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Original Research Article

Evaluating the antiproteinuric efficacy of cilnidipine in diabetic kidney disease

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ABSTRACT

Background: Diabetic kidney disease is a life threatening and disabling complication of uncontrolled diabetes mellitus. Clinical proteinuria is a well-established marker of renal dysfunction. A dual L/N-type calcium channel blocker cilnidipine dilates the afferent and efferent arterioles of the glomerulus decreasing the intraglomerular pressure and showing antiproteinuric effects. The present study was conducted to assess the antiproteinuric efficacy of cilnidipine in patients of diabetic kidney disease.
Methods: This interventional study was conducted on 50 patients of both genders aged 18 years and above with diabetic nephropathy (stage-2 to stage 4) visiting the medicine OPD at HIMS, Dehradun over a period of six months, the patients were given tablet cilnidipine (5-20 mg) once or twice a day. Baseline urine protein creatinine ratio (UPCR), serum creatinine and the estimated glomerular filtration rate (eGFR) was recorded at baseline and repeated after a period of 12 weeks. The end point was the decrease in UPCR after a period of 12 weeks. Students-paired T test was used for analysing the intragroup data.
Results: After 12 weeks of treatment with cilnidipine, a significant reduction was observed in the urinary protein creatine ratio (mean±SD) from 3.2±1.23 at baseline to 3.09±1.09 respectively ($p<0.05$). Along with this there was also a reduction in the in serum creatinine which was significant ($p<0.05$) as well as an increase in the eGFR value which was also statistically significant ($p<0.001$).
Conclusions: Cilnidipine reduces the UPCR as well as improves the kidney function in patients with diabetic kidney disease.

Keywords: Cilnidipine, Diabetic kidney disease, Proteinuria

INTRODUCTION

Diabetes is one of the most common and serious metabolic disorder known to be found in almost every population all over the world non-communicable diseases globally it has become a challenging health care problem of the 21st century, diabetes has become a leading cause of mortality in many developed countries and now there is considerable proof that it has become an epidemic in not only the developing but also the newly industrialised nations. Complications of diabetes have resulted in increased disability and reduced life expectancy with enormous health cost in virtually every society. Diabetes affects many organ systems and causes complications such as coronary artery disease, peripheral artery disease, stroke, retinopathy and renal failure. These patients are 17 times more prone to develop kidney disease which is the root cause of developing end stage renal disease (ESRD).[1] Morphological and ultrastructural changes in the kidney which includes molecular matrix expansion

and loss of charge carrier on the glomerular basement membrane as well as increased intraglomerular pressure leading to increased permeability to proteins characterise a patients of diabetic kidney disease.[2] Diabetic kidney disease produces clinical proteinuria i.e. excretion of protein in urine which is a well-established marker and reliably predicts renal dysfunction even before the reduction of glomerular filtration rate (GFR). Therefore, an early diagnosis, can predict the impending renal dysfunction at initial stages of organ damage. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers has showed reno protective effects in patients of diabetic kidney disease. These reduce proteinuria, delay progression, postpone renal insufficiency and improve survival. Therefore, are the first line agents for treatment. Other therapies include, conventionally used L-type calcium channel blocker (CCB) amlodipine but its reno protective effect is unsubstantial.[3] Hence a new unique dihydropyridine derivative 4th generation CCB cilnidipine having dual L/N-type calcium channel blocking property has emerged as a potential alternative to L-type blocking CCBs. Diabetic patients have increased sympathetic activity cilnidipine inhibits this activity by blocking N-type calcium channels located in the glomerulus of kidneys bringing about dilation of afferent arterioles and efferent arterioles equally, decreasing the intraglomerular pressure and showing antiproteinuric effects.[4] Hence this present study is aimed to study the antiproteinuric effects of calcium channel blocker cilnidipine in patients of diabetic kidney disease.

METHODS

This interventional study was conducted by the Department of Pharmacology in collaboration with the Department of Medicine, HIMS, Dehradun from August 2018 to August 2019 after clearance granted by institutional ethics committee. A total of 50 patients attending the medicine OPD diagnosed with diabetic nephropathy with uncontrolled proteinuria were included in the study for 12 weeks after taking prior written informed consent.

The study included patients of diabetic kidney disease who satisfied all of the following requirements: men or women more than 18 years of age; patients diagnosed with diabetic nephropathy (stage-2 to stage- 4); patients with proteinuria (>200 mg/dl); HBA1c ≥6.5%; estimated glomerular filtration rate (eGFR) 15-90 ml/min/1.73m^2; patients with serum creatinine levels ≤3 mg/dl.

The exclusion criteria included were patients above 75 years of age; hypertensive emergencies; stroke within 3 months of start of study; patients with chronic liver disease; pregnant and lactating females; history of severe side effects of CCBs or ACE inhibitors.

The patients eligible for the study were started on cilnidipine 5-20 mg/day after which a follow up at 12 weeks was done and the blood pressure, urine protein creatinine ratio (UPCR), serum creatinine was measured and antiproteinuric efficacy was assessed. The primary end point was change in the UPCR from the pre-treatment period to 12 weeks. The secondary end points included reduction in the serum creatinine, increase in the value of eGFR, indicating improvement in kidney function. In addition to this all adverse drug reactions during the study were recorded. The statistical analysis was based on standard descriptive statistical tests using the IBM SPSS version 20 software. Demographic data such as age and duration of disease is represented as mean±SD. The Intragroup comparison of systolic, diastolic blood pressure, serum creatinine, eGFR, UPCR and HBA1c was done using the paired students T-test the p value of <0.05 was considered significant.

RESULTS

The present study was done to assess the antiproteinuric efficacy of cilnidipine an L/N type calcium channel blocker in patients of diabetic kidney disease. A total of 50 patients attending the medicine OPD of Himalayan Institute of Medical sciences were included in the study. There was male preponderance with 30 males and 20 females. The age of the patients ranged from 50-75 years with a mean duration of diabetes mellitus for 18.72±4.4 years. The BMI of the patients was in the normal range 24.00±2.33 kg/m^2 and most of the subjects in the study were non-alcoholics and non-smokers (Table 1).

Table 1: Sociodemographic profile of diabetic kidney disease patients (n=50).

Sociodemographic characteristics	Subjects
Sex (male/female)	30:22
Age (years)	61.64±8.13
Weight (kg)	69.14±8.13
Height (m)	169.60±5.49
Body mass index (kg/m^2)	24.0±2.33
Duration of diabetes mellitus (years)	18.72±4.4
Smoker: non-smoker	12:38
Alcoholic: non-alcoholic	5:45

Values are expressed in frequency and Mean±SD.

There was a positive correlation observed between the duration of uncontrolled diabetes mellitus and an increase in the level of proteinuria (Figure 1).

The mean systolic pressure at baseline and at 12 weeks was 147.76±21.34 and 145.12±14.96 mmHg respectively there was a post therapy decrease of blood pressure which was recorded but this was not found to be statistically significant. There was also no significant fall observed in the diastolic blood pressure (Table 2).

During the study duration the patients included were on oral hypoglycaemic drugs but despite this the target blood

sugar levels were not achieved this persistent rise can demonstrate the reason leading to development of complications like diabetic nephropathy, which is clearly observed in the study (Table 3).

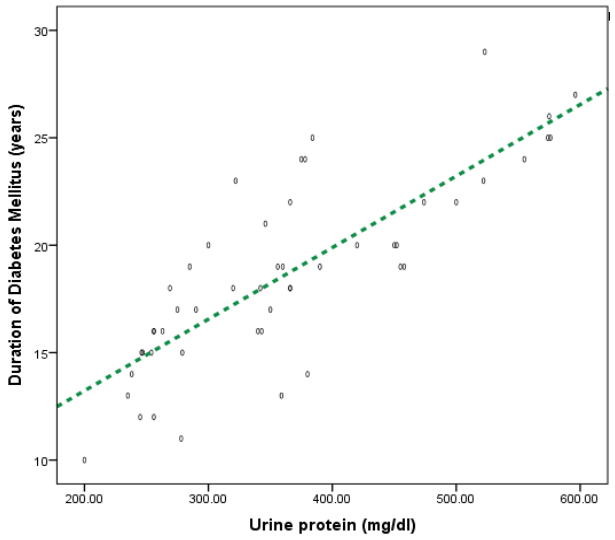

Figure 1: Correlation of proteinuria with duration of diabetes mellitus (n=50).

P<0.01.

Table 2: Clinical characteristics of diabetic kidney disease patients (n=50)

Clinical characteristics	At baseline	At 12 weeks	Mean change
Systolic blood pressure (mmHg)	147.76±21.34	145.12±14.96	2.6±6.38
Diastolic blood pressure (mmHg)	82.96±13.23	84.1±9.3	-1.1±3.9

Values are expressed in frequency and Mean±SD. Paired t-test was used for analysis *p significant is <0.05.

Table 3: Blood glucose profile of diabetic kidney disease patients (n=50).

Clinical characteristics	At Baseline	At 12 weeks	Mean change
Fasting plasma glucose (FPG) (mg/dl)	135.78±5.17	135.56±5.07	0.2±0.5
Post prandial plasma glucose (mg/dl)	173.41±9.64	173.65±10.01	-0.4±2.3
HBA1c (%)	7.7±1.57	7.66±1.47	0.04±0.4

Values are expressed in frequency and Mean±SD. Paired t-test was used for analysis *p significant is <0.05.

In the study it was also observed that there was an exceptional increase in the eGFR which was statistically significant (Table 4). A reduction in the serum creatinine level was also recorded, this reduction that was observed was highly statistically significant. In addition to this a strikingly significant reduction in urine protein and an increase in the urine creatinine levels resulting in a significantly lower value of UPCR was also observed (Table 5).

Table 4: Changes in renal functions of patients with diabetic nephropathy (n=50).

Renal functions	At Baseline	At 12 weeks	Mean change
Serum creatinine (mg/dl)*	1.39±0.23	1.37±0.25	0.16±0.21
eGFR (ml/min/1.73 m^2)*	65.73±4.88	67.48±5.51	-1.7±0.6
Serum potassium (mmol/l)*	4.67±0.63	4.62±0.63	0.05±0.21

Values are expressed in frequency and Mean±SD. Paired t-test was used for analysis *p significant is <0.05.

Table 5: Changes in protein creatinine ratio in urine of diabetic kidney disease patients (n=50).

	At Baseline	At 12 weeks	Mean change
Urine protein (mg/dl)*	369.10±92.43	365.36±79.64	7.78±6.8
Urine creatinine (mg/dl)*	118.83±24.74	123.06±24.34	-5.0±0.4
Urine protein creatinine ratio*	3.2±1.23	3.09±1.09	0.18±0.28

Values are expressed in frequency & Mean±SD. Paired t-test was used for analysis *p significant is <0.05.

Table 6: Adverse events reported during the study (n=50).

Adverse event	Number of subjects
Nausea/vomiting	3
Palpitations	0
Pedal edema	0
Urticaria	0

The adverse event that was observed during the study was nausea and vomiting. There was no complain of palpitations, pedal oedema, urticaria or angioedema that was reported (Table 6).

DISCUSSION

The following study was performed to assess the anti-proteinuric efficacy of a novel fourth-generation L/N-type calcium channel blocker cilnidipine. The mean age of the study population was 61.64±10.74 years similar to the mean age observed in another study by Hwang et al which included patients with a mean age of 61±8.5 years.[5] This might be because most of the patients enrolled in the study were diagnosed as having diabetic nephropathy developing mostly 10-15 years following the onset of

diabetes, also a number of epidemiological studies conducted in India have shown an association between increasing age and incidence of nephropathy.[6] But in comparison to these studies there are a number of other studies that have a mean age which is much lesser to our current study one such study conducted in Vatsalya hospital, Karnataka by Malleshappa had a mean age of only 44.9±13.4 years, but this can be attributed to the small sample size of the study. There was a male preponderance observed in the study this is in accordance to a number of studies like the one conducted by Malleshappa consisting of 35 males compared to only 25 females.[7] Another study by Takashi et al also consisted of 53 male and 24 female subjects.[8] The difference in the prevalence of diabetic nephropathy among males and females has a very varying picture, a number of studies have observed the effects of gender on diabetic kidney disease but unfortunately these results are always contradictory, maybe due to the sample size which is small, differences in study population or methodology. The mean duration of diabetes mellitus of the subjects enrolled in the study was 18.72±4.4 years, diabetic nephropathy is known to be a devastating microvascular complication which may begin if diabetes is poorly controlled. A gradual increase in proteinuria with an increase in duration of diabetes mellitus which was uncontrolled was observed in the following study. In the present study at enrolment the mean systolic blood pressure recorded of the patients was 147.76±21.34 mmHg and the mean diastolic blood pressure was 82.96±13.23 mmHg. After addition of cilnidipine there was a reduction of 2 mmHg in the systolic blood pressure which was not significant, the data reported in our study was similar to studies by Fukumoto et al and Malleshhappa in which there was no significant difference between the mean systolic blood pressure after treatment with cilnidipine.[7,9] Similarly, there was also no significant reduction in the diastolic blood pressure which was in accordance with the data obtained in the study by Tanaka.[10] Hence it can be inferred that the anti-proteinuric effect of cilnidipine is completely independent of its anti-hypertensive effect. In the present study the there was a reduction in the values of serum creatinine from baseline at 12 weeks, this finding observed was similar to another study done by Sarkar et al in which the suppression of serum creatinine was more in the cilnidipine group as compared to the amlodipine group.[11] There was a significant increase in the mean eGFR of the patients after treatment with cilnidipine this observation is in accordance to the study done by Hwang et al in which there was significant increase in the eGFR. This increase can be attributed to a decrease in the serum creatinine levels.[5] There was also a reduction in the mean UPCR after 12 weeks of treatment with cilnidipine this was in accordance to a number of studies one such study done by Fujita et al demonstrated a similar reduction in the UPCR levels.[12] Another study by Kojima et al also demonstrated a decline in the UPCR levels of nearly 10% after cilnidipine treatment for a period of 6 months.[13] A study by Tsuchihashi also demonstrated similar effects of reduction in UPCR.[14] The reason of this decreased UPCR levels is the property of cilnidipine being a dual L/N type calcium channel blocker dilates the efferent as well as the efferent arterioles reducing the glomerular pressure and decreasing proteinuria in diabetic nephropathy preventing its progression.[14] The major limitation of our study was a small sample size and a short duration of follow up of the patients, hence large cohorts, prospective studies and a longer follow up with more number of patients is required to validate the clinical significance of administering cilnidipine for treatment of proteinuria to help prevent the progression of diabetic nephropathy.

CONCLUSION

There is no permanent cure of diabetic nephropathy but renoprotective drugs like the ACEIs and ARBs are generally used to reduce the incidence of ESRD but in most cases proteinuria still persists in these patients. Therefore, since the last few years the processes and mechanisms resulting in diabetic nephropathy have been studied in large detail and henceforth new strategies have come up to prevent the progression of nephropathy. Cilnidipine has a unique dual property to block N/T-type calcium channels making it highly efficacious in reducing the levels of UPCR and preventing the progression of diabetic nephropathy. Cilnidipine was also found to be relatively safe without causing any serious side effects.

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