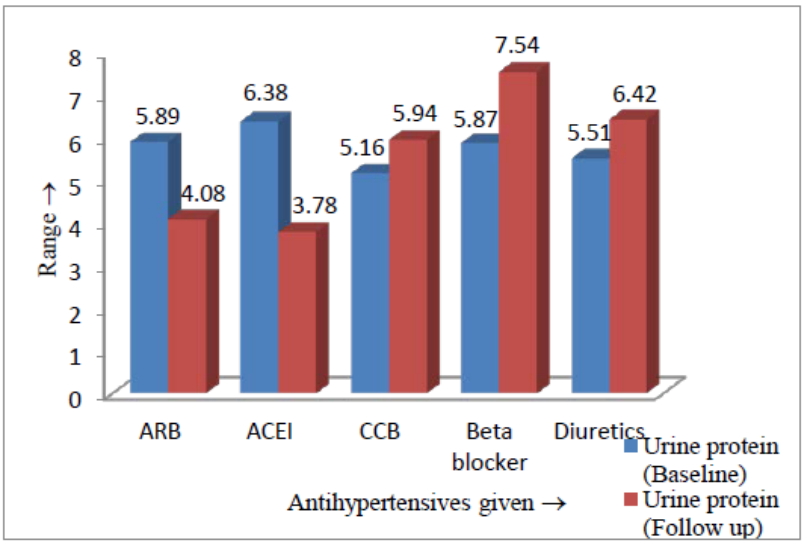

Figure No. 1: Comparison Between Baseline And Follow Up Values of Urine Protein.

Urine protein, the main indicator of Diabetic Nephropathy, was found to be decrease with the use of ARB. Other drugs don't show any effect on proteinuria. (*Fig No.1*).

It was noted that ARB reduce the risk of ESRD by reducing proteinuria since it shows a significant reduction in proteinuria which is a main indicator of diabetic nephropathy.

Considering the effect on kidney function, ACE inhibitors were better choice for reducing progression of diabetic nephropathy since it shows a notable reduction in proteinuria. (Fig. No. 1).

B. Impact of Antihypertensives on Estimated GFR (eGFR)

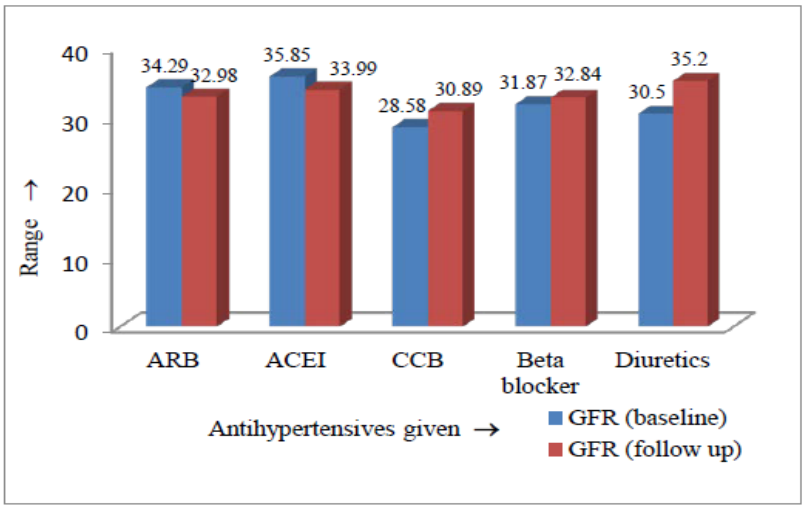

Figure No. 2: Comparison between baseline and follow up values of estimated GFR.

GFR was found to be improved in CCB, Beta blockers, and Diuretics, due to improvement in serum creatinine level. (*Fig. No.2*).

Beta blockers, CCBs and Diuretics can no longer reduce the proteinuria associated with DN patients. But they can stabilize the rising creatinine level and thus can improve the GFR.

C. Impact of Antihypertensives on Serum Creatinine

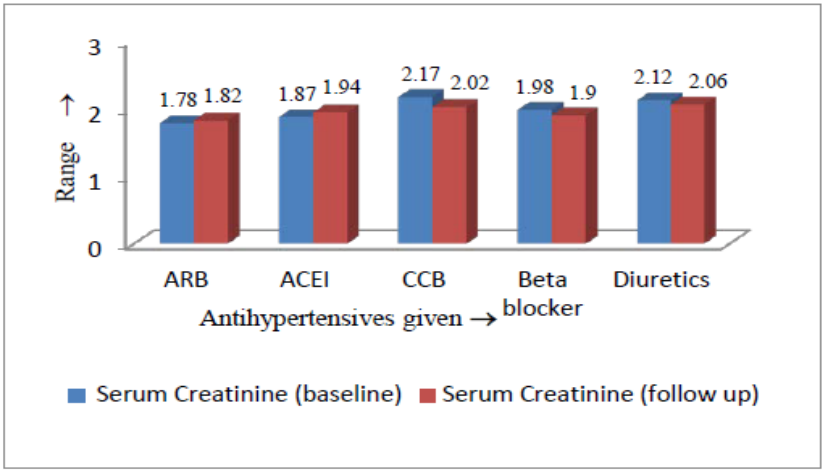

Figure No. 3: Comparison Between Baseline and Follow Up Values of Serum Creatinine.

Serum creatinine does not show much difference. But it is slightly elevated in RAAS inhibitor usage, while the other class of drugs shows betterment of values.

It was noted that ARB reduce the risk of ESRD by reducing proteinuria, but increasing the serum creatinine by 20-23%. (*Fig No.3*) These effects were independent of blood pressure lowering.

DISCUSSION

It has been demonstrated that systemic and more importantly glomerular pressure are important factors in the progression of renal failure. Proteinuria may be a reflection of intraglomerular pressure, but it may also induce renal damage on its own by causing tubulointerstitial injury. Recent studies have demonstrated that proteinuria is an important determinant of renal function deterioration, and that the lowering of proteinuria preceedes and predicts a subsequent decrease in the rate of renal function deterioration.

ARB, ACEI, CCB, Beta blockers and diuretics were the antihypertensives prescribed for DN patients in this prospective observational study. In that telmisartan (39.41%), an ARB was

identified as the most prescribed drug, its ability to decrease urine protein and reduce the decline in GFR could make it the best antihypertensive to be prescribed.

Brenner B et al (New England journal of medicine), in the RENAAL trial, 1,513 type II diabetics with nephropathy were randomly assigned to losartan or placebo, in addition to conventional antihypertensives. Losartan reduced the risk of ESRD or doubling of serum creatinine by 25%–28% compared to placebo. These effects were also independent of blood pressure lowering.[10] In this study, telmisartan accounts for the highest percentage of drug prescribed, and an enormous decline in urine protein was noticed. This was beyond the effect in creatinine and GFR.

We proposed a combined use of eGFR, serum creatinine and urinary protein for early detection of renal dysfunction. Serum creatinine, a common measurement for kidney function in routine practice, considering it to be a poor marker of kidney dysfunction. In this study, MDRD equation was adopted to compute eGFR. Another, important marker for kidney impairment is albuminuria, Albumin Creatinine Ratio (ACR). Also, there are reports on the significant correlation between ACR and eGFR.

The present results, however, suggest that it is possible to influence kidney function in diabetic nephropathy by antihypertensive treatment.

CONCLUSION

In conclusion ARB has been identified as the better antihypertensive for reducing the progression of proteinuria in DN patients. From the laboratory values, such as serum creatinine, urine protein and estimated GFR, ARB were found to be the most beneficial drug for preventing the progression of nephropathy.

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