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Original Research Paper

Diabetology

EFFICACY AND SAFETY OF CANAGLIFLOZIN COMPARED WITH LINAGLIPTIN IN INDIAN PATIENTS WITH TYPE-2 DIABETES MELLITUS INADEQUATELY CONTROLLED ON METFORMIN: AN OPEN LABEL, RANDOMIZED STUDY

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ABSTRACT

Aims This pilot study aims to compare the efficacy and safety of canagliflozin versus linagliptin in Indian patients with type-2 diabetes mellitus (T2DM) inadequately controlled with metformin. **Methods** Eighty patients were randomized to receive either canagliflozin (100 mg/day, n=40) or linagliptin (5 mg/day, n=40) for 3 months. The primary endpoints were change from baseline to month 3 in fasting plasma glucose (FPG), 2-h post prandial glucose (2-h PPPG), glycated hemoglobin (HbA1c), insulin resistance (homeostatic model assessment for insulin resistance, HOMA-IR) with canagliflozin versus linagliptin. **Results** The changes in glycemic parameters was significantly better with canagliflozin as compared to linagliptin (FPG [mg/dL]: canagliflozin -44.10±18.88, linagliptin, -27.71±12.85; 2-PPPG [mg/dL]: canagliflozin -72.27±36.84, linagliptin -42.17±22.72; HbA1c [%]: canagliflozin -0.70±0.42, linagliptin -0.48±0.30). Both treatments significantly improved insulin resistance (HOMA-IR: canagliflozin -0.37±0.21, linagliptin, -0.20±0.14, both P≤0.0001; HOMA-β: canagliflozin 354.82±297.14, linagliptin 219.30±171.53, both P≤0.0001 and C-peptide (nmol/L): canagliflozin -0.43±0.39, linagliptin -0.13±0.23, both P≤0.0001) from baseline. Significant improvements in fasting insulin (P≤0.0001), HOMA-IR (P≤0.0001), HOMA-β (P=0.014), C-peptide (P≤0.0001), reduction in body weight (P≤0.0001) and diastolic BP (P≤0.0001) were observed with canagliflozin as compared to linagliptin. **Conclusion** Canagliflozin as compared to linagliptin improved glycemic control, reduced body weight, diastolic BP, improved β-cell function and reduced insulin resistance in T2DM patients inadequately controlled with metformin.

KEYWORDS : canagliflozin, linagliptin, metformin, sodium glucose co-transporter 2 (SGLT2) inhibitor, type-2 diabetes mellitus

INTRODUCTION

Diabetes mellitus is a global pandemic with staggering consequences that challenge public healthcare systems worldwide [1]. In 2017, nearly 425 million adults were living with diabetes globally, and over 72 million people with diabetes were from India [2]. Type-2 diabetes mellitus (T2DM) is the most prevalent form of diabetes that leads to microvascular and macro-vascular complications. These include end-stage renal disease, lower extremity amputations, blindness and cardiovascular morbidity that have profound physiological, psychological and physical implications affecting both patients and caregivers and impose enormous burden on healthcare expenditures [3, 4]. Current treatment guidelines recommend treatment with biguanides as a first line treatment option [5, 6]. However, progressive nature of the disease or side effects of metformin such as gastrointestinal adverse events and vitamin B12 deficiency with long-term use, can lead to challenges in the management of hyperglycemia in patients with T2DM [7], often necessitating treatment with combination therapy including insulin or other oral anti-hyperglycemic agents (AHAs) [5, 6]. Newer AHAs such as dipeptidyl peptidase-4 inhibitors (DDP4i) and sodium-glucose co transporter type-2 inhibitors (SGTL2i) have distinct benefit/risk profile and in addition to glycemic control help improve other metabolic comorbidities associated with T2DM [8-10].

The SGLT2i possess unique pharmacological properties of reducing renal threshold of glucose reabsorption and increasing renal glucose excretion, resulting in loss of calories, and reduction of body weight and systolic blood pressure (BP). These beneficial effects on glycemic control with SGLT2i are achieved without causing hypoglycemia and are independent of insulin secretion [8, 11].

The DPP4i lower blood glucose levels by preventing the degradation of the incretin hormones such as glucagon like peptide-1 (GLP1) and glucose-dependent insulinotropic peptide, resulting in an increase in the stimulation of insulin secretion and the inhibition of glucagon secretion in a glucose-dependent manner [12]. Most of the available DPP4i except linagliptin and teneligliptin require dose adjustment in patients with renal impairment [13-15]. Both SGLT2i and DPP4i have demonstrated improved efficacy with manageable safety profile in patients with T2DM and both drug classes have certain advantages and disadvantages based on the mechanism of action of the drugs. [16, 17]. Although, there are very few studies of head-to-head comparison between these two drug classes, efficacy of SGLT2i and DPP4i in terms of improved glycemic control in patients with T2DM has been evaluated both as a monotherapy and as an add-on therapy to metformin, other AHAs and insulin-based therapies [18, 19]. The efficacy of SGLT2i versus DPP4i has been demonstrated in a 56 week follow-up study in T2DM patients on background metformin wherein patients received canagliflozin and placebo for 26 weeks and on completion of 26 weeks, patients on placebo were switched to receive sitagliptin, while canagliflozin was continued as is up to week 56. The study demonstrated non-inferiority as well as statistical superiority of canagliflozin versus sitagliptin in terms of reduction in glycated hemoglobin (HbA1c, P < 0.001) in addition to significant reduction in body

weight (P < 0.001), fasting plasma glucose (FPG, P < 0.001), and systolic BP (P < 0.001) [20]. However, these studies were conducted in the Western population and no comparative study data between SGLT2i and DPP4i is available in the Indian population. In this pilot study, we compared canagliflozin with linagliptin in a head-to-head study to determine efficacy in terms of glycemic control and insulin resistance and assessed the safety profile in Indian patients with T2DM inadequately controlled with metformin.

MATERIALS AND METHODS

The study was conducted at the Nil Ratan Sircar (NRS) Medical College and Hospital, Kolkata from April 2017 to September 2018.

Study Design

This pilot study was a 12 week, open-label, longitudinal, prospective, intervention study comparing the efficacy, insulin resistance and safety of SGLT2i, canagliflozin (100 mg/day) with DPP4i, linagliptin (5 mg/day) as add-on to metformin in patients with T2DM inadequately controlled on metformin with respect to glycemic control.

The study protocol was reviewed and approved by the Institutional Ethical Committee (IEC) of NRS Medical College and Hospital, Kolkata, India. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and in accordance with the International Conference on Harmonization's Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the approved protocol. All patients provided written informed consent prior to study participation.

Participants

Patients with recently detected (≤12 months) T2DM (30-60 years), on metformin monotherapy 1500 mg or maximum tolerable dose, HbA1c 7%-9% and FPG ≤200 mg/dL, and two hour post prandial plasma glucose (2-h PPPG) ≤350 mg/dL were enrolled in this study. Patients with history of active urinary tract infection/in recent past (<6 months)/recurrent episodes (≥2 episodes in last 6 months and ≥3 episodes in last 12 months), active genital mycotic infection /in recent past (<6 months), known anatomical abnormalities in genitourinary tract like BHP (treated and untreated), calculus, ketosis at any time after diagnosis of diabetes, pancreatitis in past, malignancy, estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m^2 (measured by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine 2009 equation) [21], type 1 diabetes mellitus, chronic liver disease (CLD), chronic heart failure (CHF) on diuretics, or critically ill, pregnant or lactating were excluded.

Treatment was discontinued in cases where a urinary tract infection, genital mycotic infection, ketosis and pancreatitis was observed. For all other adverse drug reactions, the treatment was immediately stopped, and patients were switched to another oral hypoglycemic agent.

Assessments

Primary Endpoint

The primary endpoints were change from baseline to month 3 in FPG, 2-h PPPG, HbA1c, insulin resistance (homeostatic model assessment for insulin resistance, HOMA-IR) with canagliflozin versus linagliptin treatment and to assess the safety of canagliflozin in terms of adverse events such as genital mycotic infection, urinary tract infection and ketosis.

The secondary endpoints included change from baseline to month 3 in blood pressure (BP), weight, lipid profile, renal function (serum creatinine), serum electrolytes (Na^+ and K^+). Change from baseline to month 3 in hematocrit, fasting insulin, fasting C-peptide, fasting serum ketone, routine urine examination, aerobic urine culture, albumin/creatinine ratio (ACR) and urinary glucose excretion were assessed. The routine clinical evaluations (BP and body weight) and thorough laboratory investigations (FPG, 2-h PPPG, hematocrit, serum ketone, serum Na^+ and K^+, routine urine and urine culture) were performed every four weeks and repeated at week 12. In addition, HbA1c, spot urine for ACR, fasting C-peptide, fasting insulin and 24-h urinary glucose excretion were performed at week 12. ACR was assessed using spot urine and urinary glucose excretion was measured by from baseline up to 24 h post dosing.

Study Treatment

Patients with T2DM were randomized (1:1) to receive either canagliflozin (100 mg once daily [OD]) or linagliptin (5 mg OD) during the three-month study period. The patients were randomized using a randomization table. Patients in both the groups were allowed to take metformin (tablet, ≤1500 mg/day or the maximal tolerable dose).

Statistical Analysis

The data were tabulated in a master chart and statistically analyzed to assess demographic and clinical parameters. Standard statistical methods like mean, median, standard deviation, frequency, coefficients of correlation and dispersion were used to assess the data. Data was represented through graphs and figures to convey appropriate statistical information.

RESULTS

Patient Disposition And Baseline Characteristics

A total of 140 patients were screened and 80 patients were randomized (1:1) to receive either canagliflozin or linagliptin, of which 80 patients completed the study period. Sixty patients were screen failures and were not randomized as they did not meet the pre-specified inclusion/exclusion criteria (Supplementary figure 1). Demographic and baseline characteristics were generally similar across groups (Table 1). Mean age was 48.28±6.86 and 47.45±7.44 years with linagliptin and canagliflozin, respectively and majority of the patients were men (≥55% with linagliptin or canagliflozin). Baseline glycemic control reflected mild to moderate hyperglycemia, with baseline HbA1C (%) of 8.00±0.52 and 8.07±0.44 with canagliflozin and linagliptin, respectively.

Effect On Glycemic Variables

At Month 3, both canagliflozin and linagliptin significantly reduced FPG (mg/dL; canagliflozin: -44.10±18.88; linagliptin, -27.71±12.85; both P≤0.0001), 2-h PPPG (mg/dL; canagliflozin: -72.27±36.84; linagliptin, -42.17±22.72; both P≤0.0001) and HbA1c (%; canagliflozin: -0.70±0.42; linagliptin, -0.48±0.30; both P≤0.0001) from baseline in patients with T2DM (Table 2). However, treatment with canagliflozin resulted in significantly higher reduction in FPG (P≤0.0001), 2-PPPG (P≤0.0001) and HbA1c (P≤0.01) versus linagliptin (Figure 1, Table 2) in these patients.

Effect On Insulin Resistance

At month 3, fasting insulin resistance (Insulin/FI) improved significantly with canagliflozin (-0.29±0.30, P=0.001). Significant improvements in HOMA-IR were observed for both canagliflozin (-0.37±0.21, P≤0.0001) and linagliptin (-0.20±0.14, P≤0.0001). The β-cell function as determined from HOMA-β improved significantly with both canagliflozin (354.82±297.14, P≤0.0001) and linagliptin (219.30±171.53, P≤0.0001). C-peptide levels (nmol/L) were higher in both the treatment groups at baseline (canagliflozin: 3.35±0.76, P≤0.0001; linagliptin, 3.36±0.61, P≤0.0001) and were reduced significantly at Month 3 with both canagliflozin (-0.43±0.39, P≤0.0001) and linagliptin (-0.13±0.23, P≤0.0001). Treatment with canagliflozin resulted in significant improvement in fasting insulin (P≤0.0001), HOMA-IR (P≤0.0001), HOMA-β (P=0.014) and C-peptide (P≤0.0001)

versus linagliptin (Figure 2).

Effect on body weight, BP and lipids

At Month 3, canagliflozin resulted in a significant reduction in body weight from baseline (-1.29±1.25 Kg, P≤0.0001), no significant reduction in body weight was observed with linagliptin (-0.20±0.51 Kg, P=0.019; Table 2). Canagliflozin resulted in consequent reduction in both systolic BP (-1.51±1.86 mmHg, P≤0.0001) and diastolic BP (-1.37±1.61 mmHg, P≤0.0001) from baseline. Treatment with canagliflozin resulted in significant reduction in body weight (P≤0.0001) and diastolic BP (P≤0.0001) as compared to linagliptin. However, no significant difference between canagliflozin and linagliptin for systolic BP (P=0.106) and LDL-C levels (P=0.429) were observed.

Safety

No significant changes in routine laboratory investigation from baseline in serum potassium, and serum ketones were observed at month 3 with canagliflozin or linagliptin or between canagliflozin versus linagliptin (Table 3). A significant reduction from baseline in serum sodium was observed with linagliptin, while the change from baseline for canagliflozin and between canagliflozin versus linagliptin was non-significant. A significant increase from baseline in spot urine ACR (3.88±4.37, P≤0.0001), and hematocrit (1.29±1.93, P≤0.0001) was observed with canagliflozin. No significant change in spot urine ACR (-0.88±2.81, P=0.052) and hematocrit (-0.24±1.96, P=0.430) were observed with linagliptin. The eGFR levels reduced significantly with canagliflozin (-3.10±6.01 mL/min/1.73 m^2, P=0.002), while no significant change in eGFR was observed with linagliptin (0.24±6.08 mL/min/1.73 m^2, P=0.799). There were no deaths or serious treatment-emergent adverse events (TEAEs) or study discontinuation due to an adverse event.

DISCUSSION

In this pilot study of patients with T2DM on background metformin, treatment with canagliflozin resulted in significant reduction in FPG, 2-h PPPG, HbA1c, body weight, systolic BP, and significant improvement in fasting insulin, HOMA-IR and HOMA-β versus linagliptin at month 3.

The improvements in HbA1c, FPG, 2-h PPPG from baseline with canagliflozin are in concordance with the previously reported data from global studies [22, 23]. Further the current findings complement and support the findings of another study wherein improvement in glycemic control along with reduction in body weight was observed with canagliflozin versus DPP-4i [20, 24]. The reduction in weight loss with canagliflozin is an additional beneficial factor that may not only improve glucose tolerance, BP and lipid levels but may also affect cardiovascular profile of patients with diabetes [5, 17]. Progressive loss of β-cell function and a consequent progressive reduction in insulin release is a hallmark in patients with T2DM [25]. In the current study, we observed statistically significant improvement in both β-cell functioning (HOMA-β) as well as reduction in insulin resistance (HOMA-IR) with canagliflozin versus linagliptin. The current findings are in agreement with earlier reports which observed improvement in β-cell functioning as a result of reversal of hyperglycemia with SGLT2i treatment [26-28].

A significant increase in spot urine ACR with canagliflozin from baseline as well as between canagliflozin versus linagliptin [29, 30] was observed, which was not consistent with earlier reported findings. A significant drop in eGFR was observed with canagliflozin as compared to linagliptin, which is attributed to increased intra-glomerular afferent arteriolar tone [31]. However, studies have observed that this effect is completely reversible [30]. Earlier studies have observed an increase in hematocrit with both canagliflozin and linagliptin, which is presumed to be related with enhancement of erythropoiesis in addition to the diuretic effects resulting in hemo-concentration [32].

In line with the previous findings, an increase in hematocrit levels from baseline with both canagliflozin and linagliptin was observed. Further, a significant increase in hematocrit concentration with canagliflozin as compared to linagliptin was observed. The increased hematocrit levels with canagliflozin as compared to linagliptin may indicate an improvement in hypoxia, oxidative stress and a recovery form reversible tubulointerstitial injury [32]. The increase in hematocrit can contribute to improved cardiac efficiency and can be beneficial in patients with T2DM with cardiovascular disease. The significant elevation in the canagliflozin arm and decrease in the linagliptin arm of the Spot Urine ACR values was unexpected and is unexplainable. However, the linagliptin findings are in line with the findings of CARMELINA study [33]. The small number of patients recruited, and short duration follow up makes interpretation of these apparently discrepant results untenable.

The current study has some inherent limitations such as the open-label design, small sample size and short study duration. However, though a pilot study, it is strengthened by its active-controlled design, allowing a direct comparison of canagliflozin versus linagliptin. Additionally, the study population i.e., Indian patients with T2DM provides a direct evidence on efficacy and safety of canagliflozin as compared to linagliptin rather than extrapolating the findings from global studies or those performed with Asian/predominantly Asian patients.

CONCLUSION

In this pilot study, treatment with canagliflozin versus linagliptin significantly improved glycemic control, reduced body weight and systolic blood pressure and improved β-cell functioning, and reduced insulin resistance in T2DM patients inadequately controlled with metformin. This multidimensional improvement can aid in alleviating the micro- and macro- vascular complications associated with T2DM. These findings although preliminary, can guide the physicians to select a second line anti hyperglycemic agent for patients with T2DM refractory to metformin.

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Table 1: Baseline demographics

Baseline characteristics	Canagliflozin100 mg OD (n=40)	Linagliptin 5 mg OD (n=40)
Sex		
Men, n (%)	23 (57.50)	22 (55.00)
Age, years	47.45±7.44	48.28±6.86
Body weight, kg	73.10±8.47	73.88±8.50
BMI, kg/m2	26.12±2.52	26.02±2.97
HbA1c, % (mmol/mol)	8.00±0.52	8.07±0.44
Fasting plasma glucose, mmol/L	182.95±9.01	182.93±9.01
eGFR, mL/min/1.73 m2	96.03±16.18	91.48±14.43
All values are mean±SD unless otherwise stated Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin		

Table 2: Summary of change from baseline to Month 3 in clinical parameters

	Canagliflozin (n=40)			Linagliptin (n=40)			Canagliflozin versus Linagliptin
Parameter	Baseline	Change from baseline	P - value	Baseline	Change from baseline	P - value	P –value
Body weight, kg	73.10±8.47	-1.29±1.25	≤0.0001	73.88±8.50	-0.20±0.51	0.019	≤0.0001
BMI, kg/m2	26.12±2.52	-0.47±0.46	≤0.0001	26.02±2.97	-0.06±0.17	0.020	≤0.0001
Systolic BP, mmHg	138.85±10.91	-1.51±1.86	≤0.0001	139.40±11.30	-0.76±2.30	0.042	0.106
Diastolic BP, mmHg	84.33±8.13	-1.37±1.61	≤0.0001	84.55±8.09	0.02±1.01	0.878	≤0.0001
FPG, mg/dL	182.95±9.01	-44.10±18.88	≤0.0001	182.93±9.01	-27.71±12.85	≤0.0001	≤0.0001
2-h post prandial PG, mg/dL	268.00±39.94	-72.27±36.84	≤0.0001	269.40±39.30	-42.17±22.72	≤0.0001	≤0.0001
HbA1c, %	8.00±0.52	-0.70±0.42	≤0.0001	8.07±0.44	-0.48±0.30	≤0.0001	0.007
24-h urinary glucose excretion, mg/dL	695.63±144.89	409.15±280.90	≤0.0001	695.18±138.17	-47.24±72.74	≤0.0001	≤0.0001
HOMA-β	766.88±225.66	354.82±297.14	≤0.0001	765.06±232.33	219.30±171.53	≤0.0001	0.014
C-peptide, nmol/L	3.35±0.76	-0.43±0.39	≤0.0001	3.36±0.61	-0.13±0.23	≤0.0001	≤0.0001
Insulin/FI	2.54±0.72	-0.29±0.30	≤0.0001	2.54±0.76	-0.06±0.19	0.087	≤0.0001
HOMA-IR	1.15±0.33	-0.37±0.21	≤0.0001	1.15±0.35	-0.20±0.14	≤0.0001	≤0.0001
LDL-C, mg/dL (mmol/L)	113.55±12.84	-4.29±9.61	0.007	117.90±11.76	-2.78±7.50	0.022	0.429

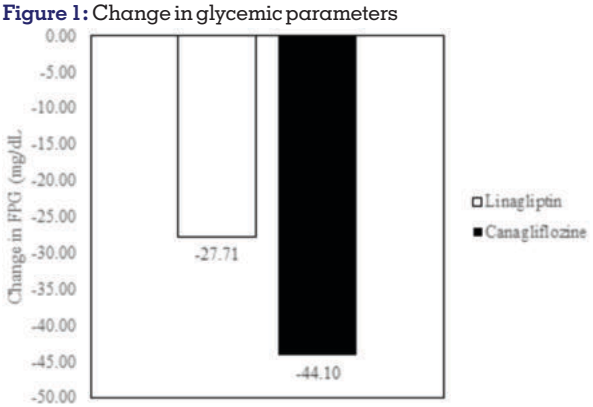
All values are mean±SD unless otherwise stated
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; Insulin/FI, fixed insulin; 2-h PPPG, 2 hour post prandial plasma glucose; LDL-C, low density lipoprotein-cholesterol

Table 3: Summary of change from baseline to Month 3 in safety parameters

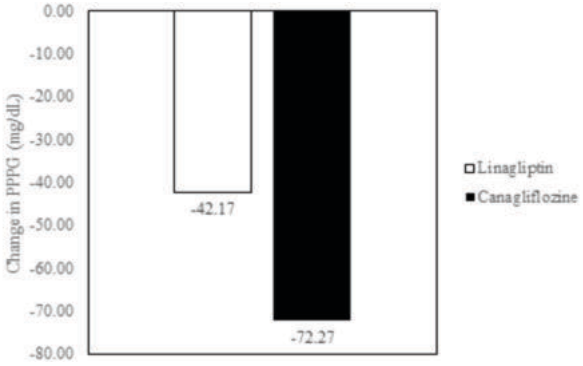
	Canagliflozin (n=40)			Linagliptin (n=40)			Canagliflozin versus Linagliptin
Parameter	Baseline	Change from baseline	P - value	Baseline	Change from baseline	P - value	P - value
Serum creatinine, µmol/L	0.86±0.14	0.03±0.06	0.001	0.86±0.13	0.00±0.07	0.812	0.013
eGFR, mL/min/1.73 m2	96.03±16.18	-3.10±6.01	0.002	91.48±14.43	0.24±6.08	0.799	0.014
Sodium, mmol/L	139.23±4.08	-0.34±7.54	0.773	139.83±3.34	-1.17±3.37	0.032	0.523
Potassium, mmol/L	3.98±0.41	-0.11±0.41	0.129	4.00±0.31	0.05±0.18	0.084	0.025
Spot urine ACR	22.83±6.03	3.88±4.37	≤0.0001	23.80±4.79	-0.88±2.81	0.052	≤0.0001
Serum ketone, mmol/L	0.16±0.05	0.00±0.07	0.728	0.16±0.05	0.00±0.05	0.534	0.849
Hematocrit	42.40±4.17	1.29±1.93	≤0.0001	41.25±3.96	-0.24±1.96	0.430	0.001

All values are mean±SD unless otherwise stated
Abbreviations: ACR, albumin-to-creatinine ratio

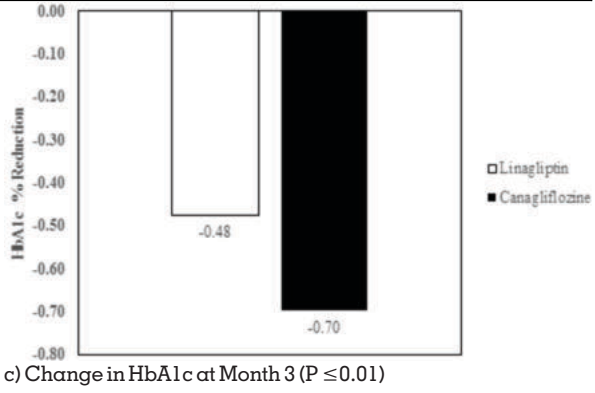
Figure 1: Change in glycemic parameters



a) Change in fasting plasma glucose at Month 3 (P ≤0.001)

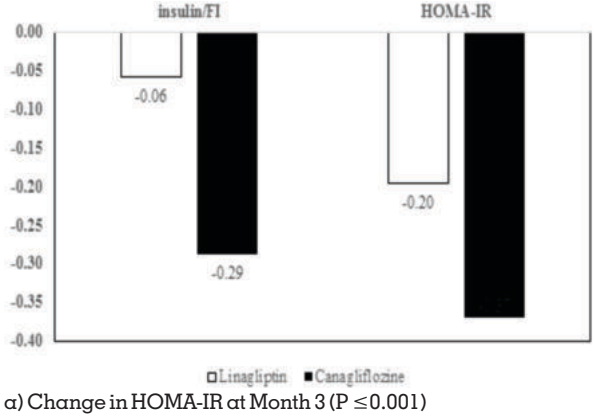


b) Change in 2-h post prandial plasma glucose at Month 3 (P ≤0.001)

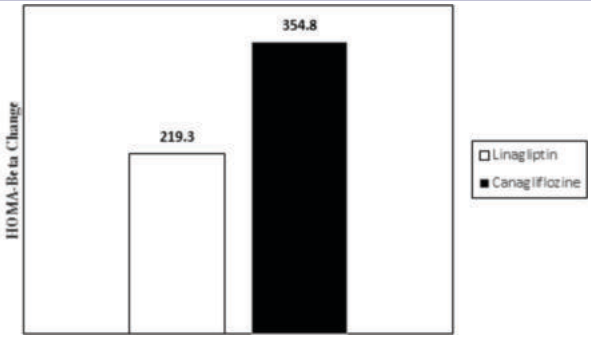


c) Change in HbA1c at Month 3 (P ≤0.01)

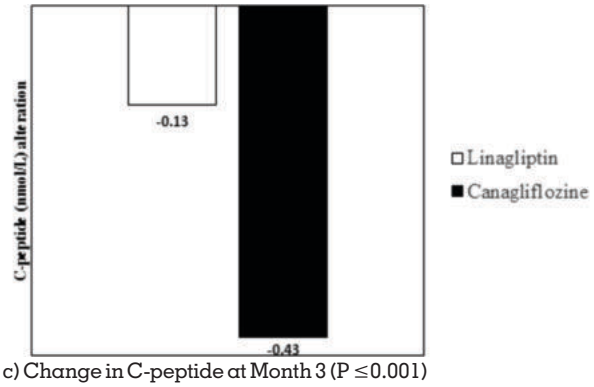
Figure 2: Insulin resistance



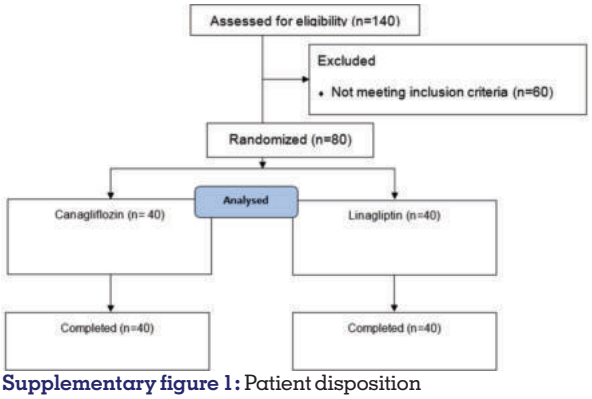
a) Change in HOMA-IR at Month 3 (P ≤0.001)



b) Change in HOMA-β at Month 3 (P ≤0.01)



c) Change in C-peptide at Month 3 (P ≤0.001)



Supplementary figure 1: Patient disposition

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