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ASSESSMENT OF SAFETY AND EFFICACY OF EMPAGLIFLOZIN AND LINAGLIPTIN COMBINATION IN TYPE 2 DIABETES MELLITUS PATIENTS IN RVM HOSPITAL

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ABSTRACT

Background: Diabetes mellitus, commonly called as diabetes-which is a collection of disruptions of metabolism that results in high blood sugar, possibly due to a shortage of insulin production by the body or cells doesn't react to the insulin that is generated. The hypoglycaemic drugs i.e.; Empagliflozin (SGLT2 inhibitor) and Linagliptin (DPP4 inhibitor) are commonly prescribed in the treatment of T2DM. **Aims and Objectives:** To assess whether combining empagliflozin and linagliptin is beneficial and safe in T2DM patients. **Materials and Method:** A total of fifty individuals within the peer group of twenty to eighty years have T2DM. The subjects were prescribed with drug Glyxambi (also named Empagliflozin)and tradjenta (also named linagliptin) in combination with the dose of 10/5 or 20/5 mg orally administered once every day for three months. The glucose/ sugar concentration in the blood is calculated i.e.; blood glucose levels after fast, postprandial blood glucose, and hemoglobin values. The results of the tests were documented. before administration of the medication and after administration of the medicine and once a month until three months. **Results:** The medication administration outcome is considerable in glycemia in the blood. It is observed statistically that the Tiptengio prescribed is efficient and secure in the management of DM patients. **Conclusion:** This study confirms that the linagliptin and empagliflozin combination is desirable forsubjects with T2DM.

KEYWORDS: Hypoglycaemicdrugs, Empagliflozin, Linagliptin.

INTRODUCTION

Diabetes mellitus, commonly called as diabetes-which is a collection of disruptions of metabolism that results in high blood sugar, possibly due to a shortage of insulin production by the body or cells doesn't react to the insulin that is generated.

Type 2 diabetes is a chronic and progressive disease that has developed into a great burden worldwide. The International Diabetes Federation (IDF) estimates an increase in patients suffering from type 2 diabetes from 415 million affected in 2015 to 642 million in 2040.[1] Approximately 5 million deaths per year are attributed to type 2 diabetes worldwide. Chronic hyperglycemia, hypertension and dyslipidemia facilitate vascular complications. The risks for macrovascular- (myocardial infarct, stroke) and microvascular events (endstage renal failure, blindness) are more than doubled.[2,3] An increased risk for heart failure in patients with type 2 diabetes as well as an increased risk for neuropathic complications, such as the diabetic foot syndrome have also been observed.[4-6]

Early and effective intervention to bring plasma glucose, blood pressure and lipids to near-normal levels has shown to reduce the complication incidence.[2,7] It is important to avoid hypoglycemic episodes since polypharmacy that increases hypoglycemia and body weight is associated with unfavorable outcomes.[8-10] The drug class of dipeptidyl peptidase inhibitors (DPP-4i) has been introduced in the year 2006 and does not increase the incidence of hypoglycemia. DPP-4i inhibit the enzyme degrading the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP). This mode of action leads to a glucose dependent stimulation of insulin secretion and likewise glucose dependent inhibition of glucagon secretion. They are body weight neutral and well tolerated.[11]

Various DPP-4i have proved cardiovascular safety regarding a combined cardiovascular endpoint (MACE-3).[12-14] Sodium-glucose-transporter-2 inhibitors (SGLT-2i) became available in 2012. SGLT-2i inhibit the reabsorption of glomerularly filtrated glucose. They effectively lower glucose by this mode of action without intrinsic hypoglycemia risk. A loss of calories is also observed, leading to a clinically significant body weight loss in clinical studies. A slight volume depletion leads to a reduction of blood pressure.[15-17] The first cardiovascular outcome study with the SGLT-2i empagliflozin recently showed a significant

reduction in cardiovascular events (MACE-3), heart failure and also a reduction in renal endpoints.[18-20]

Both, DPP-4i and SGLT-2i are used in fixed doses for diabetes therapy and are therefore easy to use. So far, most substances are also available as fixed dose combinations with metformin. In 2015, a fixed dose combination of empagliflozin with linagliptin was approved by the Food and Drugs Administration (FDA). Most guidelines for the management of type 2 diabetes suggest a step-wise escalation of therapy in the progression of the disease[9,21] and only a few guidelines propagate an early combination therapy.[22,23] In this review, the preclinical and clinical study data of a combination of the SGLT-2i empagliflozin with the DPP-4i linagliptin are discussed and the potential and placement of this combination within the treatment algorithm of type 2 diabetes are highlighted regarding the efficacy- and safety profile.

Characteristics of linagliptin

Linagliptin, first approved in 2011, is a DPP-4i with a xanthine-based molecule structure. Regarding its pharmacology, linagliptin dissociates slowly from the active center of DPP-4 and is approximately 40,000-fold higher selective towards DPP-4 in comparison to other enzymes of the DPP peptidase family.[24-27] The DPP-4 inhibition of linagliptin is competitive and reversible. Almost 90% of DPP-4 activity is inhibited after oral administration of 5 mg linagliptin and the inhibition amounts to still 85% after 24 hours in humans, Linagliptin binds almost completely to plasma proteins[27,28] and steady state concentrations with the standard dose of 5 mg once daily are observed after 2-5 days with a DPP-4 inhibition of approximately 90%. Linagliptin elimination occurs by 90% unmetabolized excretion via the liver and bile with the feces.[27-30] All other DPP-4i (except for teneligliptin) have a renal route of elimination.[31] Due to the hepathobiliary elimination, linagliptin can be safely used therapeutically in the whole spectrum of kidney function without dose adjustments. Linagliptin has a side-effect profile comparable to other DPP-4i with regard to the most common side effects: respiratory side effects (nasopharyngitis, upper respiratory tract infection, and cough), dermatological side effects (urticaria and skin rashes) as well as back pain. Linagliptin (similarly to other DPP-4i) demonstrated non-inferiority in clinical studies compared to metformin and sulfonylureas regarding glycemic efficacy.[32] The intrinsic hypoglycemia risk with linagliptin is very low and it proved to be body weight neutral, therefore more patients reached a composite endpoint (consisting of a combination of

reaching an HbA1c <7% without hypoglycemia and without weight gain) compared to patients treated with sulfonylurea.[32] Linagliptin demonstrated a better safety profile regarding a combined cardiovascular endpoint, including stroke compared to glimepiride. This result may be explained by a higher incidence of hypoglycemia associated with glimepiride.[32] A still ongoing prospective cardiovascular safety study isinvestigating this hypothesis further.[33] GLP-1 plasma concentrations levels were increased fourfold after-meal tests with linagliptin administration.[34] Linagliptin reduced the HbA1c by approximately 0.7% in monotherapy[35] and by approximately 0.5% as an add on to metformin.[36] A reduction of HbA1c by approximately 0.6% was observed when linagliptin was added to metformin and sulfonylurea, but with an increase of symptomatic hypoglycemic episodes due to the sulfonylurea component.[37] Studies investigating an initial dual oral antidiabetic combination therapy with linagliptin as one agent (no combinations with sulfonlyurea) demonstrated a significantly higher efficacy of the combination in comparison to a monotherapy – without an increase in adverse events. No increase in hypoglycemia was observed. Initial combinations may be favorable in patients with marked hyperglycemia when metformin monotherapy might not be effective enough to reach treatment goals. A fixed dose combination in a single pill may also be suitable to reduce the daily tablet number and to simplify treatment regimes. This may help to improve medication adherence.[38-40]

Characteristics of empagliflozin

The SGLT-2i empagliflozin is a competitive and selective inhibitor of the sodiumglucose transporter SGLT-2. The selectivity towards SGLT-2 is 2,500-fold compared to SGLT1-. Single oral doses of empagliflozin from 0.5 mg to 800 mg showed no clinically significant side effects. It is absorbed rapidly with peak levels after 1.0–2.1 hours. The half-life is approximately 13 hours, making once daily dosing feasible. Empagliflozin can be effectively taken with or without food and is generally well tolerated with headache being the most common adverse event. In daily dosing, a steady-state concentration is reached within 6 days.[41-44] The observed urinary glucose excretion with empagliflozin amounts to approximately 65 g/day with a daily dose of 10 mg and 75-80 g/day with 25 mg.[10,41] Empagliflozin, like the other SGLT-2i reduces body weight due to the loss of calories caused by glucosuria.[45] Additionally, a reduction of blood pressure is observed. This is explained by osmotic diuresis, favorable developments in vascular resistance and arterial stiffness and the improvement of hypertension with loosing body weight.[46] Empagliflozin is quickly absorbed after oral administration. It is not metabolized in a significant manner and

eliminated primarily unaltered by urinary excretion and by excretion with the feces.[47] Empagliflozin was marketed in 10 and 25 mg tablets. The 10 mg dose once daily is primarily and initially recommended, a dose increase to 25 mg once daily should be considered, when glycemic goals are not reached.[48] Since glomerular glucose filtration is essential for its antidiabetic action, the glomerular filtration rate affects the efficacy and use of empagliflozin. Empagliflozin is contraindicated in patients with severe renal impairment, end-stage renal disease or on dialysis. Renal function should be assessed prior to initiation of empagliflozin treatment, and therapy should not be initiated (or should be discontinued if already being used) if the estimated glomerular filtration rate (eGFR) is less than 45 ml/min/1.73 m2.[48] The clinical study programme of empagliflozin was extensive.[16,49-54] In all trials, empagliflozin demonstrated an HbA1c-lowering efficacy comparable to sulfonylureaor DPP-4i treatment.[16,49-52] In a direct comparison with glimepiride, the hypoglycemia incidence affected 24% in the glimepiride treated patients vs. 2% in the empagliflozin arm. In this study, a significant change in body weight was also observed with a weight gain of 1.6 kg in the glimepiride treatment arm and a body weight loss of 3.2 kg in the patients on 25 mg empagliflozin once daily.[50] Empagliflozin also demonstrated significant reductions in glycemic parameters and good safety and tolerability in patients already on insulin.[53,54] In patients with renal impairment (eGFR 15–90 ml/min/1.73 m2), a significant reduction of HbA1c - 0.52% was observed in the patients with mild renal impairment and -0.42% in modest renal impairment. No significant HbA1c reduction was found in severe renal impairment.[58] These results suggest that empagliflozin can be safely used in all stages of type 2 diabetes and with all combinations. Furthermore, empagliflozin may be a favorable therapy in patients with mild to moderate renal impairment in view of the relatively few alternative treatment options in this special patient group. Regarding adverse events, post-marketing reports of ketoacidosis have emerged after the approval of SGLT2i, with a number of cases reporting minimal elevation of blood sugar (i.e., euglycemic ketoacidosis).[59] The US Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) have subsequently issued a warning alerting health care practitioners and patients to the signs and symptoms of ketoacidosis.[60]

Clinical studies using a combination of empaglozin and linagliptin

In clinicaltrials.gov a total of 11 studies investigating the combination of empagliflozin and linagliptin are listed. Of these, 7 studies are completed and 4 ongoing. Table 1 gives a complete detailed list of these studies. Table 2 comprises the respective pharmacological

characteristics of linagliptin and empagliflozin and their clinical efficacy and safety data. One study was published reporting efficacy and safety of linagliptin as add on therapy to either 10 or 25 mg/d empagliflozin in patients with type 2 diabetes already on metformin.[61] The addition of linagliptin lead to a significant further reduction of HbA1c.[61] Urinary tract infections were reported in 26 (7.4%) and 34 (9.6%) patients receiving empagliflozin 10 mg and 25 mg as add-on to metformin, respectively. The incidence was higher in female than in male patients.[61] Regarding sequential combination studies of the empagliflozin and linagliptin combination, a further study reported results on the efficacy and safety of empagliflozin versus placebo as add-on therapy in patients with inadequate glycemic control with linagliptin and metformin.[62] Empagliflozin given additionally significantly lowered the glycemic parameters and the body weight with both doses. Adverse events were more frequent in the placebo group compared to the 10 mg/d and 25 mg/d empagliflozin group (68.2%, 55.4%, and 51.8%, respectively). Adverse events were reported in less than 2% of patients. Urinary tract infections occurred in eight patients (7.3%) in the placebo group, in eight patients (7.1%) taking the 10 mg dose of empagliflozin 10 mg, and four patients (3.6%) with empagliflozin 25 mg. More female than male patients were affected. Genital infections affected two patients (1.8%) receiving placebo, two patients (1.8%) receiving empagliflozin 10 mg, and five patients (4.5%) receiving empagliflozin 25 mg; also with a higher proportion of females being affected. There were no reports of pancreatitis or diabetic ketoacidosis. Hypersensitivity reactions were reported with an incidence of less than 4.5% in each group maximally with no statistical difference.[62] Results from clinical studies with fixed dose combinations of empagliflozin and linagliptin have also been published.[56,57,63] One 52-week study was carried out in drug-naive patients using two empagliflozin/linagliptin fixed dose combinations (FDC): empagliflozin 10 mg with linagliptin 5 mg (E10/L5) and empagliflozin 25 mg with linagliptin 5 mg (E25/L5). In this study, both FDCs were compared with the respective free combinations.[56] A higher efficacy of the empagliflozin/linagliptin FDCs regarding glycemic parameters was observed after 52 weeks. Relative to linagliptin alone, E25/L5 and E10/L5 achieved significant adjusted mean differences in HbA1c (-0.66% [-0.90, -0.43] and - 0.71% [-0.94, -0.48], respectively; both $P < 0.001$). Similarly, significant mean differences in HbA1c were observed with E10/L5 vs. the low dose of empagliflozin, but not with E25/L5 vs. 25 mg of empagliflozin.[56] Mean differences in body weight and fasting plasma glucose at 52 weeks with the FDCs were significant versus linagliptin, but not compared to both single doses of empagliflozin. No significant treatment differences in changes from baseline in both systolic or diastolic blood pressure were observed.[56] In

another study investigating the efficacy and safety of the FDCs as second line therapy in patients not sufficiently controlled on a metformin therapy, both FDCs showed significant mean differences in HbA1c and fasting plasma concentrations compared with the respective mono-treatments after 24 and 52 weeks.[57] A higher proportion of patients achieved an HbA1c < 7% with E25/L5 (61.8%) and E10/L5 STCs (57.8%) than with a respective mono-add-on therapy to metformin (32.6%, 28.0% and 36.1% with E25, E10 and L5, respectively). The bodyweight reduction with the FDCs were significantly higher compared to linagliptin mono-treatment but not vs. the two empagliflozin mono-components. As in the other study testing the FDCs, the efficacy on glycemic parameters was maintained over the whole 52 weeks. Adjusted mean differences in systolic and diastolic blood pressure values at 52 weeks were significant between the FDCs and linagliptin alone (-3.8 mmHg [-6.5, -1.2] and -1.6 mmHg [-3.2, 0] with E25/L5; –3.1 mmHg [-5.7, -0.4] and - 1.6 mmHg [-3.2, 0] with E10/L5), but not between the FDCs and the empagliflozin only.[57] The safety profiles of the fixed dose combinations were comparable to the safety data generated from the mono-component trials.

Expert opinion

Progression of type 2 diabetes necessitates treatment intensification in most patients. Most guidelines place metformin as first-line pharmacological treatment after life-style intervention. The further treatment escalation steps leave several choices. The proposed patient-centered individual treatment strategy draws a focus not only on the glycemic efficacy, but also on other characteristics, like blood pressure and other cardiovascular effects, side effects, especially on the intrinsic risk for hypoglycemia and effects on body weight. A combination therapy with a DPP-4i and a SGLT-2i combines complementary effects with the glucose-dependent stimulation of insulin secretion and glucose dependent inhibition of glucagon secretion by a DPP-4i with the insulin-independent action of excess glucose elimination by a SGLT-2i. Both drug classes lack a hypoglycemia risk and direct interactions reducing efficacy of either substance or safety and tolerability. The combination also offers favorable non-glycemic effects on a reduction of blood pressure and a reduction in body weight. The efficacy and safety for such a combination has been shown as initial therapy[56] as well as for the addition to metformin. In this constellation, positive efficacy and safety data not only exist for a DPP-4/SGLT-2i combination of empagliflozin and linagliptin, but also for dapagliflozin and saxagliptin.[64] The treatment escalation can be initiated in single steps from metformin therapy to a triple therapy when progression is slow and reaching the treatment goals with the addition of one compound after another is realistic. In

case of an overt progression of glycemic deterioration, the treatment intensification form metformin monotherapy could be the start of an immediate oral triple therapy. Of course, there is also the option for treatment escalation with very efficacious injectable therapies (GLP-1 receptor agonists and/or insulin), but the hurdle of an injectable therapy as well as the higher therapy costs and the hypoglycemia risk associated with insulin treatment have to be considered. In patients already on metformin and a basal insulin, a further dose increase of basal insulin or the intensification of an insulin therapy to more complex insulin regimes (e.g. basal bolus regime) may be protracted or avoided by adding a DPP-4i and a SGLT-2i without a significant increase of hypoglycemia and with the concomitant effect to even decrease the insulin dose and to reduce body weight.[65,66] On the other hand, a recent study showed almost additive and very effective lowering of HbA1c, body weight and blood pressure with a triple combination of metformin, dapagliflozin and the GLP-1 receptor agonist exenatide once weekly . Most DPP-4i and SGLT-2i are available as monosubstances as well as FDCs with metformin, including empagliflozin and linagliptin. Such a combination tablet may also be a treatment alternative for patients not tolerating metformin or with metformin contraindications. In treatment naïve patients, an initial combination of a DPP-4 inhibitor and an SGLT-2i reduced the HbA1c by 1.08-1.47%, depending on the study setting and the respective study results.[56] The FDCs reduce the daily tablet load and may increase medication adherence and treatment satisfaction. In cardiovascular safety studies, three DPP-4i have shown cardiovascular safety rearding the primary endpoint.[12-14] In the study with saxagliptn, however, there was an increase in the hospitalizations due to heart failure.[13] The still ongoing large cardiovascular safety studies CARMELINA (ClinicalTrials.gov Identifier: NCT01897532) and CAROLINA (ClinicalTrials.gov Identifier: NCT01243424) will characterize the cardiovascular safety of linagliptin further. These data are necessary before a final evidence based evaluation of a combination of linagliptin and empagliflozin vs. established standard therapies can occur. Data on cardiovascular superiority compared to conventional standard type 2 diabetes therapy became obvious in the EMPA-REG Outcome trial showing a significant reduction of cardiovascular death, the 3-point MACE and parameters for microvascular renal disease progression with empagliflozin. Additionally, the rate of hospital admissions due to heart failure was lower during empagliflzin therapy (18-20). Due to these study findings, empagliflozin recently received a label extension by the FDA and EMA for the treatment of the cardiovascular risk constellation that was prevalent in this study. The FDC of linagliptin and empagliflozin should undergo a cardiovascular endpoint study in order to show if the potentially beneficial effects are only driven by

empagliflozin or if there is an additive effect of both substances (in case CARMELINA or CAROLINA turn out with superiority for linagliptin).

METHODOLOGY

Six months Interventional study design on 50 patients was conducted at RVM hospital Ethical committee has approved.

ETHICAL COMMITTEE APPROVAL

The ML was diagnosed using the USG abdomen and Wong Bakers' pain scale.

The Institutional Human Ethical Committee of GCPK approved the study. The code is given-GCPK/IEC/NOV2021-22/B08.

SELECTION OF SUBJECTS

INCLUSION CRITERIA

- Uncontrolled diabetes patient
- Patients of all genders
- Patients aged 30-79 years
- Patients of our study site
- Outpatients and inpatients.

EXCLUSION CRITERIA

- Pregnant woman
- Lactating woman
- Patients < 30 years and > eighty years.
- Patients of oncology d0epartment
- Ketoacidosis in DM patients, genito UTI

COLLECTION OF DATA: From patient and patient case report.

STATISTICALANALYSIS

Descriptive statistics presentation of data in Bar chart, Pie chart values shown as Frequency, percentage, mean, SD and SE. Comparison of mean **FBS, PBS, AND HBA1C** values Before and follow up by using paired t-test. In all analyses, $P<0.05$ was considered significant. SPSS statistical software, version 22, is employed to conduct all the statistical analyses.

TABLE 2.

Age(Years)	Frequency	Percent
25 to 35	6	12
36 to 45	12	24
46 to 55	16	32
56 to 65	10	20
66 to 75	6	12
Total	50	100

TABLE 3.

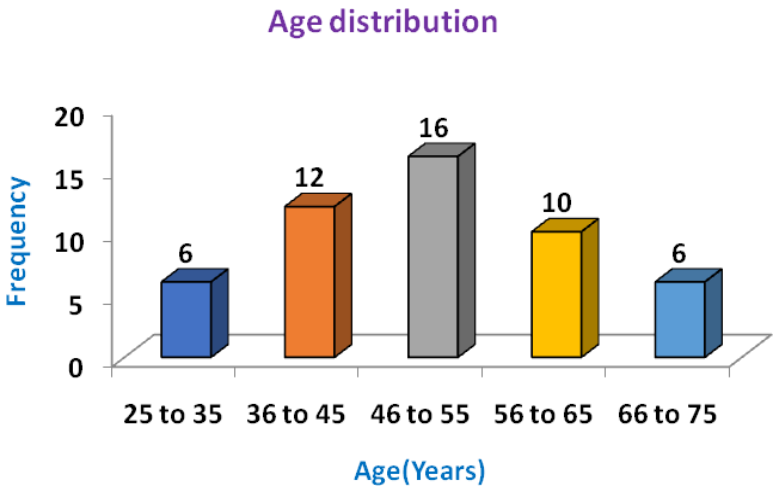

Figure 7.

Table 4.

Gender	Frequency	Percentage
Male	21	42
Female	29	58
Total	50	100

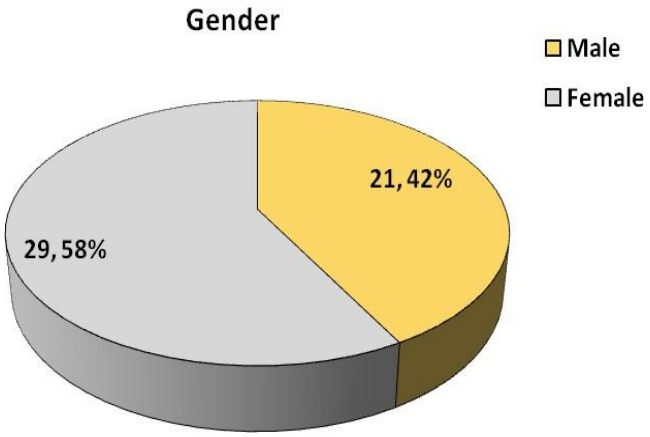

Figure 8.

Table 5.

Parameter	N	Minimum	Maximum	Mean	SD
Na	50	127	147	138.22	4.60
K	50	3	5	4.16	0.55
UREA	50	17	98	40.30	21.81
SR.Cr	50	1	9	1.60	1.33

Table 6.

Gender	Parameter	N	Minimum	Maximum	Mean	SD
Male	Na	21	127	147	138.71	5.60
	K	21	3	5	4.05	0.59
	UREA	21	20	98	41.33	21.79
	SR.Cr	21	1	4	1.48	0.75
Female	Na	29	130	145	137.86	3.79
	K	29	3	5	4.24	0.51
	UREA	29	17	91	39.55	22.18
	SR.Cr	29	1	9	1.69	1.63

Table 7.

FBS	Parameter	Mean	Mean difference	t-value	Sig.
Pair 1	Before	224.88±75.07	53.66	5.73	0.0000*
	After	171.22±53.35			
Pair 2	Before	224.88±75.07	70.2	7.7	0.0000*
	1^{ST} MONTH	154.68±43.13			
Pair 3	Before	224.88±75.07	83.88	8.51	0.0000*
	2^{ND} MONTH	141±38.60			
Pair 4	Before	224.88±75.07	96.78	9.9	0.0000*
	3^{RD} MONTH	128.1±32.60			

*- P<0.05; FBS values are significant in terms of statistics between before, after, 1ST MONTH, 2ND MONTH, AND 3RD MONTH by using paired Student t-test.

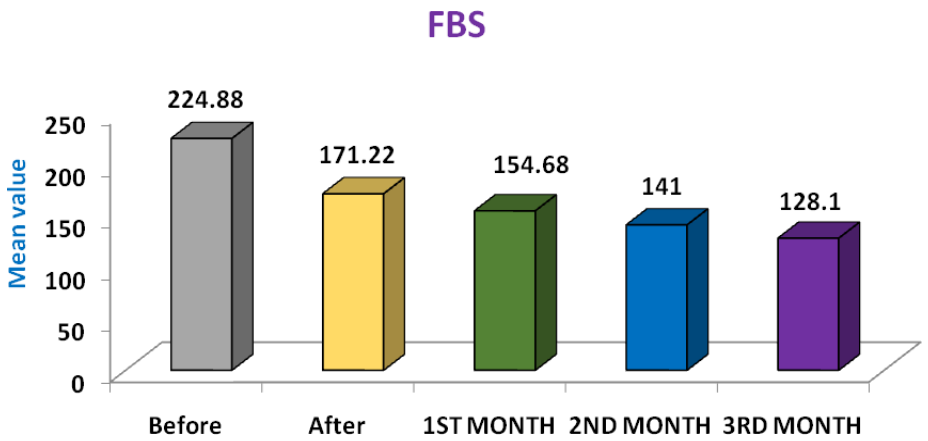

FIGURE 9.

Table 8.

PBS	Parameter	Mean	Mean difference	t-value	Sig.
Pair 1	Before	332.88±87.70	89.56	8.71	0.0000*
	After	243.32±84.37			
Pair 2	Before	332.88±87.70	114.34	7.34	0.0000*
	1ST MONTH	218.54±74.10			
Pair 3	Before	332.88±87.70	132.82	12.25	0.0000*
	2ND MONTH	200.06±58.25			
Pair 4	Before	332.88±87.70	153.72	13.46	0.0000*
	3RD MONTH	179.16±54.65			

*- P<0.05; PBS values are significant in terms of statistics between before, after, 1ST MONTH, 2ND MONTH, AND 3RD MONTH by using paired Student t-test.

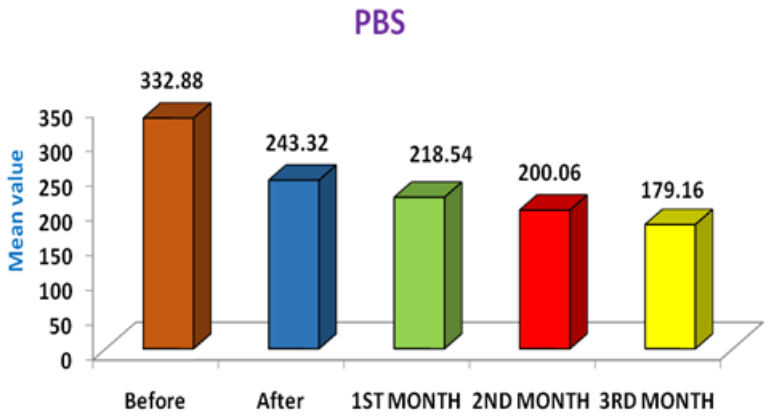

Figure 10.

Table 9.

HbA1C	Parameter	Mean	Mean difference	t-value	Sig.
Pair 1	Before	8.266±1.30	0.32	4.44	0.0000*
	After	7.95±1.077			
Pair 2	Before	8.266±1.30	0.54	5.49	0.0000*
	1ST MONTH	7.73±0.97			
Pair 3	Before	8.266±1.3019	0.77	6.93	0.0000*
	2ND MONTH	7.492±0.93			
Pair 4	Before	8.266±1.30	0.99	7.70	0.0000*
	3RD MONTH	7.272±0.87			

*- P<0.05; HBA1C values are significant in terms of statistics between before, after, 1ST MONTH, 2ND MONTH, AND 3RD MONTH by using paired Student t-test.

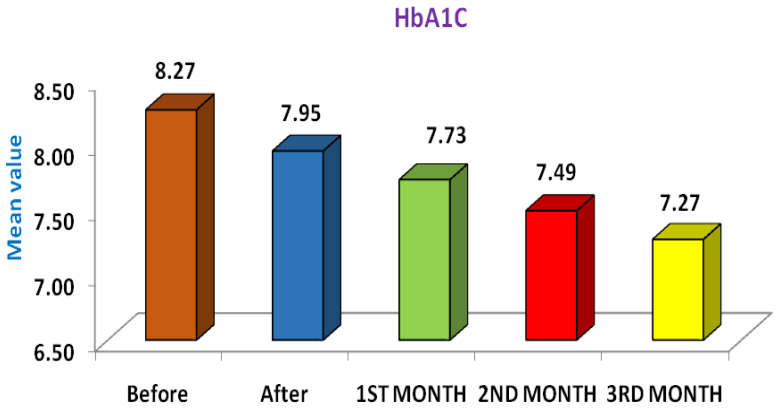

Figure 11.

Table 10.

UTI risk	Frequency	Percent
Yes	8	16
No	42	84
Total	50	100

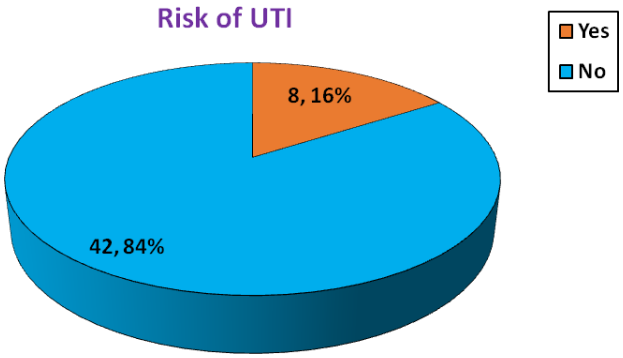

Figure 12.

Table 11.

Hypoglycemia risk	Frequency	Percent
Yes	3	6
No	47	94
Total	50	100

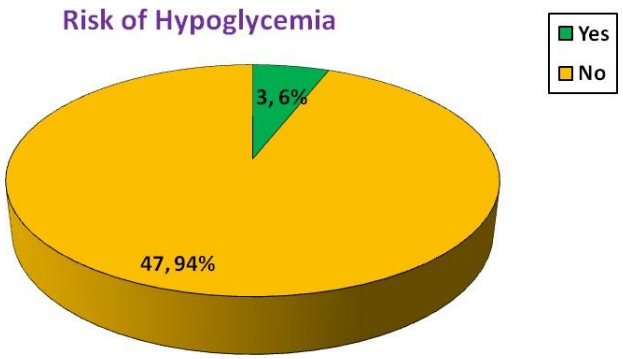

Figure 13.

DISCUSSION

In the current study, 50 patients who had attended both outpatient and inpatient departments identified with T2DM are treated using the combination of treatments drugs empagliflozin 10mg dose and linagliptin of 5mg dose. Out of them, 21 are male and 29 are female. Female showing predominance. Out of 50, 8 patients(16%) had developed UTI and 3 patients (6%) had developed hypoglycemia. Lab investigations of FBS, PBS, HbA1C, and renal function test was performed. The high glucose level in the blood indicates T2DM. It shows a greater decline in glucose levels with empagliflozin and linagliptin. The lab investigation was done prior to examining the subject's glucose concentration levels in the blood and immediately after the drug administration, further, it is performed once every monthfor three months. UTI and hypoglycemia are often prone to happen when treated with empagliflozin and linagliptin A hypoglycaemic situation happens when a patient havingDM doesn't have enough glucose in their bloodless than 70mg /dl following the administration of medication. A UTI situation happens when a patient having DM gives a favorable environmentto pathogens that develop due to the existence of elevated glycemia and frequent urination. These parameters are expressed as frequency, Percentage, standard deviation, mean andstandard error. Values are statistically reliable by paired sample-T test 5.

CONCLUSION

- The dose administration was used to determine the reduction in blood glycemia.
- Following treatment, patient symptoms and signs improved noticeably.
- Analysis of FBS, PBS, HbA1C, and renal function test has drastically reduced the intensityof the symptoms and reduced blood glycemia level.
- Out of 50 patients, who received the drug, after administration, 8 patients reported UTI and3 patients reported hypoglycemia.

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