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Comparison of Efficacy of Treatment with Empagliflozin versus Teneligliptin in Patients of Uncontrolled Type 2 Diabetes Mellitus. An Open Label Randomized Controlled Trial

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ABSTRACT

Background: As per ADA 2020 guidelines, empagliflozin (SGLT2i) and teneligliptin (DPP4i) are recommended as add on therapy in uncontrolled T2DM patients on metformin monotherapy.

Aim & Objective: To compare the efficacy of empagliflozin versus teneligliptin on diabetic status as add on therapy to metformin monotherapy in patients of uncontrolled T2DM.

Material and Methods: The study was randomized, prospective, open label, comparative interventional study conducted at Dr RPGMC Tanda. Out of total 66 patients, 32 (Group A) received empagliflozin 25mg/day and 34(Group B) received teneligliptin 20mg/day and in addition to metformin 1000 mg BD.

Statistical Analysis: The data was presented as mean+/- SD. Student t test was used. The p value<0.05 is significant.

Results: Both the groups achieved clinically acceptable levels of fasting plasma glucose, post prandial blood sugar and HbA1C levels over 6 months period.

Moreover, the patients in group A had statistically significant lower levels of fasting plasma glucose, post prandial blood sugar and HbA1C levels in comparison to group B at 1 month ($p < 0.001$) and 3 months ($p = 0.003$).

Conclusion: Both the groups achieved clinically acceptable levels in patients of uncontrolled T2DM. However, reduction in FBS levels, 2 h-postpandial sugars and HbA1C in group A was significantly higher than group B (p value < 0.001).

Keywords: RCT, Uncontrolled type 2 diabetic mellitus, Empagliflozin, Teneligliptin

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia [1].

Pharmacologic Therapy for Type 2 Diabetes

Initial Therapy

- Metformin should be started at the time type 2 diabetes is diagnosed unless there are contraindications; for most patients this will be monotherapy in combination with lifestyle modifications [2].

Combination Therapy

- If the HbA1C target is not achieved after approximately 3 months and the patient does not have atherosclerotic cardiovascular disease or chronic kidney disease (ASCVD or CKD), consider a combination of metformin and any one of the preferred six treatment options: sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 (DPP-4) inhibitor, SGLT2 inhibitor, GLP-1

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receptor agonist, basal insulin, the choice of which agent to add is based on drug-specific effects and patient factors [2].

- Till date, only a few studies have been done comparing efficacy of empagliflozin versus teneligliptin as add on therapy to metformin monotherapy for treating T2DM. Further, to the best of our knowledge, no such study has been conducted in India. Hence, this study was conducted to compare the efficacy and safety of empagliflozin versus teneligliptin as add on therapy to metformin in patients of uncontrolled T2DM [2].
- In most of the comparative studies of empagliflozin with teneligliptin, the duration of study was six months or twelve months. Since, this was a time bound academic study; the participants were followed-up for six months [2].

MATERIALS AND METHODS

Study Design and Setting

The study was randomized, prospective, open label, comparative interventional study. The study was conducted in the Department of Pharmacology and the Department of Medicine at Dr. R.P.G.M.C, Kangra at Tanda which is 700 bedded multispeciality tertiary health care center situated in the foothills of Dhauladhar mountain range, at altitude of 32.0986360N and longitude of 76.3003390 E, amidst the serene Kangra valley of Himachal Pradesh in India.

IEC approval vides letter no. IEC/139/2019: dated 17/12/2019.

CTRI registration no. (REF/2020/03/032516) Trial completed on 24/10/2021.

Study population:

The study population was the consenting adult patients of T2DM of different socio-economic strata, from the Kangra and adjoining 5 districts of Himachal Pradesh. The patients were selected on an outpatient department basis.

Inclusion criteria:

- Willing to give written informed consent for the study.
- Adult patients of age more than 18 years of either sex.
- Ambulatory subjects who were suffering from type 2 diabetes mellitus and prescribed anti-diabetic drug at medicine OPD.

Exclusion criteria:

- Subjects age less than 18 years.
- Subjects not willing to participate.
- Coexisting cardiac, renal, liver and CNS emergency conditions.
- Any condition resulting in severe learning disability (e.g. brain injury) or unable to comprehend for other reasons.
- Acute complications of diabetes mellitus such as hyperglycemic hyperosmolar state and diabetic ketoacidosis.
- Pregnancy and lactating mothers.
- Known hypersensitivity or contraindications to study drugs.
- Patients already on study drugs.

Study duration: The study stretched over a period of one year for the enrollment of patients and follow-up was done at the end of first, third and sixth month after initiating the treatment.

Study intervention: Detailed history of the patients with T2DM was elicited, clinical examination was done and hematological and biochemical investigations were carried out.

Once diagnosed, the registered patients of T2DM were informed about the study through the patient information sheet and were allowed to understand thoroughly about the study and related aspects in their own language.

After a written informed consent, the participants were assigned to either group either A or B, based on computer generated random numbers.

GROUP A Participants	**Empagliflozin 25 mg/day + metformin 1000 mg twice a day with meals.**
GROUP B Participants	Teneligliptin 20 mg/day + metformin 1000 mg twice a day with meals.

- Before initiating the treatment, baseline blood biochemistry parameters were done.
- Patients were contacted telephonically on the next day of initiating the therapy and enquired for any adverse event.
- Patients were called for follow up at 1 month, 3 month and 6 months for therapeutic outcome and adverse event monitoring.
- HbA1c <7% was taken as adequate control of diabetes mellitus. Blood biochemical parameters were also repeated.
- Randomization was computer generated.

Measurement of outcome:

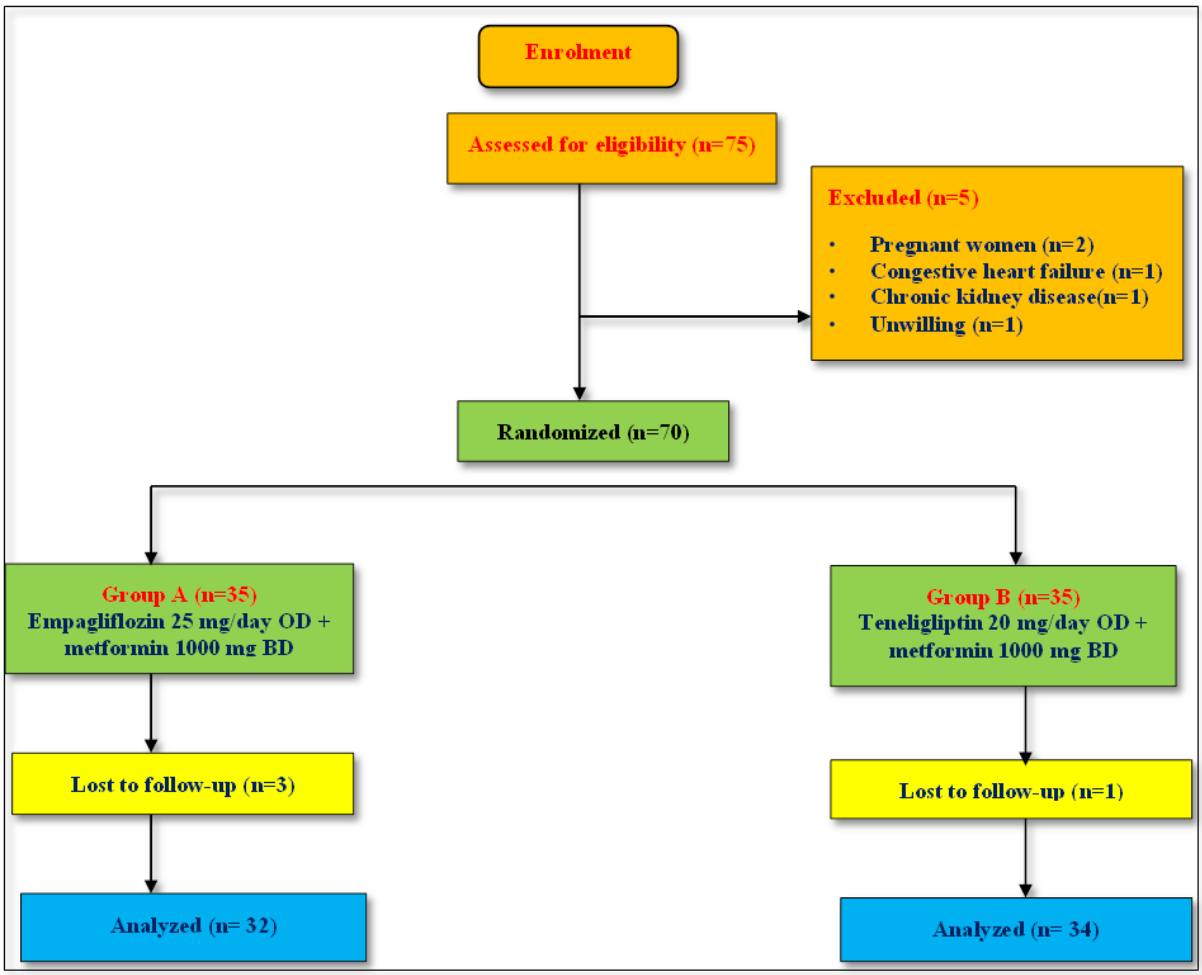
Efficacy
1) No. of patients with controlled diabetes.
a) Without addition of new drug (per protocol).
b) With addition of new drug (intent to treat).
2) No. of patient with uncontrolled diabetes even after addition of new drug.

Statistical analysis

The data were recorded on Microsoft excel spreadsheet. Statistical analysis was done using Microsoft excel and online SPSS software. Quantitative data was presented as mean ± SD. Categorical data was presented as frequency and percentage. Student's t-test was used for comparing continuous variables between the two groups. Chi square or Fisher's exact test was used for comparing the qualitative data between the two groups. An intention-to-treat analysis was done to compare the data. p value < 0.05 was considered significant.

OBSERVATIONS AND RESULT

Consent diagram



As shown in consort diagram, 75 patients were enrolled and assessed on the basis of eligibility criteria. (n) represents number of patients. 70 patients were randomized in 2 groups.5 patients were excluded on the basis of exclusion criteria. Group A (n=35) were given with empagliflozin 25 mg/day OD + metformin 1000 mg BD. Group B(n=35) were given with teneligliptin 20mg/day OD + metformin 1000 mg BD. 3 patients in Group A were lost to follow up.1 patient in group B were lost to follow up.32 patients in Group A and 34 patients in Group B were analysed.

As shown in **Table 1**, in group A and B, majority of patients were in 50-60 years of age group. 16(50%) patients in group A and 17 (50%) in group B were males. 16 (50%) patients in group A and 17 (50%) in group B were females. 18(56%) patients in group A and 18(53%) patients in group B had

family history of hypertension. 18(56%) patients in group A and 18(53%) patients in group B had family history of diabetes. 13(41%) patients in group A and 12(35%) patients in group B had history of smoking. 10(31%) patients in group A and 11(32%) patients in group B had history of alcohol intake.

Table 1. Baseline Sociodemographic Characteristics.

Baseline Characteristics	Group A (N=32)	Group B (N=34)	p value
Age (years)			
30-40	2(6%)	3(9%)	0.812
40-50	8(25%)	6(18%)	
50-60	15(47%)	15(44%)	
>60	7(22%)	10(29%)	
Gender			
Male	16(50%)	17(50%)	1.000
Female	16(50%)	17(50%)	
% Age of Hypertensive	16(50%)	15(44%)	0.632
% Age of family history of diabetes	18(56%)	18(53%)	0.787
% Age of smokers	13(41%)	12(35%)	0.635
% Age of incidence of alcohol intake	10(31%)	11(32%)	0.585
BMI	27.04±2.82	26.67±2.83	0.713

Improvement in fasting blood glucose in two groups

As shown in **Table 2** and **Figure 1**, there was progressive significant decrease in fasting plasma glucose in both the groups over 6 months. In Group A values improved from baseline of 217+48 mg/dl to 131+8 mg/dl ($p < 0.001$) at 1 month; 117+8 mg/dl ($p < 0.001$) at 3 months; 106+8 mg/dl ($p < 0.001$) at 6 months.

Similarly, In Group B values improved from baseline of 225+47 mg/dl ($p < 0.001$) to 161 +21 mg/dl ($p < 0.001$) at 1 month; 125+14 mg/dl ($p < 0.001$) at 6 months.

Moreover, the patients in group A had statistically significant lower levels of FBS in comparison to group B at 1 month ($p < 0.001$) and 3 months ($p = 0.003$).

Table 2. Improvement in fasting blood glucose in two groups.

FBS	Group A (n=32)	Group B (n=34)	p-value#
Baseline	216 ±48	225±47	0.473
1- Month	131 ±8***	161±21***	<0.001+++
3-Months	117±8***	125±14***	0.003+++
6-Months	106 ±8***	109±7***	0.110
p- value	***<0.001 (Baseline vs. 1-month)	***<0.001 (Baseline vs. 1-month)	
	***<0.001 (Baseline vs. 3-month)	***<0.001 (Baseline vs. 3-month)	
	***<0.001 (Baseline vs. 6-month)	***<0.001 (Baseline vs. 6-month)	

*Data expressed as mean +SD; #Student t- test; +Intergroup comparison; * Intragroup comparison*

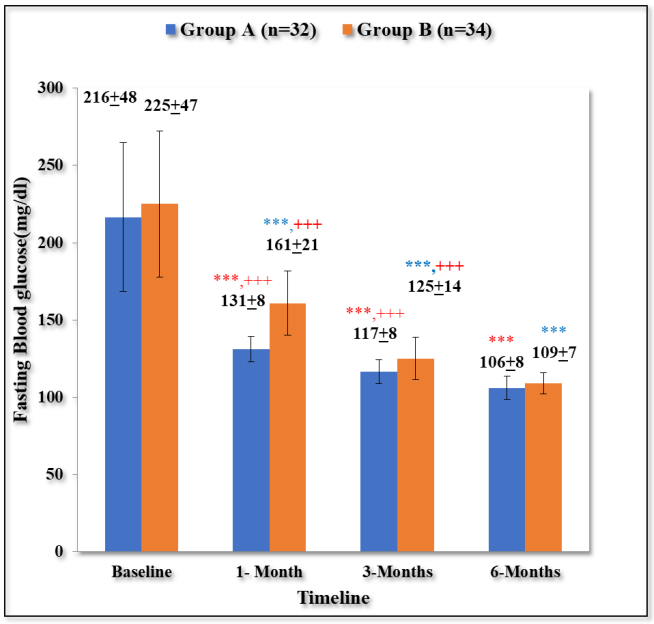


Figure 1. Improvement in Fasting Blood Glucose in Two Groups.

Improvement in 2-h plasma glucose in both groups

As shown in **Table 3** and **Figure 2**, there was progressive significant decrease in 2-h plasma glucose in both the groups over 6 months. In Group A values improved from baseline of 289±44 mg/dl to 172±14 mg/dl ($p < 0.001$) at 1 month; 149±11 mg/dl ($p < 0.001$) at 3 months; 148±9 mg/dl ($p < 0.001$) at 6 months.

Similarly, In Group B values improved from baseline of 289±40 mg/dl ($p < 0.001$) to 206±29 mg/dl ($p < 0.001$) at 1 month; 166±14 mg/dl (p value < 0.001) at 6 months.

The patients in group A had statistically significant lower levels of 2- h plasma glucose in comparison to group B at 1 month ($p < 0.001$) and 3 months ($p < 0.001$). However, both the groups were comparable at baseline ($p = 0.198$) and 6 months ($p = 0.146$).

Table 3. Improvement in 2-h Plasma Glucose in Both Groups.

2-h glucose	Group A (n=32)	Group B (n=34)	P-value#
Baseline	289±44	289±40	0.198
1-Month	172±14***	206±29***	<0.001+++
3-Months	149±11***	166±14***	<0.001+++
6-Months	148±9***	144±9***	0.146
p-value	***<0.001 (Baseline vs. 1-month)	***<0.001 (Baseline vs. 1-month)	
	***<0.001 (Baseline vs. 3-month)	***<0.001 (Baseline vs. 3-month)	
	***<0.001 (Baseline vs. 6-month)	***<0.001 (Baseline vs. 6-month)	

*Data expressed as mean +SD; #Student t- test; +Intergroup comparison; *Intragroup comparison*

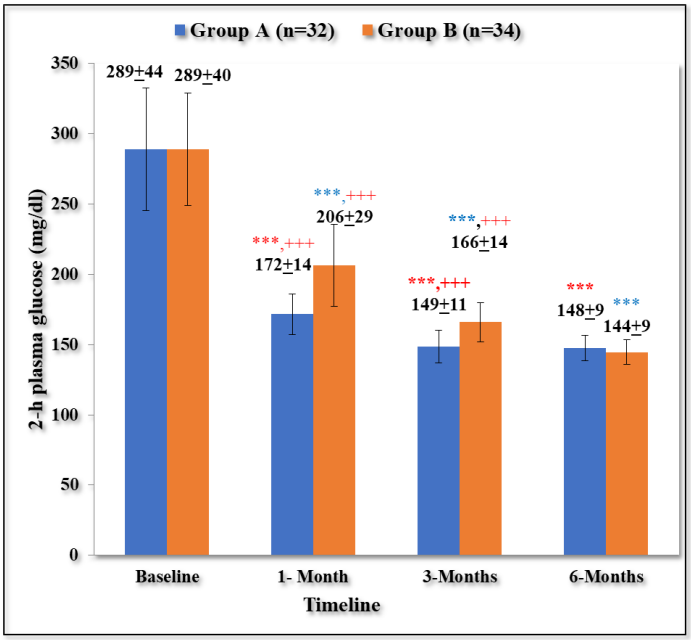


Figure 2. Improvement in 2-h plasma glucose in both groups.

Improvement in HbA1c (%) in two groups

As shown in **Table 4** and **Figure 3** there was progressive significant decrease in HbA1c in both the groups over 6 months. In Group A values improved from baseline of 11±0.8% to 8±0.2% ($p < 0.001$) at 3 months and 7±0.2% ($p < 0.001$) at 6 months. Similarly, In Group B values improved from baseline of 10±1% to 9±1% ($p < 0.001$) at 3 months and 7±0.3% ($p < 0.001$) at 6 months.

Both the groups were comparable at baseline ($p = 0.530$). The patients in group A had statistically significant lower HbA1c levels in comparison to group B at 3 months ($p < 0.001$) and 6 months ($p < 0.001$).

Table 4. Improvement in Hba1c (%) in two groups.

HbA1c	Group A (n=32)	Group B (n=34)	p-value[#]
Baseline	11 ± 0.8	10 ± 1	0.530
3-Months	8 ± 0.2***	9 ± 1***	<0.001^{+++}
6-Months	7 ± 0.2***	7 ± 0.3***	<0.001^{+++}
p- value	***<0.001 (Baseline vs. 3-month)	***<0.001 (Baseline vs. 3-month)	
	***<0.001 (Baseline vs. 6-month)	***<0.001 (Baseline vs. 6-month)	

*Data expressed as mean +SD; [#]Student t- test; +Intergroup comparison; *Intragroup comparison*

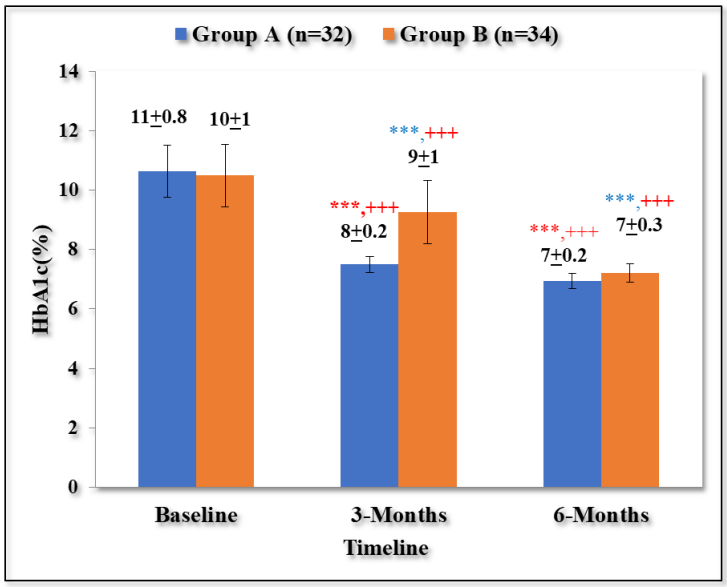


Figure 3. Improvement in Hba1c (%) in two groups.

DISCUSSION & CONCLUSION

Both the groups improved diabetes mellitus at the end of 6 months but empagliflozin was more effective in early follow up.

Similar observations were made by Haring Hans Ulrch [4], Inzucchi Silio E [7], Kawamori Ryuzo [5], and Hussain Mazhar [6].

LIMITATIONS

Being post graduate thesis, the follow-up could not be extended beyond 6 months. Follow-up for longer duration would have added more evidence about safety and efficacy of our study drugs.

FINANCIAL DISCLOSURE

No unnecessary financial burden was put on the patient for the treatment and investigations at any point of time throughout the study period. I did not get any financial benefit from any pharmaceutical company or any other source for this study.

CONFLICT OF INTEREST

No conflict of interest pertaining to any part of the study.

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