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Research Article

Comparative Effectiveness of Glimepiride versus Linagliptin as add-on to Metformin in Type-2-Diabetes Mellitus

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Abstract

Background: In addition to lifestyle modifications, metformin is the recommended first-line pharmacotherapy for patients with type 2 diabetes mellitus (T2DM). The use of glimepiride or linagliptin as add-on to metformin (GM or LM) has been noticed on prescriptions in major pharmacies in Nigeria.

Aims: The aim of this study was to compare the efficacy of glimepiride or linagliptin as add-on to metformin in T2DM.

Methods: A preliminary case-crossover randomized experimental/observational study comprising 30 participants (i.e., 15 for each of the combination therapies) was designed and designated GM and LM groups, respectively. Baseline physiological and health-indicators of the participants were primarily observed followed by a practical/analytical drug efficacy measurement of postprandial blood glucose (PPBG) levels at 1, 2, 4, and 6 h once weekly for 2 weeks and thereafter crossover to the other regimen for another two weeks' assessment.

Results: Baseline results were consistent across subgroup analyses in both treatment types. The statistical analysis demonstrated that LM achieved significant PPBG lowering potential compared to baseline blood glucose status ($p<0.05$). There was no significant difference in the observed physiological and biochemical indicators of organ system function for both treatments during the study. Treatment with LM was associated with reduced post-meal blood glucose compared with GM ($p<0.05$). Postprandial blood glucose change over measurement points were higher with LM ($p<0.05$).

Conclusion: Blood glucose control was better achieved with LM compared to GM. Propensity to hypoglycemia was higher with LM. More studies involving larger patient population in several centres are required to validate the outcome of these findings.

Keywords: Glimepiride, Linagliptin, Metformin, Fasting Blood Glucose, Postprandial blood glucose, Type 2 Diabetes Mellitus

INTRODUCTION

Oral hypoglyceamic agents are designed to help with type 2 diabetes mellitus (T2DM). Diabetes mellitus (DM) is a leading cause of mortality and reduced life expectancy[1]. The long-term complications associated with T2DM carries a crushing burden of morbidity and mortality, and most patients die prematurely from a cardiovascular event. This menace requires a proactive measure of efficient and effective glyceamic control. The major oral hypoglyceamic drug types in use are biguanides, sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones/glitazones, dipeptydyl-peptidase (DPP-4) Inhibitors (Gliptins). The biguanide class of which metformin is a classical example, has been used as first line recommended in the treatment of T2DM for years. It acts as an insulin sensitizer by increasing insulin sensitivity in the liver while inhibiting hepatic gluconeogenesis[2]. The treatment guidelines for T2DM allow the use of metformin as the optimal first-line drug unless contraindicated. After metformin, the use of 1 or 2 additional oral or injectable agents is recommended with a goal of minimizing adverse effects. An additional oral hypoglyceamic agent is included to metformin if the glyceamic level is not optimal[1, 3]. This could be a sulfonylurea (glimepiride) or a dipeptidyl peptidase-4 inhibitor (Linagliptin) among other classes. There are a number of clinical conditions presenting with insufficient metformin efficacy in glyceamic control reported in the literature [4, 5]. This necessitates the addition of a second drug for therapeutic success. The comparative efficacy studies of available combinations of hypoglyceamic remedies are very scanty. Glimepiride works by stimulating the secretion of insulin from pancreatic Islet beta cells. It has a long duration of action and lower risk of developing hypoglycaemia in clinical trial [6].

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. It is a competitive reversible inhibitor thereby enhancing the release of insulin from beta cells in the pancreas[7]. It is a drug of choice in its class as it is excreted chiefly through the enterohepatic system. Linagliptin can be used without recourse to dose adjustment in patients with renal and hepatic impairment [7, 8]. Hence a combination therapy of GM or LM simultaneously

addresses two different but complementary mechanisms to improve glyceamic control in T2DM [8]. These combinations (GM or LM) are widely used by the University of Uyo Teaching Hospital. Also, there has been no study in Uyo seeking to compare the daily or momentary effect of this combination of drugs in patients. The possible disparity in the glyceamic control between these therapies necessitates this study. This study was therefore aimed at assessing the blood glucose impact of the combinations.

METHODS

Study protocols and design

A case- crossover randomized study of treatment effect of 2 hypoglyceamic T2DM approaches involving (GM as 2/500 mg and LM as 5/500 mg) once daily dosing using primary/secondary observational study was designed. The research was conducted between August 2021 and September 2021. Preliminarily, a questionnaire was filled by participants that enquired about demographics as section A (5 questions) and other relevant patient lifestyle and disease parameters as section B (7 questions). Further data for the study were collected from the outcomes of vital signs (blood pressure, body temperature, respiration rate, pulse rate) alongside body weight, height, blood glucose levels and biochemical parameters (i.e., cholesterol, uric acid) determinations at baseline and in the course of the study. Serial finger prick/samplings for blood glucose level and other biochemical parameters were done using multifunctional analyzer (Heyuanpius, China). Fasting blood glucose of participants was obtained at 8 am before a regimented breakfast alongside drug dosing with the respective test drugs (GM for group 1 or LM for group 2). Postprandial blood glucose (PPBG) levels were taken at 1, 2, 4 and 6 h. Analysis of urine samples received before breakfast was similarly collected and performed using Medi-test Combi-9 strips.

This protocol of the study was initiated on the first week of study with each participant's start-up treatment (GM or LM) handed to them as supplies for 7 days. Drugs were coded and group members were similarly assigned codes with GM or LM codes based on their starting regimen. The drugs were supplied by the researcher. This was a single–blind trial as the participants did not know the treatment type. Sampling/data collection commenced the following week (i.e., after one week of taking either treatment). Participants were on a treatment for 2 weeks and shifted to the other treatment for the last 2 weeks. The participants were advised on a responsible lifestyle protocols during the study. They were similarly advised on adherence to their drug regimen throughout the study. Telephone calls were employed as follow-up to encourage compliance.

Sample size

This study was carried out on 30 (T2DM) patients (randomly divided into 2 groups of 15 participants). Convenient sampling size was adopted.

Inclusion criteria

Patients with T2DM were enlisted for the study. Any patient visiting the pharmacies, designated as a study centre, who has been placed by their physicians on either combination of drugs was eligible to participate.

Exclusion criteria

Patients with co-morbidities with diabetes mellitus were excluded from the study.

Data analysis

The data obtained from the study were analyzed using statistical package for social sciences (SPSS) version 20(IBM, USA). Quantitative variables were described in terms of mean and standard deviation (SD) for demographics and with standard error of the mean (SEM) for other biological parameters. Binary imputes or ordinal values were used for description of categorical/qualitative variables. Wilcoxon Signed Rank test was used for comparison between the outputs of the two treatments. Values were considered to be statistically significant at $p<0.05$ and test at one tail, with the assumption that the null hypothesis is true.

Ethical approval

Ethical approval for this study was obtained from University of Uyo Institutional Review Board for Human Research, UU/IRB/P/1025. All participants gave their written consent to the study and filled the consent form appropriately. The study was carried out according to the Helsinki declaration [9].

RESULT

A representative sample of 30 adults made up of 18 males and 12 females completed the research on "Preliminary Comparative effectiveness of glimepiride versus linagliptin as add-on to metformin in Type-2-Diabetes Mellitus." The participants were 60% males and 40% females. The age of the participants ranged between 52-68 years with mean ± SD (54.37 ± 6.21 years). The weights of participants ranged between 58-79 kg with a mean weight ± SD of 61.46± 10.51 kg. Participants' demographic characteristics are presented in Table 1. The participants in this study appear to have similarities with respect to age and lifestyle practices.

Table 2 presents the mean PPBG values for the treatments while Table 3 gives the change in PPBG for the different time points as compared with the baseline values. LM treatment produced lower PPBG values compared with the alternative treatment ($P<0.05$). The blood sugar lowering was significantly evident at > 4 h post meal/drug administration in this study. Furthermore, the unit change in postprandial blood glucose (ΔPPBG) values were significantly higher for LM ($p<0.05$). Table 4 revealed the acute biochemical parameters that relate to the safety of the drug combinations. There was no significant difference in the treatments. The mean differences in body mass index (BMI) at baseline and after the first 2 weeks of treatment were assessed and were expressed in Table 4. Comparing the outcome for GM with LM did not reveal any significant difference ($p>0.05$).

Figure 1 presents the relative levels of blood glucose after food. GM showed higher blood glucose levels than LM ($p<0.05$). Figure 2 is a graphical presentation revealing the effect of LM at 4 and 6 h post drug administration. LM revealed remarkably lower glucose levels. Figure 3 presents the biochemical and lipid profile for the participants during the study. There was no difference in the lipid profile of participants in the study that can be matched with the drug treatment type. Figure 4 presents the participants' self-reported drug side-effects experienced during the study. The numbers of cases of reports of cardiovascular, gastrointestinal and nervous side-effects attributable to the drugs are presented. The participants on the drug combination types revealed similar characteristics with respect to the side-effects.

Table 1: Demographic characteristics and lifestyle practices of participants

	GM		LM	
Parameters	***Frequency***	***Percentage***	***Frequency***	***Percentage***
N (%)	15 (100)	100	15	100
Average age in years ±SD	55 ± 7.5		54 ± 11.6	
Sex				
Males	8	53.3	10	66.7
Females	7	46.7	5	33.3
Marital status				
Married	12	80.0	7	46.7
Single	3	20.0	8	53.3
Duration of years of DM	4.7±1.6	-	7.5± 2.6	-
Currently prescribed drug				
GM	12	80	10	66.7
LM	3	20	5	33.3
Eating habit				
Eats everything	5	33.3	8	53.3
Selects food	10	66.6	7	46.7
Drinking habit				
Alcohol	7	46.7	8	53.3
Beverages	6	40.0	3	20.0
Water up to 2L/daily	6	40.0	5	33.3
Water more than 2L/daily	4	26.7	3	20.0
Urine output				
Up to 2L/day	8	53.3	10	66.7
Less than 2L/day	7	46.6	5	33.3
Feelings of				
Thirst	3	20.0	5	33.3
Hunger	4	26.7	8	53.3
Tiredness	3	20.0	1	6.7

NB. Participants with features may be counted twice. Those without certainties with the responses were left out and not counted.

Table 2: Postprandial blood glucose levels for the treatments

Wk	GM					LM					
	T0	**T1**	**T2**	**T4**	**T6**	**T0**	**T1**	**T2**	**T4**	**T6**	**P-value**
1	7.36±0.51	8.87±0.23	7.54±0.44	6.21±0.24	6.63±0.45	6.64±0.34	8.36±0.34	6.93±0.22	6.38±0.34	5.28±0.21	0.03
2	6.45±0.24	7.15±0.21	7.11±0.12	6.14±0.15	6.11±0.27	6.65±0.67	7.24±0.23	6.14±0.23	5.45±0.23	5.80±0.32	0.03
3	6.86±0.34	8.13±0.37	7.23±0.32	6.76±0.41	6.14±0.34	7.88±0.45	8.16±0.15	6.48±0.32	5.87±0.23	6.12±0.51	0.02
4	7.12±0.12	7.86±0.22	6.95±0.42	6.21±0.23	6.21±0.15	6.56±0.21	7.02±0.25	6.35±0.25	6.38±0.43	6.58±0.56	0.04

Mean values ± SEM are recorded for Time (T0- T6) values; T0 –T6 represents time 0 to 6 h, respectively. Units for blood glucose readings are in mmol/L. GM and LM are glimepiride+ metformin and linagliptin+metformin, respectively.

Table 3: Unit postprandial blood glucose change for the treatments

	GM				LM				P-value
Week	***T1***	***T2***	***T4***	***T6***	***T1***	***T2***	***T4***	***T6***	
1	1.53±0.16	1.30±0.25	1.54±0.45	1.70±0.30	1.36±0.45	1.68±0.23	1.54±0.35	1.67±0.15	0.06
2	1.31±0.21	1.11±0.32	1.67±0.34	1.92±0.12	1.79±0.23	1.76±0.14	1.87±0.12	1.78±0.14	0.03
3	1.12±0.14	1.02±0.22	1.45±0.12	2.31±0.34	1.68±0.34	1.87±0.22	1.89±0.25	2.10±0.13	0.07
4	1.14±0.16	1.05±0.15	1.46±0.23	1.16±0.18	1.78±0.23	1.76±0.18	2.12±0.15	2.21±0.32	0.02

Mean values ± SEM are recorded for Time (T0- T6) values; T0 –T6 represents time 0 to 6 h, respectively. GM and LM are glimepiride+ metformin and linagliptin+metformin, respectively.

Table 4: Change in physiological and biochemical parameters from wekly follow up on urine samples

	GM										**LM**									
WK	Δ BMI 1	Δ BMI 2	Protein		Glucose		Bilirubin		Blood		Δ BMI 1	Δ BMI 2	Protein		Glucose		Bilirubin		Blood	
			WK 2	WK 4	WK 2	WK 4	WK 2	WK 4	WK 2	WK 4			WK 2	WK 4	WK 2	WK 4	WK 2	WK 4	WK 2	WK 4
01	0.23	0.14	0	0	0	0		0	0		0.37	0.21	0	1	0	0	0	0	0	0
02	0.15	0.21	1	0	0	0	0	0	0	0	0.13	0.15	0	1	0	0	0	0	0	0
03	0.25	0.12	0	0	0	0	0	0	0	0	0.21	0	0	0	0	0	0	0	0	0
04	0.48	0.24	0	0	0	0	0	0	0	0	0.42	23	1	0	0	0	0	0	0	0
05	0.35	0.14	2	0	0	0	0	0	0	0	0.34	0	0	0	0	0	0	0	0	0
06	0.78	0.25	0	0	1	0	0	0	0	0	0.26	0.31	0	0	0	0	0	0	0	0
07	0	0.15	0	0	0	0	0	0	0	0	0.36	0.24	1	0	0	0	0	0	0	0
08	0.11	0.46	0	0	0	0	0	1	0	0	0	0.26	0	0	0	0	0	0	0	0
09	0.32	0.19	0	0	0	0	0	0	0	0	0	0.21	0	0	0	0	0	0	0	0
10	0.44	0.35	0	0	0	0	0	0	0	0	0.23	0.28	0	0	0	0	0	0	0	0
11	0.23	0.22	1	0	1	0	1	0	0	0	0.18	0.17	1	0	1	0	0	0	0	0
12	0.36	0.19	0	0	0	0	0	0	0	0	0.32	0.28	0	0	0	0	0	0	1	0
13	0.13	0.21	2	0	0	1	0	0	0	1	0.35	0.34	0	1	0	0	0	0	0	0
14	0.41	0.27	0	0	0	0	0	0	0	0	0.25	0.49	0	0	1	0	0	0	0	0
15	0	0.12	1	0	0	0	1	0	0	0	0.16	0.14	0	0	0	0	0	0	0	0

ΔBMI_1: Change in Body Mass Index at cross-over (with respect to baseline) while ΔBMI_2 is with respect to cross-over and end of study. GM and LM are glimepiride+ metformin and linagliptin+metformin, respectively.

WK : Week of observations. Values 0, 1, 2 and 3 are categorical values representing negative (-), mild (+), moderate (++) or high values (+++) of the parameters/markers in urine.

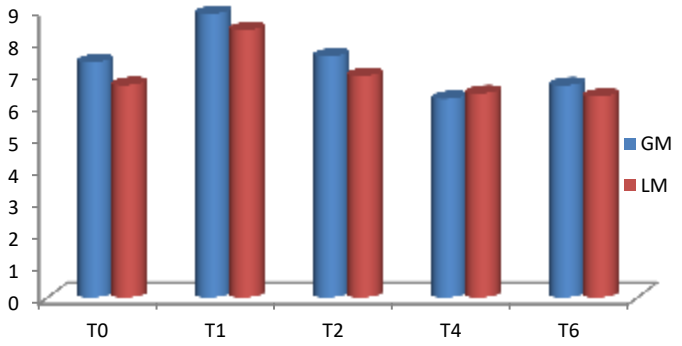

Figure 1: Graphical representation of a plot of the mean postprandial glucose levels of GM **(Blue) and LM (Red)**

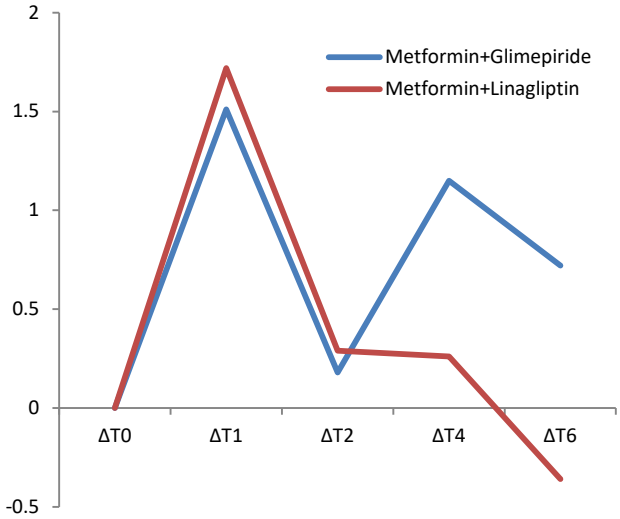

Figure 2: Unit change in blood glucose following drug administration (ΔT1, T2, T4 and T6 are at 1, 2, 4 and 6 h, respectively)

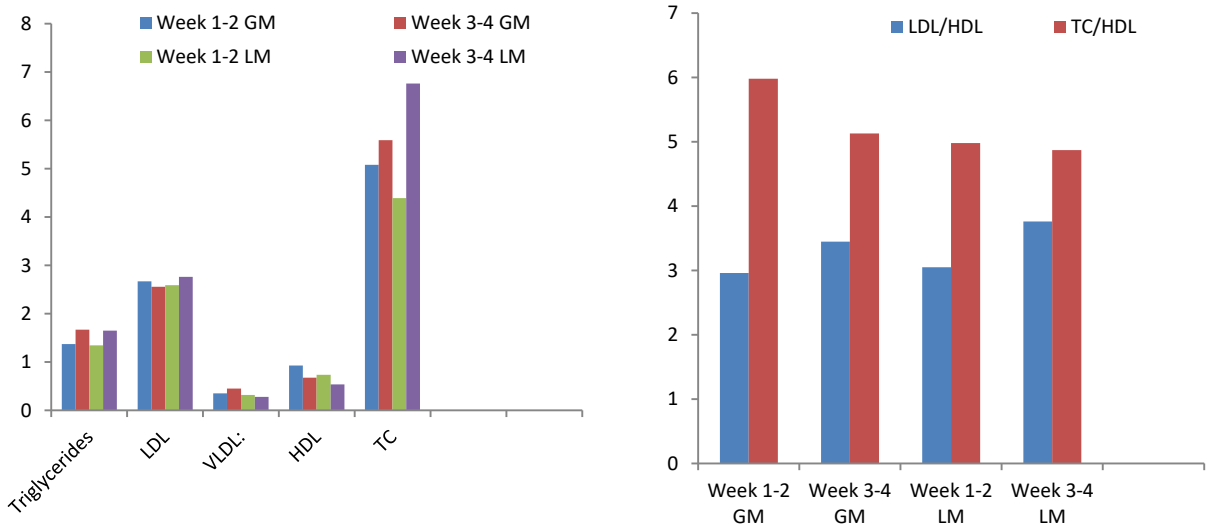

Figure 3: Biochemical and lipid disposition for the treatment groups

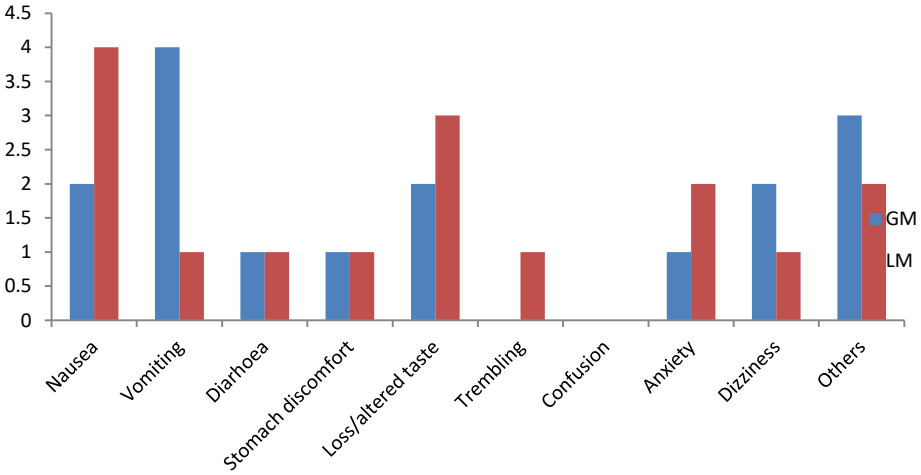

Figure 4: Effects of drug treatments on participants

DISCUSSION

The combination of metformin and a sulfonylurea is among the most commonly prescribed hypoglyceamic drugs. In a study by Charpentier et al., the addition of glimepiride to metformin resulted in superior glyceamic control compared with the single use of glimepiride or the biguanide [10, 11]. The combination treatment was reported to be more effective at reducing HbA1c compared with metformin alone. Dipeptidyl peptidase (DPP4) inhibitors are also candidates for combination therapy with metformin. These feature in many prescriptions because of their glucose-lowering mechanisms,

proven efficacy, low propensity to cause hypoglycemia, and weight neutrality. The addition of linagliptin to metformin has provided better glyceamic control than monotherapy with either metformin or linagliptin alone [7]. Based on this background, this study seeks to compare the effectiveness of linagliptin or glimepiride as add-on to metformin.

In this study, 93.3% of the participants lie in the age group of 55-65 years. This distribution of age of participants and the outcome relate well with practice based outcomes as this represents the age distribution of persons presenting with T2DM in everyday life. These individuals also have the highest rate of diabetes-related end-stage renal disease [12]. This survey also considered the lifestyle practices of participants, so as to highlight its importance in the ultimate consideration of the outcome of drug performance. Participants in the study had a mean baseline (fasting blood) glucose level of 6.21 ± 0.65 mmol/L. At the onset of investigation, the GM group had 6.15 ± 0.15 mmol/L while the LM group was 6.85± 0.45 mmol/L. The crossover design made the effect of the treatment such that each participant also served as the control.

A non-parametric protocol using Wilcoxon signed rank test revealed that there was significant difference in the efficacies of the treatments (i.e., GM versus LM). The null hypothesis was therefore rejected at α= 0.05, one tail). Hence, it follows that both combination therapies did not deliver similar benefits in terms of glyceamic control. This is consistent with a recent long-term Phase III comparative trial by Gallwitz et al. (2012) in which the DPP4 inhibitor, linagliptin, demonstrated non-inferior glyceamic efficacy compared with glimepiride as add-on therapy to metformin in patients with T2DM [13]. Table 2 shows the mean unit change in blood glucose (postprandial values compared with the baseline). The mean blood glucose at 1 h was found to be higher than the baseline. The effect of both treatments on blood glucose elevation immediately after food was relatively similar. Comparing at 2 h after meal, the unit change in blood glucose (lowering capacity) for LM group was significantly higher than GM group, (p<0.05). A similar study by Devarajan and co-workers assessed sitagliptin as add-on to metformin with the alternative treatment in this study [14]. The efficacy of GM was established. Linagliptin has been reported to be of higher and more promising value in the DPP4 inhibitor group and has shown its value in this present study.

However, in the graphical analysis in Figure 3, the curve representing GM demonstrated a decrease in the glyceamic level which was significantly lower than the alternative treatment [15]. In kidney or liver disease, the hypoglyceamic effect of glimepiride can be increased and prolonged, mainly due to a decrease in insulin metabolism or hepatic glucose output. The risk of hypoglycemia is increased. In chronic kidney disease, (stage 4 or 5), the use of this combination therapy has been reported to be such as required caution. This is due to the fact that elimination of unchanged glimepiride is greatest in patients with more severe renal disease [16]. The blood glucose reduction profile for the treatment involving glimepiride was erratic as observed at beyond 2 h post dose. A sharp change in postprandial blood glucose (ΔPPBG) may predispose users to hypoglyceamia.

The curve representing LM in the graphical presentation revealed a sustained reduction in plasma glucose level. This is similar to a study by Michael et al.(2018) which demonstrated that LM was effective in treating older people with T2DM to achieve their HbA1c targets with a favourable safety and tolerability profile [17]. This study however showed that LM combination presents low risk of hypoglycaemia beyond 4 h post-dose period.

Linagliptin is primarily non-renally excreted as 80% of the drug is eliminated via the bile and gut and only 5% is eliminated via the kidney. This explains the sustained effect of LM combination [18]. In this study, no episodes of symptoms relating to severe hypoglycemia (e.g dizziness, chills) were recorded. Only minor drug-related effects in relatively small number of participants were observed. The drug combinations for the comparisons were therefore adjudged relatively effective in this preliminary comparative study.

Limitation of this study

The possibility of generalizing the outcome of this study to a larger population, especially where there exists some socio-cultural differences with that of the study participants is a major issue. This is because lifestyle plays pivotal roles in blood glucose management. Similarly, a smaller sample size was designed to observe preliminarily any possible difference in the effect of the treatments.

CONCLUSION

This study showed that the management of T2DM with LM has higher and sustained blood glucose lowering effect than GM. A larger sample size and multi-centered study will be required to observe a broader perspective of the available treatments.

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Authors Contributions

All authors contributed equally to this work

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Conflict of Interests

The authors have no conflicts of interest to declare

Ethical Approval

Approved

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