To Evaluate the Therapeutic Efficacy of Vildagliptin on Microalbuminuria in Type 2 Diabetes Mellitus

Arindam Nag[1], Partha Pratim Dey[2]

ABSTRACT

Introduction: Diabetic kidney disease (DKD) represents one of the most frequent microvascular complications of diabetes with an overall prevalence of approximately 40% in type 2 diabetes population. Microalbuminuria is one of the most serious problems in type 2 DM. Vildagliptin, DPP-4 inhibitors, is a novel oral anti-diabetic drug for the treatment of type 2 diabetes mellitus (T2DM). The objective of the study was to evaluate the therapeutic efficacy of vildagliptin on microalbuminuria in type 2 diabetes mellitus.

Material and methods: We included in our study 103 T2DM patients with microalbuminuria. Exclusion criteria: NSAIDs induced nephropathy, Lupus nephropathy, Polycystic Kidney Disease, Medullary Sponge Kidney, All causes of nephritic and nephrotic syndrome, ESRD due to diabetes mellitus and moderate to severe hepatic failure. We measured Urinary ACR value of parameters at 0,3.6,9,12 months respectively. Vildagliptin was given to those patient and was observed that after giving vildagliptin was there any change in albumin to creatinine i.e microalbuminuria.

Result: The mean of ACR baseline (mean±s.d.) of patients was 125.1436 ± 58.810 with range 50.7000 - 298.0000 and the median was 100.0000. The mean of ACR of 3, 6, 9, 12months (mean±s.d.) of patients were 110.3184 ± 57.5647, 106.7340 ± 48.8492, 103.7252 ± 45.6745, 95.4466 ± 62.342 respectively. Association of ACR in five groups was not statistically significant (p=0.6118).

Conclusion: We found that after 12 months of therapy with vildagliptin, a DPP-4 inhibitor, there was some reduction of ACR and it is approximately 30%.

Keywords: Type 2 DM, (Type 2 Diabetes Mellitus), Urinary ACR, (Urinary Albumin Creatinine Ratio). NSAIDS, (Non Steroidal Anti Inflammatory Drugs), ESRD, (End Stage Renal Disease).

INTODUCTION

Diabetes Mellitus is a burning problem now-a-days. The microvascular complications of diabetes encompass long term complications affecting small blood vessels. These classically have included retinopathy, nephropathy and neuropathy. Microalbuminiuria in *Diabetic nephropathy* is defined as the presence of persistent albuminuria ranging 30-300mg/24hours. *Overt nephropathy is* characterized by progressive decline in renal function resulting in end stage renal disease. Microalbuminuria is one of the most serious problems in Diabetes, specially in type II. Diabetic kidney disease (DKD) represents one of the most frequent microvascular complications of diabetes with an overall prevalence of approximately 40% in type 2 diabetes population. DKD is defined by the presence of albuminuria and decreased glomerular filtration rate (GFR) into 5 chronic kidney disease (CKD) stages. CKD stage 1 is characterized by normal GFR and urine findings (mostly alburninuria) or structural abnormalities of the kidney. Stages 2-5 are defined by specific values of GFR. Patients with diabetic kidney disease, even in stage 1, have a markedly increased risk of cardiovascular complications and hypoglycemia compared to patients without DKD. Numerous studies have shown that the risk of diabetic kidney disease Is tightly linked to poor glucose control in both type 1 and type 2 diabetes.

Mechanisms underlying possible nephroprotective properties of DPP-4 inhibitors include reduction of oxidative stress and inflammation and improvement of endothelial dysfunction. Effects of DPP-4 inhibitors may be both glucagon-like peptide-1 (GLP-1) dependent and independent. Ongoing prospective studies focused on the nephroprotectlve effects of DPP-4 inhibitors will further clarify its possible role in the prevention/attenuation of diabetic kidney disease beyond its glucose lowering properties.

Vildagliptin belongs to a class of drugs called DPP-4 inhibitors. DPP-4 inhibitors prevent the hormone incretin from being degraded, allowing insulin to be released from the pancreatic beta cells. While incretin remains in the blood stream, the pancreas is stimulated to produce more insulin. Meanwhile, glucagon release from the pancreas is staggered, preventing glucose level increase. In other words, linagliptin, along with diet and exercise, can help the body produce more insulin and lower blood glucose. Managing blood sugar can mean a lower HbA_{1c}, an index for glycemia control that theoretically correlates with glucose level in the blood. However, the use of HbA_{1c} to predict diabetes in patients can sometimes be limited due to other external factors, such as blood transfusion, acute blood loss, or drug interference. Objective of the study was to evaluate the therapeutic efficacy of vildagliptin on microalbuminuria in type 2 diabetes mellitus.

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MATERIAL AND METHODS

The present study was conducted in 103 consecutive Type 2 Diabetes mellitus Patients, who attended Out Patient Department or were admitted in the department of Internal Medicine at R.G.Kar Medical College, Kolkata, West Bengal for the period of 1 year from 1st April 2017, to 31st October 2018. The present study was a clinical observational study.

Inclusion Criteria: 1)Patient with microalbuminuria in type 2 diadetes mellitus

Exclusion criteria: 1) Not willing to participate in study 2) NSAIDs induced nephropathy 3).Lupus nephropathy 4) Polycystic Kidney Disease 5)Medullary Sponge Kidney 6) All causes of nephritic and nephrotic syndrome 7)ESRD due to diabetes mellitus 8)Moderate to severe hepatic failure.

A detailed clinical history were taken from all patients with emphasis on symptoms of diabetes, duration of disease. Informed consent taken from the eligible patients before doing thorough physical examination.

Urinary ACR or albumin to creatinine ratio will be the indicator to detect microalbuminuria.The patients those will be chosen will have microalbuminuria with T2DM. Vildagliptin will be given to those patient and it will be observed that after giving vildagliptin is there any change in albumin to creatinine i.e microalbuminuria and if any then how much.

All patients were subjected to the following investigation at the time inclusion into the study complete haemogram, Blood Urea, Serum Creatinine, Serum sodium, Serum Potassium, Serum Glucose(fasting and post prandial), Complete lipid profile, Liver Function Test, USG Whole abdomen. We measure all value of parameters at 0,3.6,9,12 months respectively.

The study required non-invasive investigations to be conducted on the outpatients and indoor patients. Hence, an ethical clearance has been tamed from the institution, R.G. Kar Medical College and Hospital, Kolkata.

STATISTICAL ANALYSIS

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. One-way analysis of variance (one-way ANOVA) was a technique used to compare means of three or more samples for numerical data (using the F distribution). A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

RESULTS

5(4.9%) patients had ≤40Yrs of age group, 14(13.6%) patients had 41-50 yrs of age group, 60(58.3%) patients had 51-60 yrs of age group and 24(23.3%) patients had 61-70 yrs of age group.

The mean of age (mean±s.d.) of patients was 55.1165 ± 7.6905 yrs with range 35.0000 - 68.0000 yrs and the median was 56.0000 yrs.

37(35.9%) patients had female and 66(64.1) patients had male.

The mean of urea baseline (mean±s.d.) of patients was 46.6505 ± 18.4814 mg/dl with range 21.0000 - 80.0000 mg/

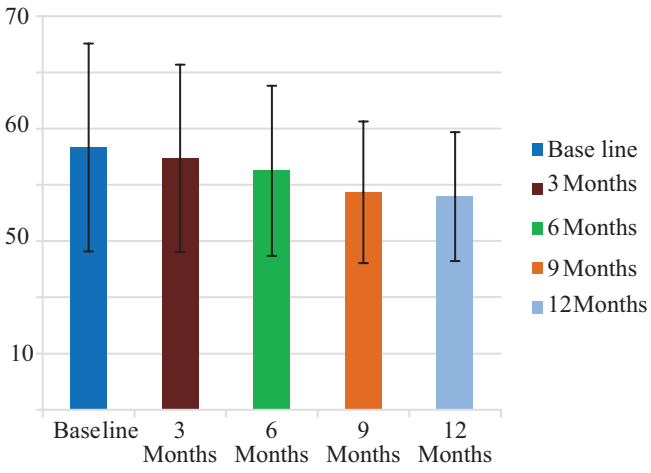

Figure-1: Distribution of Mean Urea in Five Group(Mean± S.D)

		Number	Mean	SD	Minimum	Maximum	Median	p-value
FPG	Base line	103	201.5728	25.6556	178.0000	323.0000	195.0000	<0.0001
	3 Months	103	184.4078	15.2922	160.0000	246.0000	180.0000	
	6 Months	103	173.9806	16.7636	145.0000	231.0000	175.0000	
	9 Months	103	147.7670	18.5262	96.0000	186.0000	148.0000	
	12 Months	103	146.3495	16.3609	104.0000	180.0000	147.0000	

Table-1: Distribution of Mean FPG in Five Groups

		Number	Mean	SD	Minimum	Maximum	Median	p-value
PPPG	Base line	103	281.9806	37.0021	206.0000	391.0000	280.0000	<0.0001
	3 Months	103	267.3010	35.7101	202.0000	345.0000	266.0000	
	6 Months	103	248.0777	30.9812	198.0000	329.0000	249.0000	
	9 Months	103	205.4854	29.4808	114.0000	260.0000	199.0000	
	12 Months	103	195.7476	24.8173	146.0000	254.0000	197.0000	

Table-2: Distribution of Mean PPPG in Five Groups

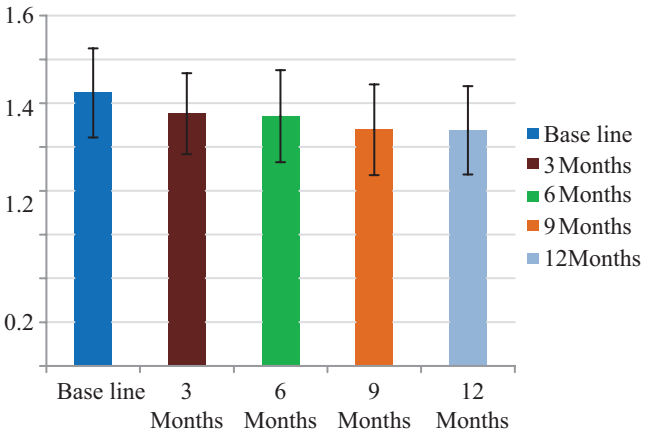

Figure-2: Distribution of Mean Creatinine in Five Groups (Mean±S.D)

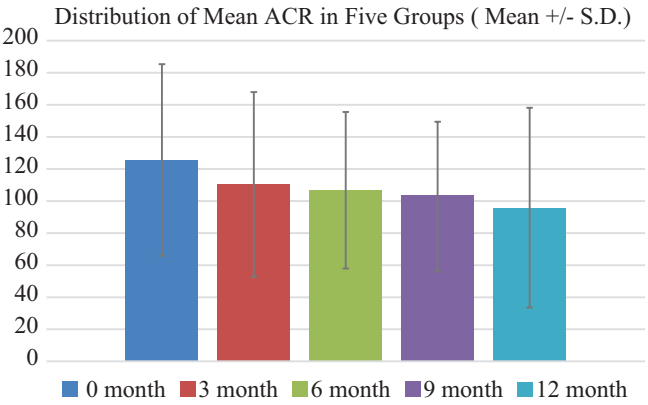

Figure-3: Distribution of Mean ACR in Five Groups (Mean±S.D)

dl and the median was 49.0000 mg/dl. The mean of urea 3 months (mean±s.d.) of patients was 44.7379 ± 16.6451 mg/dl with range 21.0000 – 77.0000 mg/dl and the median was 43.0000 mg/dl. The mean of urea 6 months (mean±s.d.) of patients was 42.4951 ± 15.1294 mg/dl with range 21.0000 - 78.0000 mg/dl and the median was 40.0000 mg/dl. The mean of urea 9 months (mean±s.d.) of patients was 38.6796 ± 12.6097 mg/dl with range 19.0000 - 68.0000 mg/dl and the median was 38.0000 mg/dl. The mean of urea 12 months (mean±s.d.) of patients was 37.9126 ± 11.4567 mg/dl with range 21.0000 - 70.0000 mg/dl and the median was 40.0000 mg/dl. Association of urea in five groups was statistically significant (p=<0.0001) (Figure 1).

The mean of creatinine baseline (mean±s.d.) of patients was 1.2464 ±.2036 mg/dl with range 0.7800 - 1.8000 mg/dl and the median was 1.2000 mg/dl. The mean of creatinine 3 months (mean±s.d.) of patients was 1.1515 ±.1849 mg/dl with range 0.7600 – 1.6000 mg/dl and the median was 1.1000 mg/dl. The mean of creatinine 6 months (mean±s.d.) of patients was 1.1400 ±.2102 mg/dl with range 0.7600 - 1.7000 mg/dl and the median was 1.1000 mg/dl. The mean of creatinine 9 months (mean±s.d.) of patients was 1.0779 ±.2074 mg/dl with range 0.7600 - 1.7000 mg/dl and the median was 1.0000 mg/dl. The mean of creatinine 12 months (mean±s.d.) of patients was 1.0756 ±.2017 mg/dl with range 0.7800 - 1.7000 mg/dl and the median was 1.0000 mg/dl. Association of creatinine in five groups was statistically significant (p=<0.0001) (Figure 2).

The mean of FPG baseline (mean±s.d.) of patients was 201.5728 ± 25.6556 mg/dL with range 178.0000 - 323.0000 mg/dL and the median was 195.0000 mg/dL. The mean of FPG 3 months (mean±s.d.) of patients was 184.4078 ± 15.2922 mg/dL with range 160.0000 – 246.0000 mg/dL and the median was 180.0000 mg/dL. The mean of FPG 6 months (mean±s.d.) of patients was 173.9806 ± 16.7636 mg/dL with range 145.0000 - 231.0000 mg/dL and the median was 175.0000 mg/dL. The mean of FPG 9 months (mean±s.d.) of patients was 147.7670 ± 18.5262 mg/dL with range 96.0000 - 186.0000 mg/dL and the median was 148.0000 mg/dL. The mean of FPG 12 months (mean±s.d.) of patients was 146.3495 ± 16.3609 mg/dL with range 104.0000 - 180.0000 mg/dL and the median was 147.0000 mg/dL. Association of FPG in five groups was statistically significant (p=<0.0001) (Table 1).

The mean of PPPG baseline (mean±s.d.) of patients was 281.9806 ± 37.0021 mg/dL with range 206.0000 - 391.0000 mg/dL and the median was 280.0000 mg/dL. The mean of PPPG 3 months (mean±s.d.) of patients was 267.3010 ± 35.7101 mg/dL with range 202.0000 – 345.0000 mg/dL and the median was 266.0000 mg/dL. The mean of PPPG 6 months (mean±s.d.) of patients was 248.0777 ± 30.9812 mg/dL with range 198.0000 - 329.0000 mg/dL and the median was 249.0000 mg/dL. The mean of PPPG 9 months (mean±s.d.) of patients was 205.4854 ± 29.4808 mg/dL with range 114.0000 - 260.0000 mg/dL and the median was 199.0000 mg/dL. The mean of PPPG 12 months (mean±s.d.) of patients was 195.7476 ± 24.8173 mg/dL with range 146.0000 - 254.0000 mg/dL and the median was 197.0000 mg/dL. Association of PPPG in five groups was statistically significant (p=<0.0001). Table 2

The mean of ACR baseline (mean±s.d.) of patients was 125.2436 ± 58.810 with range 50.7000 - 298.0000 and the median was 100.0000. The mean of ACR 3 months (mean±s.d.) of patients was 110.3184 ± 57.5647 with range 38.7000 – 265.0000 and the median was 86.0000. The mean of ACR 6 months (mean±s.d.) of patients was 106.7340 ± 48.8492 with range 37.0000 - 231.0000 and the median was 92.0000. The mean of ACR 9 months (mean±s.d.) of patients was 103.7252 ± 45.6745 with range 21.5000 - 209.0000 and the median was 102.0000. The mean of ACR 12 months (mean±s.d.) of patients was 95.4460. ± 62.342 with range 10.0000 - 260.0000 and the median was 70.0000. Association of ACR in five groups was not statistically significant (p=0.6118). Figure 3

DISCUSSION

The cause of albuminuria is functional and mechanical impairment of the basement membrane of the glomerular capillary wall. Microalbuminuria is a manifestation of impaired endothelial function.[1] The causes of the impairment are hypertension, hyperglycemia, and dyslipidemia, or various types of oxidative stress and an increase in the inflammatory reaction, and a variety of factors are involved in a complex manner.[2] Klausen et al.[3] demonstrated that the

risk of CVD in the general population began to increase at urinary albumin excretion levels even below the defined threshold for microalbuminuria Blood pressure decreases as a result of increased natriuresis in response to administration of GLP-1, suggesting that it may decrease albuminuria[4], but according to the results of the present study, vildagliptin administration had no effect on blood pressure. Since the kidney is a site of strong expression of DPP-4, strong control of the hormones, cytokines, and inflammation that are the substrates of DPP-4 may be involved in reducing It has been reported that hypertriglyceridemia causes progression of diabetic nephropathy, and that improvement of TG metabolism reduces albuminuria.[5] In other words, a decrease in sd-LDL proportion as a result of a decrease in sd-LDL in response to an improvement in TG metabolism may be linked to decreasing urinary albumin. Similarly, Hirano et al.[6] have reported that increases in sd-LDL contribute to aggravating diabetic nephropathy, and reducing sd-LDL may contribute to decreasing albuminuria. Moreover, the decrease in albuminuria may have occurred as a result of an improvement in the dysfunction of the vascular endothelium as a result of the improvement in LDL heterogeneity[7]

Dimitris Xidakis, et al[8] showed in there study that treatment with vildagliptine had no significant influence on the eGFR or on the body weight but hemoglobin A1c (HbA1c) levels were significantly reduced (7.8 ±1.1% vs 6.8 ±0.9%, $p<0.05$). There was a significant reduction of 46.4% in ACR but only in the DN2 patients (microalbuminuria). Albuminuria in DN3 patients was also reduced but did not reach statistical significance over the period of 12 months. No severe side-effects of vildagliptin were reported in these patients. Another study showed that vildagliptin could counteract kidney injury in terms of albuminuria, creatinine clearance and histological findings in streptozotocin (STZ)-induced diabetic rats (Liu *et al*. 2012[9]). The authors suggested that the activation of GLP-1 receptor, modulation of cAMP, decreased oxidative stress and downregulation of TGFB1 might be involved in the reno-protective pathways of vildagliptin. Moreover, Kodera and coworkers (Kodera *et al*. 2014[10]) reported that DPP-4 inhibition using PKF275-055 improved kidney parameters in STZ-induced diabetic rats through inhibition of inflammatory events as macrophage infiltration and suppression of nuclear factor-κB.

CONCLUSION

In our study we had an effort to observe the chance in urinary albumin to creatinine ratio (ACR) with giving vildagliptin which is thought to be a predictor of renal impairment assessment in diabetes. We found that after 12 month of therapy with vildagliptin, a DPP-4 inhibitor, there was some reduction of ACR and it is approximately 30%.

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