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THE STUDY OF EFFECT OF CANAGLIFLOZIN ON POST-PRANDIAL HYPERGLYCEMIA IN TYPE 2 DIABETES MELLITUS

General Medicine

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ABSTRACT

BACKGROUND : Diabetes MellituS, now a leading cause of morbidity and mortality for the forseeable future.

Pathophysiological features:

1) Impaired insulin secretion
2) Peripheral insulin resistance
3) Excessive hepatic glucose production

Clinically these patients demonstrate virtually absent first phase of insulin and c peptide response to iv glucose, a reduced second phase response and marked flattening of glucose insulin secretion dose response curve.

This study on Gliflozins mainly work on sodium glucose cotransporter 2 inhibitors which block the reabsorption of glucose system in the kidney. This significantly lowers HbA1C level in severe hyperglycemic type 2 diabetes mellitus patients.

Aims and Objectives : To study the effect of canagliflozin on post prandial plasma glucose in Type2 diabetes mellitus patients mostly eating parboiled rice.

MATERIALS AND METHODS: 84 patients of type2 diabetes mellitus of >15 yrs of age having elevated FPG/normal FPG but with increasing PPBG attended to NRI Institute of medical sciences, Sangivalasa, Visakhapatnam during the study period from 1st January 2017 to 31st December 2017.

RESULTS : This study included total of 84 cases of T2 DM and was designed to evaluate the effect on 2hr PPG level. Before canagliflozin therapy the mean PPG was 272.345mg/dl and after treatment with canagliflozin 200mg it was decreased by 50.77mg% (134.071mg/dl) at the end of 24 weeks.

CONCLUSION :

From this study it is evident that

- Canagliflozin monotherapy is useful in early stages of T2 DM with elevated PPPG.
- Parboiled rice is the predominant staple diet in T2DM patients in Andra Pradesh, so prescribing Canagliflozin is very much convenient to control 2hr PPPG.

KEYWORDS

T2DM, Type 2 Diabetes Mellitus, FPG, Fasting plasma glucose, PPPG, Post Prandial Plasma Glucose, Canaglifiozin. Parboiled rice.

Diabetes mellitus now a leading cause of morbidity and mortality for the foreseeable future. Type2 DM characterized By Three Pathophysiologic Feature 1) Impaired insulin secretion 2) Peripheral insulin resistance 3) Excessive Hepatic glucose production[1]. Type 2 DM patient are often hyperinsulinemic but degree of hyperinsulinemia is inappropriately low for the glucose concentration. Clinically these patients demonstrate virtually absent 1st phase insulin and c-peptide response to iv glucose, a reduced 2nd phase response and marked marked flattening of glucose insulin secretion dose response curve. These patient also demonstrated abnormal temporal pattern of insulin secretion i.e basal insulin secretion is greater and post prandial insulin secretion is attenuated.Post prandial hyperglycemia(PPHG) is primarily due to decreased 1st phase insulin secretion and the drug used to treat PPHG are 1.insulin analogue ie insulin aspart and insulin lispro 2. oral anti diabetic drug i.e. repaglenide, nateglenide, alpha glucosidase inhibitor, miglitol. In Andhra Pradesh the staple diet is rice and it has high glycemic index, causes increase in PPHG[1]. As insulin injection is not always convenient by the people,oral anti diabetic drug is preferred. But they are insulin secretagogue stimulate insulin and produce hypoglycemia.Sodium glucose cotransporter2 inhibitor system acts on the proximal tubule of the kidney and inhibits glucose reabsorption and causes glucose excretion in the urine[3,4,5].The drugs in this class are canagliflozin,dapagliflozin,emplagliflozin[6].

Flozins mainly work on the sodium glucose cotransport2 inhibitor system in the kidney without significantly affecting the sodium glucose cotransport1 system in the gut[5] exception being canagliflozin which has a larger effect on the gut's sodium glucose cotransport1 system.As a result it lowers blood glucose by acting both on the kidney and gut[7,8,9].

It significantly lowers the HbA1c level in severe hyperglycemic Type 2 DM patient.[2]It has been established that it is PPHG and not FPG which is the marker of cardiovascular disorder associated with diabetes with normal FPG. So controlling PPHG is imperative .[8]Canagliflozin is selected as the drug of choice in this study for the treatment of increasing PPG in TYPE 2 DM patients with rice as the staple diet to see the effect without changing the base line medication.

AIMS & OBJECTIVES:

1.To observe the effect of canagliflozin on post prandial blood glucose in Type2 DM in parboiled rice eating patients.

MATERIALS AND METHODS:

Approval: Prior permission was obtained from Institutional Review Board / Institutional Ethical Committee before the study was undertaken in the department of Medicine of NRI Institute Of Medical Sciences, Sangivalasa, Visakhapatnam Dist.Andhra Pradesh ,India, on patients admitted during the year january2017 to december2017.

Diagnosis was based on doing FPG, HbA1C, 2hr OGTT. Baseline medications were not changed.

Only those case having increased postprandial hyperglycemia was considered with canagliflozin OD,BD doses.

Follow up was done for each case for 6 months.

STUDY GROUP.

INCLUSION CRITERIA: The study included Type 2 DM patient of >15 yr age having elevated FPG/normal FPG with increasing PPG attended to NRIIMS during study period.

EXCLUSION CRITERIA

- Pregnancy
- Diabetic ketoacidosis
- Irritable bowel syndrome, inflammatory bowel disease
- Renal failure or renal dysfunction (Chronic Kidney Disease)
- Acute or chronic disease which may cause tissue hypoxia such as:
- Cardiac or respiratory failure
- Recent myocardial infarction
- Shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Lactation

DETAILS OF METHODS USED

TURBIDOMETRY

This method directly determinates the Glycosylated hemoglobin A1c (HbA1c) in whole blood, using an antigen and antibody reaction

OBSERVATIONS

Table – 1
Age and Sex Distribution

Age(years)	Male	Female	Total
30 – 44	10	07	17
45 – 59	35	15	50
> 60	14	03	17
Total	59	25	84

Total 84 cases of Type 2 diabetes mellitus taking parboiled rice with various age group cases were enrolled in my study. Among the patents 59 cases were male(70.23%) and 25 cases were female(29.76%). Majority of the patients belong to 45 – 59 years (59.52%).

Table – 2 Effect on plasma glucose level 24 wks before and after canagliflozin administration without changing the base line treatment

Sex and number of patients	2hr PPPG (mg/dl) before canagliflozin therapy	2hr PPPG(mg/dl) after canagliflozin therapy
Male (n = 59)	271.37	132.964
Female (n = 25)	272.89	134.263
Total (n = 84)	272.345	134.071

This study included total 84 cases of Type2DM ,predominantly taking parboiled rice and was designed to evaluate the effects on 2hrPPG level. Before canagliflozin therapy the mean PPPG was 272.345 mg/dl and after treatment (100mg OD) it was decreased by 50.77mg%(134.071mg/dl) at the end of 24weeks.The study showed that canagliflozin significantly reduced the post prandial plasma glucose level at the end of 24 wks.($p<0.0001$)

Table – 3 Canagliflozin administration as an adjunct to metformin

Sex and no of patients	Plasma glucose level (mg/dl)during metformin therapy		Plasma glucose level(mg/dl) after metformin+ canagliflozin therapy	
	FPG	2hrPPPG	FPG	2hrPPPG
Male (n=36)	171.07	235.92	104.923	129.78
female (n=10)	153.8	228.9	105.9	138.7

In our study total 46 cases were taken and treated on sulfonylurea alone and metformin +canagliflozin(100mgBD) combination given if 2hr PPPG are high, then 2hr PPPG was compared. The results showed tha canagliflozin together with metformin reduced post prandial plasma glucose by 44.9mg% in male and 39.4mg% in female, along with decrease of FPG after 24 weeks of treatment.

Table – 4 Canagliflozin administration as an adjunct to insulin

No of patients	Plasma glucose level (mg/dl) during insulin therapy		Plasma glucose level (mg/dl) after insulin + canagliflozin therapy	
	FPG	2hrPPPG	FPG	2hrPPPG
Male (n=11)	216	253	108	143.25
Female (n=3)	222	211	116	138.49

Total 15 cases were taken and treated with insulin alone and there after canagliflozin (200mgOD)was added along with insulin for 24weeks. It showed that there occurs significant reduction of 2hr PPPG by 43.38mg% in male and 34.36mg% in female respectively,when canagliflozin as administered as an adjunct to insulin.

DISCUSSION:

Post prandial plasma glucose contributes more to overall hyperglycemia in early stages of Type 2 DM. It is a direct and independent risk factor for cardiovascular complications. So controlling post prandial plasma glucose is imperative. Canagliflozin is selected as the drug of choice in this study because Canagliflozin effectively reduces PPG level without the disadvantages like additional burden on beta cell, hypoglycemia, weight gain .

In our study total 84 cases of type 2 DM are taken with various age group, majority of the people were between 45 – 59 yrs (59.52%). As per National Diabetes Statistics, the majority of diabetes population is in the age group 40 - 59 years (Table – 1).

This study included total 84 cases of Type 2 DM, predominantly taking parboiled rice and was designed to evaluate the effects on 2hrPPG level. Before canagliflozin therapy the mean PPPG was 272.345 mg/dl and after, it was decreased by 50.77mg% i,e to 134.071mg/dl at the end of 24weeks.The study showed that canagliflozin significantly reduced the post prandial plasma glucose at the end of 24wk. ($p<0.0001$) (Table – 2). 11Stenlof conducted a randomized placebo controlled phase 3 study to compare the efficacy and safety of canagliflozin and placebo in patients with type2 diabetes mellitus that was not controlled with diet and exercise.The study enrolled 584 patients between 18-80 years of age.In patients to whom cannagliflozin 100mg OD is given the HbA1C levels decreased to less than 7 and when when placebo is given HbA1C levels decrease to less than 7 .

In the present study, benefits of combination therapy of metformin+ canagliflozin was shown. Total 46 cases were taken with canagliflozin alone having mean 2hrPPPG-235.92mg/dl in male and 228.9mg/dl in female. After adding canagliflozin[100mg OD],2hrPPPG was reduced to 129.78mg/dl (decreased by 44.9mg%) in male and 138.7mg/dl(reduced by 39.4mg%) in female along with reduction of FPG to 105.9mg/dl(decreased by 35.1mg%) (Table – 3). So canagliflozin significantly decreased post prandial plasma glucose level as an adjunct to metformin,when PPPG was uncontrolled with parboiled rice¬. 12Rosenstock J conducted a randomized double blind placebo controlled multinational phase 3 study to evaluate the efficacy and safety of canagliflozin various doses in patients with type 2 diabetes that had not been adequately controlled with metformin. There was decrease in 2hrs PPBG levels in 26 week study period. In patients to whom cannagliflozin 100mg OD is given 2hr PPBG decreased to 2.4mmol/l in and when when placebo is given 2hr PPBG decreased to 0.3mmol/l in 20.6% people.

In study where insulin is used in conjugation with canagliflozin 200mg OD and Placebo in patients with type2 diabetes mellitus, there was change in HbA1C levels from baseline at 18 weeks .These individuals were 66% and had a median age of 63 years. Reductions in HbA1C with cannagliflozin 200mg OD versus placebo were -0.62% and improved glycemic control and decreased body weight.

In our study total 15 cases treated with insulin alone with increasing PPG was taken. After adding canagliflozin[200mg OD]2hrPPPG was compared.(During insulin therapy PPPG was 253mg/dl in male and 211mg/dl in female). In these patients, canagliflozin was advised together with insulin and the result was shown that 2hr PPPG was reduced to 143.25mg/dl(decreased by 43.38mg%) in male and 138.49mg/dl (decreased by 34.36mg%)in female (Table – 4).13,15Neal B,et al conducted a double blind placebo controlled study for 18 weeks in patients with type2 diabetes mellitus who are on

insulin used in conjuction with canagliflozin.

It is observed that 3% of the female patients had urinary tract infections after using this drug.

CONCLUSION:

From this study it is evident that :

1. Canagliflozin monotherapy is useful in the early stage Type2 DM with elevated post prandial plasma glucose.
2. Patient on metformin medication when PPG is uncontrolled, adding canagliflozin significantly reduced 2hr PPPG in patient taking parboiled rice.
3. Patient on insulin therapy with increasing post prandial plasma glucose, adding canagliflozin decreased PPPG effectively.
4. Parboiled rice is the predominant staple diet in diabetic (Type2) patients of Andhra Pradesh, so prescribing Canagliflozin is very much convenient to control 2hr PPPG.
5. It is observed that 3% of the female patients had urinary tract infections after using this drug.

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