How to Cite:
Dhone, P. G., Padmni , S., Rahul, G., & Faheem, M. M. (2022). Study the effect of Canagliflozin in patients of type 2 diabetes mellitus inadequately controlled on maximum dose of three oral hypoglycemic agents. *International Journal of Health Sciences*, *6*(S6), 1842–1853. https://doi.org/10.53730/ijhs.v6nS6.9857

Study the effect of Canagliflozin in patients of type 2 diabetes mellitus inadequately controlled on maximum dose of three oral hypoglycemic agents

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***Abstract*---**Metformin is the first- line pharmacotherapeutic agent implemented after life style modification to achieve the desired glycemic levels in patient with T2DM. [4] However, Metformin alone in many patients fail to maintain the desired glycemic levels in long term and they will require additional combination therapies.[5] Even though effective initially , agents included in the class of sulfonylurea has common side effects like hypoglycemia and weight gain.[6] It is also observed that drugs acting on pancreatic β cells will cause early exhaustion of β cells and the use of agents that utilize the insulin dependent pathways. After the analysis of data collected at the end of the study it was found that there was a significant reduction in fasting and post prandial blood sugar levels, HbA1c value and body weight. Along with these benefits few adverse effect including simple urinary tract infection, genital mycotic infection were recorded, these ADRs were mild and symptoms subsided after routine treatment. To conclude Canagliflozin 100 mg when added to the ongoing triple drug therapy in patients with inadequately controlled T2DM has shown significant reduction in fasting and post prandial blood sugar levels,

HbA1c value and body weight in the duration of 6 months with acceptable safety profile.

***Keywords*---**diabetes, hypoglycemic agents, metformin.

Introduction

Diabetes is known to physicians since ancient times. Aretaeus, the Greek physician described the condition as diabetes (Greek- siphon) which means passing more amount ofwater than normal and word Mellitus (Latin- honey) was introduced by Thomas Willis, to indicate sweet urine passed by these patients. Diabetes mellitus (DM) refers to a bunch ofdisorders of metabolism that share the phenotypic sign of hyperglycemia. [1] Different variants of DM are caused due to the interaction of various genetic factors with environmental factors. [2] Depending on the pathogenic process leading to hyperglycemia DM is classified, as Type I, Type II, Gestational Diabetes & Other specific types as maturity onset diabetes of youth (MODY), lipodystrophic diabetes, secondary diabetes due to pancreatitis, hemochromatosis, drug-induced, infectious, insulin receptor antibodies. [3]

As per American diabetes Association (ADA) guidelines Metformin is the first- line pharmacotherapeutic agent implemented after life style modification to achieve the desired glycemic levels in patient with T2DM. [4] However, Metformin alone in many patients fail to maintain the desired glycemic levels in long term and they will require additional combination therapies.[5] Even though effective initially , agents included in the class of sulfonylurea has common side effects like hypoglycemia and weight gain.[6] It is also observed that drugs acting on pancreatic β cells will cause early exhaustion of β cells and the use of agents that utilize the insulin dependent pathways become difficult due to deterioration of β-cell function and increase in insulin resistance. Also, gradual increase in weight may be associated with worsening markers of insulin resistance. [7]

As dysfunction of β-cell advances most of the patients eventually need insulin treatment for the control of blood glucose level. [8] Unfortunately most of the patient are reluctant to initiate insulin therapy and delay it for significant period leading to loss of crucial time and will lead to worsening of the disease.[9] Enough evidences are suggestive of that, not less than one- quarter of patients refuse to initiate insulin therapy when prescribed.[20] Even with the availability of several antihyperglycemic agents, it is seen that only 53% patients with DM achieve HbA1c<7.0%.[21] Therefore an unmet need is felt for effective anti-diabetic agent that when used alone or in combination will improve glycemic control in patient with T2DM especially with no or minimum risk of Hypoglycemic episodes and weight gain. Therefore, the search for agents with new mechanism of action and good safety profile became very essential.

A new mechanism for the reduction of blood glucose level is by inhibiting the reabsoption of glucose by the kidney taking place predominantly via Sodium glucose co- transporter 2 (SGLT2) and Sodium glucose co-transporter 1(SGLT1). [22] In a normal healthy individual, 180 g of glucose is filtered and is reabsorbed on a daily basis with a maximum transport rate of 300 mg/min. This rate

increases by about 20% in uncontrolled T2DM patients and the value comes to be 352 – 419mg/min .[23] This increased SGLTs expression observed in the patient of T2DM is a physiological response to abnormal increased exposure of glucose to nephron and is maladaptive.[24] The class of OHA known as SGLT2 inhibitor antagonizing these transporters. The members of this class of oral hypoglycemic agents (OHA) are Canagliflozin, Dapagliflozin and Empagliflozin. So, in this study, we have added Canagliflozin 100 mg 1 once a day (OD) for 24 weeks, to ongoing triple-drug therapy in patients with T2DM who are inadequately controlled on a maximum dose of three OHA. The purpose of the study was to evaluate the efficacy and safety of Canagliflozin when added to ongoing triple-drug therapy.

Aim and Objectives

"To Study Effect of Canagliflozin in patients inadequately controlled on maximum dose of three oral hypoglycemic agents"

Objectives of the study

- To Study of Effect of Canagliflozin as on HbA1c in patients with type 2 diabetesmellitus
- To study effect of Canagliflozin on body weight of patient.
- To assess the safety of Canagliflozin as per ADR reported by patients.

Material and Method

Study was be conducted as per ICH and GCP guidelines and schedule 'Y'
Recruitment duration: One and half year (1 year 6 months)

Sample size

Sample size (n) for the study was calculated using the following formulaPrevalence [5] : 8%

$$\text{Formula: } n = \frac{Z^2\ p\ (1-p)}{D2}$$

Where,
'n' is the sample size
'Z' determines the acceptable likelihood of errors. The value of Z is generally set to 1.96representing the level of errors of 5% i.e. 95% level of confidence
'p' denotes the prevalence of the disease in given population'D' denotes the margin of error which is usually taken as 5%For this study the values came to be
Z = 1.96
p= 0.08
D= 0.05

Therefore, sample size came to be114 patients

Study duration

Study was started on 26th November 2016. Each subject enrolled in the study was treatedfor six months (24 weeks)

Study design

- 24 week prospective, open label, single center, single arm, interventional clinical study
- Study was conducted as per ICH GCP guideline, schedule 'Y' and declaration of Helsinki.
- Study was conducted after obtaining permission from institutional ethics committee and Medicine department, MGM medical college and hospital Aurangabad
- Patient fulfilling inclusion and exclusion criteria was enrolled into study.

Patients were assessed at baseline, at 3 months and 6 months for the following investigations

- Blood sugar – fasting & post meal.
- Glycated hemoglobin level (HbA1C)
- Body weight
- eGFR calculation by MDRD formula e-GFR=186×(Serum creatinine)$^{-1.154}$×(AGE)$^{-0.203}$×(0.742 if Female)
- Urine routine

Eligibility Criteria
Inclusion criteria

- Both male and female patients with Type 2 diabetes mellitus
- Patient on maximum dose of three OHA with inadequate response
- Patients of Age between 18 to 65 years4. HbA1c > 8.5%
- BMI > 25 kg/m^2
- Patients willing to give written inform consent
- Patient willing to comply with study procedure

Exclusion criteria

- Newly diagnosed patients of T2DM
- Type 1 diabetes mellitus
- Gestational diabetes
- Patients with eGFR value less than 55 ml/ min/ 1.73 m^2
- Patient on insulin therapy
- Patients with recurrent UTI
- Patients with history of diabetic ketoacidosis
- Patients with history of myocardial infarction, unstable angina, revascularizationprocedure

- Patients with history of cerebrovascular accidents
- Patients with uncontrolled hypertension
- Patients with history of hepatic diseases
- Patients with history of renal diseases

Informed consent

Patients willing to participate and eligible in the view of investigator were given the patient information sheet in his or her vernacular language and all study related tests and procedures were explained to him/her in a language which the patients understands. Patients were explained about the risks and complications of the study drugs and other modalities of treatment available for T2DM . After imparting sufficient information, if the patient desired to be a part of the study then his/her written informed consent (signature/thumb impression) was taken on the informed consent form which was approved by the institutional ethics committee (see appendix).

Drug and dosage administered

Drug	Dosages used	Duration
Canagliflozin	100 mg OD	6 months (24weeks)

Study conduct

Brief discussion about the visits of the study and procedures performed in each visit

Visit 1 Screening

Informed consent, check for inclusion and exclusion criteria,demographic details, patient information sheet given for reading

General physical examinationLaboratory investigations

- Blood sugar – Fasting & post meal
- Glycated hemoglobin level (HbA1C)
- Body weight
- Serum creatinine
- e-GFR calculation by MDRD formula e-GFR=186× (Serum creatinine)$^{-1.154}$×(AGE)$^{-0.203}$×(0.742 if Female)
- Urine routine

Visit 2- after reciving lab.reports / after 7 days

Enrollment. Informed consent, check for inclusion and exclusion criteria, demographic details

General physical examinationLab. Reports reviewed

Patient assigned to receive Canagliflozin 100 mg along with ongoing oral hypoglycemic agents

Visit 3- 12 weeks +/- 7 days

General physical examinationSafety assessment Laboratory investigations

- Blood sugar – Fasting & post meal
- Glycated hemoglobin level (HbA1C)
- Body weight
- Serum creatinine
- e-GFR calculation by MDRD formula
- Urine routine

Visit 4 - 24 weeks +/- 7 days

General physical examinationSafety assessment Laboratory investigations

- Blood sugar – Fasting & post meal
- Glycated hemoglobin level (HbA1C)
- Body weight
- Serum creatinine
- e-GFR calculation by MDRD formula
- Urine routine

Result

Table 1
Age-Group of patients in study

Age-Group	No .of patients	Percentage
30-40	27	23.7%
41-50	38	33.3%
51-60	35	30.7%
>60	14	12.3%
Total	114	100%
Mean age in the study ±SD*	48.56 ± 9.75	

*SD- standard deviation

Table no. 1 shows the age group of patients under the study. The patients in the group 30-40 years of age were 27 that come to be 23.7%, in the group 41-50 years of age were 38 that comes to be 33.3%, in the group of 51-60 years of age were 35 i.e. 30.7% and thatin the group more than 60 years of age were 14 that

comes to be 12.3%. mean age of patients in the study was 48.56 with standard deviation ± 9.75

Table 2
Gender wise of patients in study

Gender	No .of patients	Percentage
Male	55	48.2%
Female	59	51.8%
Total	114	100%

Table no. 2 shows the gender wise patients in the study. In this study number of male patients were 55 i.e. 48.2% and number of female patients were 59 i.e. 51.8%

Table 3
Mean Fasting Blood Sugar level at Baseline, 3 Months & 6 Months

Fasting blood Sugar level	Mean*	SD**	Minimum	Maximum
Baseline	193.03	61.69	107.80	408.60
3 Months	167.88	43.95	106.10	315.20
6 Months	146.27	31.80	100.60	248.10

*Mean fasting blood sugar level at baseline, 3 months and 6 month; minimum and maximum value recorded at baseline, 3 months and 6 month
**SD- standard deviation

Table no.3 shows the mean fasting blood sugar value recorded at baseline, 3 months and 6 months. Mean fasting blood sugar value at baseline was 193.03 mg/dl with standard deviation ± 61.69. Mean fasting blood sugar value at 3 months was 167.88 mg/dl with standard deviation ± 43.95. Mean fasting blood sugar value at 6 months was 146.27 mg/dl with standard deviation ± 31.80.

Table 4
Mean Post prandial blood Sugar level at Baseline, 3 Months & 6 Months

Post prandial Blood Sugar level	Mean*	SD*	Minimum	Maximum
Baseline	299.50	95.94	134.80	584.40
3 Months	245.16	60.16	130.10	380.10
6 Months	212.09	45.87	114.80	317.30

*Mean post prandial blood sugar level at baseline, 3 months and 6 month; minimum and maximum value recorded at baseline, 3 months and 6 month
**SD- standard deviation

Table no. 4 shows the mean post prandial blood sugar value recorded at baseline, 3 months and 6 months. Mean post prandial blood sugar value at baseline was 299.50 mg/dl with standard deviation ± 95.94. Mean post prandial blood sugar value at 3 months was 245.16 mg/dl with standard deviation ± 60.16. Mean post

prandial blood sugar value at 6 months was 212.09 mg/dl with standard deviation ± 45.87.

Table 5
Mean HbA1c level at Baseline, 3 Months & 6 Months

HbA1c	Mean*	SD**	Minimum	Maximum
Baseline	11.90	2.16	8.20	16.00
3 Months	10.34	1.72	7.10	13.50
6 Months	8.88	1.34	5.70	11.70

*Mean HbA1c value at baseline, 3 months and 6 month; minimum and maximum value recorded at baseline, 3 months and 6 month
**SD- standard deviation

Table 6
Mean eGFR at Baseline, 3 Months & 6 Months

eGFR	Mean*	SD**	Minimum	Maximum
Baseline	89.84	40.21	49.00	251.00
3 Months	93.49	40.20	49.00	251.00
6 Months	95.48	40.99	45.00	251.00

*Mean eGFR value calculated at baseline, 3 months and 6 month; minimum and maximum value recorded at baseline, 3 months and 6 month
**SD- standard deviation

Table no.6 shows the mean eGFR value recorded at baseline, 3 months and 6 months. Mean eGFR value at baseline was 89.84 with standard deviation ± 40.21. Mean eGFR value at 3 months was 93.49 with standard deviation ± 40.20. Mean eGFR value at 6 months was 95.48 with standard deviation ± 40.99.

Discussion

So, this study was conducted by adding Canagliflozin 100 mg 1 once a day (OD) for 24 weeks, to ongoing triple-drug therapy in patients with T2DM who are inadequately controlled on a maximum dose of three OHA. The purpose of the study was to evaluate the efficacy and safety of Canagliflozin when added to ongoing triple-drug therapy. At 6 months Canagliflozin 100 mg when added to the ongoing triple drug therapy has provided significant reduction in HbA1c from baseline $P < 0.0001$. Difference in mean changes in HbA1c was – 3.02 %. Subgroup analysis based on baseline HbA1c has shown that HbA1c reduction was greater in the higher baseline group; reduction in low baseline group was also sizable. Reduction in HbA1c was more in first 3 months of therapy i.e. mean difference from baseline to 3 months is – 1.56% and that form 3 months to 6 months was – 1.46 %.

Significant reduction is recorded in the values of fasting blood sugar with mean difference from baseline to 6 months of – 46.76 mg/dl $P< 0.0001$. It was also observed that the reduction in fasting plasma sugar value was more from baseline to 3 months – 25.15 mg/dl as compared to 3 months to 6 months – 23.61. Reduction in baseline post prandial sugar value by – 87.41 mg/dl at 6

months P< 0.0001. Post prandial sugar value has reduced more from baseline to 3 months – 54.34 mg/dl as compared to 33.07 mg/dl from 3 months to 6 months. In our study we have found Canagliflozin 100 mg once a day was significantly effective in reducing HbA1c, body weight, fasting and post prandial blood sugar. It was also found to be renoprotective as it has shown significant reduction in serum creatinine and improvement in eGFR value. The probable mechanism for the reduction in blood sugar levels and eventually HbA1c is the inhibition of SGLT2 at kidney and hence increasing the excreation of sugar in urine. The was also observed that reduction in HbA1c was to a greater extent in patients with high baseline value. This loss of sugar (glucose) via urine accounts to the loss of calories and explains the mechanism for weight loss noted in the patients.

In the prospective observational study conducted by S.R. Pattanaik at department of endocrinology, MKCG Medical college, Berhampur, Odisha. 51 patient were enrolled and were given Canagliflozin 100 mg once a day for 3 months to ongoing triple drug therapy of Glimepride, Metformin & Teneligliptin. Their mean reduction of HbA1c was found to be reduced by 1.1 % P <0.0001, body weight was reduced by 0.62 kg P< 0.0032, fasting blood sugar value has reduced by 32.5 mg/dl P< 0.0001, post prandial blood sugar was reduced by 109 mg/dl P< 0.0001, mean reduction in serum creatinine value was by 0.1 mg/dl P< 0.0001. Although the study was conducted for 3 months, the results are highly significant in all the parameters as that of our study. [25]

In the study conducted as 26 week, randomized, double blind, placebo controlled , phase 3 clinical trial on 584 subjects by K. Stenlof et. al. by administering Canagliflozin 100 or 300 or placebo once a day have significantly reduced the HbA1c value by -0.77%,-1.03% and -0.14% from baseline at 26 weeks respectively; P<0.001 for both. [26] Furthermore the clinical trial conducted on Canagliflozin as CANTATA-M, CANTATA-D between 2010 to 2012 , at 24 weeks have reported reduction in HbA1c value by -0.77% and 0.73 % respectively by the administration of Canagliflozin 100 mg in patients in adequately controlled on exercise and diet (P<0.001). [27] Several studies are conducted to evaluate the efficacy of Canagliflozin as add on to double drug treatment for achieving the desired glycemic control in patients with T2DM. Wilding et. al in 2013 reported that in his study conducted on 469 patients as a 52 week, randomized, double blind, placebo controlled, phase 3 trial by adding Canagliflozin 100 and 300 mg to sulfonylurea and Metformin have shown significant reduction in HbA1c value, body weight, fasting and post prandial blood glucose level as compared to placebo. [28] In a pooled analysis done by Alan Sinclair et.al for four randomized, double blind, placebo controlled phase 3 studies on Canagliflozin concluded that Canagliflozin improved glycemic control, body weight, systolic blood pressure and was well tolerated in older patients with T2DM. [29]

Conclusion

After the analysis of data collected at the end of the study it was found that there was a significant reduction in fasting and post prandial blood sugar levels, HbA1c value and body weight. Along with these benefits few adverse effect including simple urinary tract infection, genital mycotic infection were recorded, these

ADRs were mild and symptoms subsided after routine treatment. To conclude Canagliflozin 100 mg when added to the ongoing triple drug therapy in patients with inadequately controlled T2DM has shown significant reduction in fasting and post prandial blood sugar levels, HbA1c value and body weight in the duration of 6 months with acceptable safety profile.

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