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Jour of Diab and Endo Assoc of Nepal 2020; 4 (1): (21-28)
ISSN Print 2594-3367 ISSN Online 2631-2107

Journal of Diabetes and Endocrinology Association of Nepal

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Study of metformin in diabetes mellitus with stage 3 and 4 chronic kidney disease

Peeyush D[1], Lamsal M[2], Maskey R[3], Sharma SK[3]
[1]Associate Professor, Department of Gastroeneterlogy and Hepatology, BPKIHS, [2]Professor and Head, Department of Biochemistry, BPKIHS, [3]Additional Professor, [4] Professor and Head, Department of Internal Medicine, BPKIHS.

Abstract

Background: Chronic Kidney Disease is one of the major complications of Diabetic patients. Cardiovascular mortality increases in patient with diabetes and more so with diabetic CKD. Clinician treating diabetic CKD finds option limited as metformin is considered contraindicated when serum creatinine is greater than 1.5 mg/dl in males and greater than 1.4 mg/dl in females. The primary aim of the study is to evaluate the efficacy of metformin in terms of glycemic control in patient with diabetic stage 3 and 4 CKD. **Methods:** This is Randomised open labelled clinical trial done in the Department of Internal Medicine, B. P. Koirala Institute of Health Sciences, Dharan, Nepal . Primary end point were glycemic status at 6 months as defined by with fasting, post prandial blood sugar, glycosylated hemoglobin in comparison to baseline. **Results:** Altogether 73 diabetic patients with diabetic CKD stage 3 and 4 were included in the study.41 patients were included in insulin group and 32 patients in metformin group. In metformin group, the fasting and past prandial blood sugar declined progressively compared to insulin group, where fasting and post prandial blood sugar declined more rapidly. **Conclusions:** Metformin is found to be efficacious in diabetic CKD as it had already proved to be effective in diabetes without CKD. In this study metformin was not associated with lactic acidosis and the level of lactate with metformin treatment was similar to that of treatment with insulin. The vast majority of case reports relating metformin to lactic acidosis report at least one other disease/illness that could result in lactic acidosis. Despite increasing disregard of contraindications to metformin by physicians, the incidence of lactic acidosis has not increased,as does the result of this study. So metformin may be safe even in patients with diabetic CKD stage 3 and 4.

Key Words: Chronic Kidney Disease, Diabetes, Metformin

Introduction

Diabetes mellitus, a state of chronic hyperglycemia, is a common disease with prevalence estimates of 171 million people worldwide.[1] Chronic kidney disease is a common condition that affects more than 50 million people worldwide[2] and can be found in up to 23% of patients with diabetes[3]. Cardiovascular mortality increases in patient with diabetes and more so with diabetic CKD.[4]

Metformin is one of the best available oral hypoglycemic agent which being a cheap and has minimal hypoglycemic incidence. However, clinician treating diabetic CKD finds option limited as metformin is considered contraindicated when serum creatinine is greater than 1.5 mg/dl in males and greater than 1.4 mg/dl in females.[5] Therefore there are limited options for treating diabetic CKD. Current armentorium for treating type 2 diabetes in CKD Stage 3 and 4 are Insulin, Sulphonylureas, Pioglitazones, acarbose etc. However, all these drugs, specially the oral hypoglcemic agents (OHA) have its own limitations in the use in CKD patients. In regards to metformin, there is no evidence till date to support or not to use Metformin in Stage 3

Corresponding author:
Dr Denis Peeyush, Associate Professor, , Department of Gastroeneterlogy and Hepatology, BPKIHS

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and 4 CKD as the topic is never studied creating doubt what to recommend.

In absence of evidence against use of metformin in CKD 3-4 due to lack of clinical trial ever been conducted in this group of population, we conducted a randomised open labelled clinical study in on use of metformin in diabetic patients with Chronic Kidney Disease stage 3 and 4. The primary aim of the study is to evaluate the efficacy of metformin in terms of glycemic control in patient with diabetic stage 3 and 4 CKD

Materials and Methods:

This is Randomised open labelled clinical trial done in the Department of Internal Medicine, B. P. Koirala Institute of Health Sciences, Dharan, Nepal . This research was approved and ethical clearance was obtained from Institutional Ethical Review Board, B. P. Koirala Institute of Health Sciences. The inclusion criteria was Diabetic CKD Stage 3 and 4 i.e eGFR ≤ 60 ml/min/1.73m2 and >15ml/min/1.73m2 BSA and who gave Informed written consent. The exclusion criteria were Diabetic CKD with eGFR <15ml/min/m2 (CKD stage 5) , Non diabetic CKD, Inability to provide consent, Lactic acidosis at the time of presentation, Pregnancy and HbA1c>9% . Primary end point were glycemic status at 6 months as defined by with fasting, post prandial blood sugar, glycosylated hemoglobin in comparison to baseline.

Among 379 diabetic patients screened, 73 patients were included in this study. Out of 303 patient excluded, 161 patients had chronic kidney disease other than stage 3 and 4, 66 patients had evidence of infection, 22 patients did not gave consent, 22 patients had HbA1C greater than 9, 20 patients had chronic liver disease, 13 had chronic obstructive pulmonary disease and 2 patients had evidence of malignancy.

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3 patients included in this study were randomised into insulin group and metformin group with or without sulfonylureas based on computer generated six table of random numbers. After randomisation, patients entered into washout phase during which all the anti- diabetic medications were withheld and were started with either insulin or metformin depending on the group the patient belongs to.

Metformin was started with 1000 mg per day and subsequently increased by 500 mg per week to maintain fasting blood sugar below 140 mg per dl and post prandial blood sugar below 180 mg per dl. Patients were followed up at 1 week, 2 weeks, 1 month and then monthly for 6 months. During each follow up patient were inquired about the side effect of the drugs like episodes of hypoglycemia, anorexia, nausea, vomiting, adominal pain, shortness of breath etc. Vital signs were checked and systemic examination performed along with arterial blood gas analysis done on same setting and other investigations like fasting and post prandial blood sugar sent on each visit, serum creatinine at 1 month, 3 month and 6 month and HbA1C on 3 month and 6 month. When glycemic control was not achieved with highest dose of metformin that is 2500 mg per day then Glimepiride or Repaglinide was added and in insulin group, the dose of insulin was increased.

Data was analyzed using Statistical Package for the Social Science (SPSS) 11.5 version. For descriptive analysis mean and standard deviation were used and percentage was used for numerical data. For analytical statistics mean was compared between the two groups and chi square test was used for categorical data to find out significant difference between the groups at the level of 95 % confidence interval, the level of significance was set at 5 % i.e $P<0.05$.

Results

Altogether 73 diabetic patients with diabetic CKD stage 3 and 4 were included in the study.41 patients were included in insulin group and 32 patients in metformin group. All except one in metformin group did not completed the study.

Jour of Diab and Endo Assoc of Nepal 2019; 3 (2): (25-31)
ISSN Print 2594-3367 ISSN Online 2631-2107
Journal of Diabetes and Endocrinology Association of Nepal
ORIGINAL ARTICLE OPEN ACCESS

Table 1. Baseline characteristics of study subjects.

	Insulin group (N=41)	Metformin group (N=32)	p value
Age in years (mean ± SD)	59.85 ± 7.09	61.59 ± 8.67	0.349
Male sex- no (%)	24 (58.53)	18 (56.25)	
Smoker-current/former (%)	9/5 (22/12)	2/12 (6/37)	
Duration of diagnosis of diabetes mellitus(mean±SD)	9.39 ± 4.96	7.56 ± 4.83	0.118
Blood Pressure (mean±SD) Systolic Diastolic	135.85 ± 17.03 81.46 ± 10.14	136.25 ± 17.55 80 ± 8.8	0.923 0.519
Glycosylated hemoglobin (mean±SD)	7.895 ± 0.479	7.853 ± 0.296	0.665
Fasting blood sugar (mean±SD)	198.41 ± 3.77E+01	204.03 ± 2.67E+01	0.477
Post prandial blood sugar (mean±SD)	302.29 ± 47.4	311.16 ± 39.52	0.397
Urea (mean±SD)	49.71 ± 7.64	46.38 ± 7.17	0.062
Creatinine (mean±SD)	1.766 ± 0.261	1.678 ± 0.172	0.105
eGFR (mean±SD)	38.34 ± 8.47	39.16 ± 7.24	0.628
Arterial blood gas (mean±SD) pH Lactate	7.39 ± 1.76E-02 1.073 ± 0.257	7.3869 ± 1.62E-02 1.075 ± 0.242	0.438 0.975

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Table 2: Comparision of fasting, post prandial blood sugar and glycosylated hemoglobin between insulin and metformin group at baseline, 3 months and 6 months.

		Insulin group	Metformin group	p value
At baseline	Fasting blood sugar	198.41± 3.77E+01	204.03± 2.67E+01	0.477
	Post prandial blood sugar	302.29 ± 47.4	311.16 ± 39.52	0.397
	HbA1c	7.895 ± 0.479	7.853 ± 0.296	0.665
At 3 month	Fasting blood sugar	137.46 ± 5.92	150.56 ± 11.89	0
	Post prandial blood sugar	175.07 ± 10.4	208.69 ± 23.93	0
	HbA1c	7.11±0.4	7.33±0.28	0.01
At 6 month	Fasting blood sugar	135.49 ± 7.75	135.68 ± 5.26	0.907
	Post prandial blood sugar	170.93 ± 9.46	177.42 ± 13.15	0.017
	HbA1c	6.493 ± 0.306	6.7 ± 0.265	0.004

Values are expressed as mean ± SD

As shown in fig 3 and 4, in metformin group, the fasting and past prandial blood sugar declined progressively compared to insulin group, where fasting and post prandial blood sugar declined more rapidly. Similar observations was made from fig 5, comparing decline in glycosylated hemoglobin at 3 month and 6 month between insulin group and metformin group with or without sulfonylureas.

Table 3: Comparision of Arterial blood gas between insulin and metformin group at baseline, 3 month and 6 month.

		Insulin group	Metformin group	p value
Baseline	pH	7.39 ± 1.76E-02	7.3869 ± 1.62E-02	0.438
	Lactate	1.073 ± 0.257	1.075 ± 0.242	0.975
3 month	pH	7.3893 ± 9.05E-03	7.3835 ± 1.23E-02	0.026
	Lactate	1.01 ± 0.21	1.02 ± 0.22	0.764
6 month	pH	7.3927 ± 1.10E-02	7.3926 ± 1.06E-02	0.968
	Lactate	1.044 ± 0.229	1.039 ± 0.204	0.921

Values are expressed as mean ± SD

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Table 4: Comparision of creatinine and eGFR between insulin and metformin group at baseline, 3 month and 6 month.

		Insulin group	Metformin group	p value
Baseline	Creatinine	1.766 ± 0.261	1.678 ± 0.172	0.105
	eGFR	38.46 ± 7.909	39.91 ± 7.359	0.700
3 month	Creatinine	1.76 ± 0.22	1.67 ± 0.16	0.056
	eGFR	38.34 ± 7.608	39.74 ± 7.174	0.999
6 month	Creatinine	1.768 ± 0.276	1.687 ± 0.175	0.156
	eGFR	38.49 ± 8.438	39.48 ± 7.275	0.926

Values are expressed as mean ± SD

Discussion:

Chronic kidney disease is common accounting for upto 23% of the patients with diabetes. There are very limited options for treating this group of population and treating these patients in developing countries and remote areas is very difficult. Patients and physicians treating them, both found themselves helpless with the expensive medications, lack of storage system, unavailability of medications.

Despite a lack of evidence derived from the clinical trial, metformin is currently contraindicated in diabetes when serum creatinine is >1.5 mg/dl in males and >1.4 mg/dl in females because of fear of lactic acidosis.

The clinical practice turns the other way. Several reports found that physicians have ignored contraindications to prescribing metformin and yet the incidence of lactic acidosis has remained low. Holstein et al.6 had reported 73% of the studied patients had at least one contraindication to metformin treatment with most common contraindication being impaired serum creatinine clearance of 38.5±13.4 ml per min, accounting for 19% of the studied population. Similar practice was observed with other studies done by Calabrese et al.7 where contraindication to metformin therapy was found in 27% of the total studied (n=263) with most common contraindication being deranged renal function accounting for 12% of the population. The study conducted by Emslie Smith et al.8 also showed that 19% of the studied patients (n=1847) had renal dysfunction as a contraindication to metformin use.

Follow up study of UKPDS studied patients showed significant reduction in risk of myocardial infarction with metformin by 39% and 36% reduction in diabetes death compared with originally conventional treated arm.9 Hypoglycemia is significantly less with metformin and CKD patients are more prone for hypoglycemia. This beneficial effect outweighs the hypothetical risk for lactic acidosis.

As the recommendations and clinical practice are seen in different directions with additional beneficial effects proven with metformin, raises question regarding whether serum creatinine threshold is appropriate or not. This study was thus conducted to evaluate the efficacy of metformin in terms of glycemic control in diabetic CKD stage 3 and 4 and to look for the incidence of lactic acidosis, hypoglycemia and change in renal function. These factors were compared with insulin.

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This study was a randomised open labelled clinical trial. Seventy three patients were enrolled in the study and randomised into insulin group and metformin group. Forty one patients fall in insulin group and thirty two patients in metformin group out of which one patient lost to follow up as he had to leave the station. The dose of insulin was gradually increased for glycemic control in insulin group and in metformin group the dose of metformin was gradually increased over the period of weeks, then months to the maximum dose of 2550 mg per day. If glycemic control was not achieved with maximum tolerated dose of metformin then glimepiride or repaglinide was added for glycemic control.

The mean age of subjects in insulin group was 59.85 years and in metformin group was 61.59 years. Although patients were older in metformin group it had no statistical significance (p=0.349). Tiwari et al10 reported that in type 2 diabetes there is excess risk of nephropathy in males. In this study also males dominated in both the study groups being 58.53 % in insulin group and 56.25 % in metformin group.

Chronic kidney disease is found in 23% of patients with diabetes. Progression to macroalbuminuria or overt nephropathy occurs in 20 to 40 percent of patients over a period of 15 to 20 years after the onset of diabetes.11 In our study average duration of diagnosis of diabetes mellitus and progression to CKD stage 3 and 4 was 9.39 years in insulin group and 7.56 years in metformin group. This might be explained by the fact that the lack of adequate medical facility and ignorance of the patients towards health and disease in our country.

Smoking is an independent risk factor for the development of nephropathy in patients with type 2 diabetes and is associated with accelerated loss of renal function. Smoking cessation alone may reduce the risk of disease progression by 30 percent.12 In this study out of 73 patients 15.06 percent were current smokers. Smokers were higher in insulin group comprising 9 patients and 2 in metformin group. 5 patients were former smokers in insulin group and 12 were former smokers in metformin group.

In this study the efficacy of metformin was evaluated by measurement of fasting blood sugar, post prandial blood sugar and glycosylated hemoglobin level.

Out of 32 patients in metformin group, 5 patients achieved glycemic control at dose of 2000 mg per day when patients were followed up at 1 month. After 1 month, when maximum dose of metformin was needed in 27 patients out of 32, among whom 4 patients had achieved glycemic control with metformin alone and in remaining patients glimepiride was added to all except one who was given repaglinide.After 1 month of treatment, the fasting and post prandial blood sugar had decreased by 43.50 mg per deciliter and 76.38 mg per deciliter respectively from the baseline. Glycosylated hemoglobin decreased by 0.523 percent at 3 month and 1.15 percent at 6 month of the study. Similar to our study,in the study done by Lalor et al.13 the reduction of fasting blood glucose by metformin was found to be 51.20 mg per deciliter at 3 months. The earlier study done by Nathan DM et al.7 showed that metformin decreases the glycosylated hemoglobin by 1.5 percent which is 0.35 percent higher than our study. Insulin decreased the glycosylated hemoglobin by 1.402 percent. The decrease in glycosylated hemoglobin was 0.252 percent higher in insulin group comparing with metformin group with or without sulfonylureas which was significant (p 0.004). The efficacy of metformin in terms of glycemic control had been studied by Alan et al.14 which had shown that metformin lowered the fasting blood glucose in a dose related manner. The metformin dose ranged from 500 mg per day to 2000 mg per day and duration of study was for 14 weeks. The reduction in fasting blood sugar ranged from 24 to 88 mg per deciliter at dosages of 500 to 2000 mg per day respectively. In our study also dose related effect of metformin was found. When metformin was given at 1000 mg per day for 1 week, fasting blood glucose reduced by 17.19 mg per deciliter, with 2000 mg per day fasting blood

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glucose was reduced by 43.50 mg per deciliter from the baseline and when maximum dose of metformin was given i.e; 2550 mg per day fasting blood glucose reduced by 46.56 mg per deciliter from the baseline.HbA1c was also monitored for efficacy analysis by Alan et al14 and when compared with placebo the adjusted mean difference between the metformin and placebo group was 0.6 percent at 500 mg per day to 2 percent at doses of 2000 mg per day.

As CKD patients are more prone for hypoglycemia this dose related effect of metformin is useful therapeutic option to titrate drug therapy to achieve target glucose concentration.

This study was also vigilant on the incidence of lactic acidosis. There was no evidence of lactate accumulation in metformin group. The mean lactate level was 1.073 mmol per liter in insulin group and 1.075 mmol per liter in metformin group at baseline. After 6 months of follow up mean lactate level was 1.044 mmol per liter in insulin group and 1.039 mmol per liter in metformin group. There was no evidence of lactic acidosis. The large systemic review and metaanalysis conducted by Shelley R Salpeter et al.15 which included 206 comparative trials and cohort studies had compared lactate level in metformin treated and non metformin treated group. Six of the trials had reported on plasma lactate level in patients with renal dysfunction. The mean lactate level in metformin treated group 1.24 mmol per liter and 1.13 mmol per liter in non metformin treated group. This metaanalysis included 46 percent of studies with renal dysfunction. No cases of lactic acidosis were reported and upper limit incidences for lactic acidosis were 6.3 cases per 100,000 patient years for metformin and 7.8 cases per 100,000 patient years in patients not treated with metformin. The lactate level between the metformin and non metformin group in patients with renal dysfunction was also compared in the study done by Rachmani R et al.16 During two years of study lactate level was 1.61 mml per liter in metformin treated group and 1.63 mmol per liter in non metformin treated group. There was no reported cases of lactic acidosis in this study. Surprisingly, in our study lactate level was decreased in both insulin group and metformin group (0.028 mg per deciliter in insulin group and 0.036 mg per deciliter in metformin group). The decrease in lactate level in both groups explains that diabetes mellitus itself can cause lactic acidosis and plasma lactate levels is not infuenced by metformin. During the close monitoring for six months adverse effects such as intolerance to metformin with nausea, vomiting, diarrhea, lactic acidosis, hypoglycemia or change in renal function were not encountered in either of the two groups.

The strength if this clinical trial is similarities in the baseline characteristics of the patients and exclusion of the confounding factors that can cause lactic acidosis. As the study is randomised the selection bias is avoided. Being the open labelled trial we can't strictly control the patient's adherence and if the patient had received alternative drug over the counter. We tried to avoid this by checking the drugs the patients have been taking but if the plasma metformin levels could have been monitored this limitation could have been eliminated.

Conclusions:

Metformin is found to be efficacious in diabetic CKD as it had already proved to be effective in diabetes without CKD.

In this study metformin was not associated with lactic acidosis and the level of lactate with metformin treatment was similar to that of treatment with insulin.

The vast majority of case reports relating metformin to lactic acidosis report at least one other disease/ illness that could result in lactic acidosis.

Despite increasing disregard of contraindications to metformin by physicians, the incidence of lactic acidosis has not increased,as does the result of this study. So metformin may be safe even in patients with diabetic CKD stage 3 and 4.

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Further larger and longer period studies are needed to assess the risk of lactic acidosis in patients with type 2 diabetes and CKD.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053, 2004
2. Dirks JH, de Zeeuw D, Agarwal SK, Atkins RC, Correa-Rotter R, D'Amico G, Bennett PH, El Nahas M, Valdes RH, Kaseje D, Katz IJ, Naicker S, Rodriguez-Iturbe B, Schieppati A, Shaheen F, Sitthi- Amorn C, Solez K, Viberti G, Remuzzi G, Weening JJ: Prevention of chronic kidney and vascular disease: toward global health equity: the Bellagio 2004 Declaration. Kidney Int 98 (Suppl.): S1– S6, 2005
3. Middleton RJ, Foley RN, Hegarty J, Cheung CM, McElduff P, Gibson JM, Kalra PA, O'Donoghue DJ, New JP: The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol Dial Transplant 21:88–92, 20068
4. Valmadrid CT, Klein R, Moss SE, Klein BE: The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older- onset diabetes mellitus. Arch Intern Med 160:1093–1100, 2000
5. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. BMJ. 2003; 326:4-5. Editorial.
6. Holstein A, Nahrwold D, Hinze S, Egberts EH. Contra-indications to metformin therapy are largely disregarded. Diabet Med 1999;16:692-6.
7. Calabrese AT, Coley KC, DaPos SV et al. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. Arch Intern Med. 2002; 162:434-7.
8. Emslie-Smith AM, Boyle DI, Evans JM et al. Contraindications to metformin therapy in patients with type 2 diabetes— a population based study of adherence to prescribing guidelines. Diabet Med. 2001; 18:483-8.
9. Bailey CJ. Treating insulin resistance in type 2 diabetes with Metformin and thiazolidinediones. Diabetes Obes. Metab. 2005; 7: 675–91.
10. Tiwari SC. Recent advances in diabetic nephropathy: Clinical Medicine Update, IACM. 2002; 169-199.
11. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N ENg J Med 1999; 341:1127-1133.
12. Ritz E, Ogata H, Orth SR. Smoking: a factor promoting onset and progression of diabetic nephropathy. Diab Metab 2000;26: Suppl 4:54-63.
13. Lalor BC et al. Placebo-controlled trial of the effects of guar gum and metformin on fasting blood glucose and serum lipids in obese, type 2 diabetic patients. Diabet Med. 1990 Mar-Apr;7(3):242-5.
14. Alan J. Garber et al. Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-controlled, Dose-Response Trial. Am J Med. 1997;102;491–497.
15. Salpeter SR, Greyber E, Pasternak GA et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Cochrane Database Syst Rev. 2006; 1:CD002967.
16. Rachmani R, Slavacheski I, Levi Z et al. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. Eur J Intern Med. 2002; 13:428-33.