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Safety and efficacy of different basal insulin in type 2 diabetes mellitus with chronic kidney disease in Ramadan: prospective observational study

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Abstract

Background Diabetic kidney disease populations are categorized as high risk for fasting in Ramadan due to various potential fasting-related complications. Insulin analogues are recommended to be used in place of human insulin during fasting, as they carry a lower risk of hypoglycaemia and stable glycaemic variability. A paucity of data exits on the safety and efficacy of different basal insulin types during fasting for this population. This study aims to evaluate the safety and efficacy of three basal insulin among patients with Type 2 Diabetes Mellitus and concomitant mild to moderate chronic kidney disease who are keen to fast during Ramadan.

Materials and methods A single-centered, prospective observational study was conducted among 46 patients with type 2 diabetes mellitus and concomitant chronic kidney disease stage 2 and 3 who were on three different types of basal insulin (Glargine U-100, Levemir, and Insulatard), fasted in Ramadan 2022. All variables were listed as median (IQR). Hypoglycaemia events and glycemic variability obtained from Freestyle Libre continuous glucose monitoring were compared between insulin groups. Changes in glycated haemoglobin, fasting plasma glucose, renal profile, body weight, body mass index, and waist circumference pre and post-Ramadan were evaluated.

Results The glycaemic variability was found highest in Insulatard with a median (IQR) of 37.2(33)% versus Levemir 34.4(32.4)% versus Glargine U-100 36.8(30.6)%, p = NS. Levemir had reported the lowest median time of below range of 2.5(13)% followed by Glargine 4(25)% and Insulatard 5(8)%; p = NS. The findings of this study indicated that glycated haemoglobin, fasting plasma glucose, renal profile, body weight, body mass index, and waist circumference did not alter statistically between the three groups post-Ramadan. Individually, Insulatard showed a significant reduction in weight and waist circumference (0.9kg, p = 0.026; 0.44 cm, p = 0.008) while Levemir showed a reduction in waist circumference (0.75cm, p = 0.019).

Conclusion This study revealed that Insulatard, Levemir, and Glargine demonstrated similar levels of safety and efficacy among those with diabetic kidney disease who observed fasting during Ramadan.

Keywords Diabetic kidney disease, Glycaemic variability, Time below range

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Introduction

Fasting in Ramadan is an obligation for Muslims and is the fourth pillar of Islam [1]. While Islam exempts those with chronic diseases from fasting, the majority of Muslims living with diabetes and chronic kidney disease (CKD) opt to fast irrespective of knowing their high-risk status of developing complications, namely, hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, dehydration, thrombosis, and worsening renal function. Based on two previous studies, Epidemiology of Diabetes and Ramadan (EPIDIAR) and CREED, 78.7% and 94.2% of people with type 2 diabetes fasted at least 15 days during Ramadan [2, 3]. This poses a considerable management challenge for the medical practitioners. As a result, the International Diabetes Federation and the Diabetes and Ramadan International Alliance (IDF-DAR) have developed risk stratification guidelines and treatment recommendations for this group of patients who wish to fast in Ramadan [4]. Within the chronic kidney disease population, individuals with stable kidney function between stages 1–3 are categorized as being at low to moderate risks, which allows them to fast with medical advice. Conversely, those with unstable kidney function in stages 1–3 (defined as rapidly declining glomerular filtration rate, presence of fluid overload, and frailty), as well as individuals in advanced CKD stages 4–5 are strongly advised against fasting [5].

Type 2 diabetes mellitus (T2DM) is a metabolic disorder linked to the gradual deterioration of beta cell function. This condition ultimately renders oral glucose-lowering drugs ineffective, and most patients will eventually require insulin therapy for better glycaemic control. The risk of hypoglycaemia among insulin-treated patients increased with fasting and the progression of chronic kidney disease. Advancements in insulin therapy have resulted in a shift from human insulin to insulin analogue, further subdivided into prandial, basal, and premixed formulations. Insulin analogues have several advantages over regular human insulin, such as a lower risk of hypoglycaemia and a longer action compared to human insulin [6]. Human insulin insulatard has an onset of action of 1–2 h and duration of action of up to 12 h [7]. Conversely, Levemir and Glargine are insulin analogues with a longer duration of action of up to 24 h and have a minimal peak, resulting in fewer hypoglycaemic episodes than human insulin.

Glycemic variability is one of the factors that influence the choice of insulin in Ramadan. Ramadan fasting is associated with major glycaemic excursions between fasting during the day and postprandial hyperglycaemia with episodes of unreported hypoglycaemia [8]. Post-Iftar is associated with the consumption of irregular meals, making it challenging to control post-prandial hyperglycaemia. It has been observed that individuals with chronic kidney disease are also particularly vulnerable to high glycaemic variability [9]. Research has indicated that high glycaemic variability is a strong predictor of hypoglycaemia [10, 11]. Furthermore, large glucose fluctuations may independently contribute to diabetes-related complications [12]. Known for its flat pharmacokinetics profile, insulin analogues have been recommended as a viable substitute to human insulin in individuals who are keen to fast during Ramadan [13–18].

One of the challenges encountered during Ramadan fasting is the deterioration in glycated haemoglobin (HbA1c) levels due to the anticipated variety of food taken. Studies have indicated that insulin analogues have better glycemic control compared to human insulin [19]. However, there is still insufficient data in this area on Ramadan fasting. In the real-world observational trial (ORION study), Glargine U-300 showed a reduction of HbA1c from pre- to post-Ramadan, while other Ramadan studies showed no significant change [15–17].

During the entire month of Ramadan, individuals are obliged to abstain from drinking and eating from predawn to sunset. Fear of dehydration, which can lead to worsening kidney function amongst patients with diabetic kidney disease (DKD), has been a concern in fasting. In the past, studies had shown deterioration in kidney function, contributed by dehydration and hyperglycaemia [20, 21]. However, recent literature reviews have presented more promising results, following adequate structured Ramadan counselling and advancement in diabetes treatment [22–24].

Numerous studies have examined the effects of fasting on different components of metabolic biomarkers as there are profound changes in dietary habits and physical activity. Fasting in Ramadan has been associated with weight reduction, changes in BMI, and alterations in waist-hip circumference [25, 26].

In this study, we evaluated the safety and efficacy profile of three different basal insulin amongst patients with DKD with the main aim of providing safe practice during Ramadan.

Materials and methods

Study design

This prospective, non-interventional, observational, comparative study was conducted over 14 weeks, from February 2022 until May 2022. Ramadan fell on the 2nd of April 2022 till 1st May 2022. Patients were recruited from Pusat Perubatan UiTM Sungai Buloh and Hospital Al-Sultan Abdullah UiTM Puncak Alam. The study focused on patients with T2DM with HbA1c 6.5–10% with co-existing CKD stages 2 and 3. Eligible patients were individuals who had been using one of the three basal insulin for a minimum of 8 weeks prior to recruitment and expressed desire to fast for more than 15 days

in Ramadan. Those who fell under the category of the Very High-risk group based on the International Diabetes Federation and Diabetes and Ramadan International Alliance (IDF-DAR) guideline, currently pregnant, breastfeeding, on oral steroid treatment, and has recent hospital admission for the past six months were excluded from this study. Ethical approval was obtained from the University Research Ethics Committee of University Technology MARA (UiTM) (REC no: REC/01/2022 (PG/FB/7).

Eight weeks preceding Ramadan, patients were asked to attend the first clinic visit for a comprehensive briefing on the study procedures and provide written informed consent. During this visit, various demographic details, such as age, gender, and disease characteristics, including duration of diabetes, complications of diabetes, types of oral hypoglycaemic agents, and types of insulin treatments, were gathered and documented using an assessment form. Additionally, anthropometric measurements, encompassing weight, height, body mass index (BMI), waist circumference, and blood pressure were obtained during the clinic session. Subsequently, patients were provided with standard pre-Ramadan counselling which include insulin dose adjustment. Patients were counselled to reduce pre-*suhoor* prandial insulin dosage to 30–50% and remain similar to the prandial insulin dose at Iftar. Regarding basal insulin, those with HbA1c>7.5% were to continue with a similar dose, whereas those with HbA1c<7.5% reduced the insulin dose by 30–50%. For those on twice-daily basal insulin, the evening dose was reduced to half and switched to *suhoor* while the morning dose shifted to *Iftar.* Those utilizing once-daily basal insulin were advised to take it at *Iftar.* Those on concomitant Sulphonylurea and SGLT2-inhibitor were advised to take at *Iftar*. Patients were educated on the risks of hypoglycaemia, receiving information on how to identify its condition and effectively manage it. Blood samples for fasting blood sugar, renal profile, and HbA1c were obtained during this first clinic visit.

A total of 54 patients were recruited of which 6 patients dropped out from the study two weeks pre-Ramadan and 2 patients had lost data from the reader. Therefore, a total of 46 patients completed this study. Patients were divided into three groups based on the types of basal insulin (Insulatard, Levemir, Glargine). The majority of the patients were on basal bolus and the remainder were on a combination of oral hypoglycaemic agents and night basal insulin. Two weeks before Ramadan, patients were contacted to reinforce the need to adjust their insulin doses to attain stable insulin levels and adjustments of other medications as well.

In Ramadan, patients were called to the clinic for the application of Abbott Freestyle Libre continuous glucose monitoring sensors. This glucose monitoring system works through sensors that were inserted under the skin by us through an applicator. This subcutaneous sensor needed to be scanned by a separate reader to keep a record of glucose measurement and pattern of glucose over two-week periods. All patients were instructed to check capillary blood glucose on symptoms of hypoglycaemia or hyperglycaemia. Due to the limitation of the reader, we had to segregate the patients into two groups, some of them received during the first two weeks and the remaining during the last 2 weeks of Ramadan. Patients were required to document the doses of insulin requirements, types of food intake, and any hypoglycaemic events.

The final clinic visit took place two weeks post-Ramadan. During this visit, blood samples for fasting blood sugar, renal profile, and HbA1c were obtained together with anthropometric measurements. Patients returned the reader, and data, including the number of low glucose events (LGE), time below range (TBR), time in range (TIR), time above range (TAR), glycaemic variability in the form of coefficient of variation (CV) were retrieved for further analysis (Fig. 1).

Sample size

At the time the study was conducted, no published data was available comparing the safety and efficacy of different basal insulin in Ramadan, focusing on diabetes mellitus with concomitant mild to moderate CKD. Hassanein et al.'s (2016) research study was used as a reference to calculate the sample size as it is the closest insulin comparison study. Utilizing, the two proportions-hypothesis testing with a 95% confidence interval, 80% power study, and 10% dropout, the sample size needed was 18 patients in each group. Therefore, the total sample size was calculated at 54. Out of 54 enrolled patients, six withdrew from the study, and two reported missing data from Freestyle Libre continuous glucose monitoring.

Endpoints

The endpoint of this study was looking at the safety and efficacy of each basal insulin. The safety of insulin was evaluated based on the number of low glucose events, time below range, glycaemic variability obtained from continuous glucose monitoring, and changes in renal function from pre- to post-Ramadan. The efficacy of insulin was assessed based on changes in HbA1c and anthropometric measurement post-Ramadan.

Definition

Using the risk fasting score as per Diabetes and Ramadan guidelines, those score between 3.5 and 6 is categorized as a moderate risk which advises not to fast and those scores above 6 are categorized as high risk which should not fast [27]. CKD stage 2 is defined as an

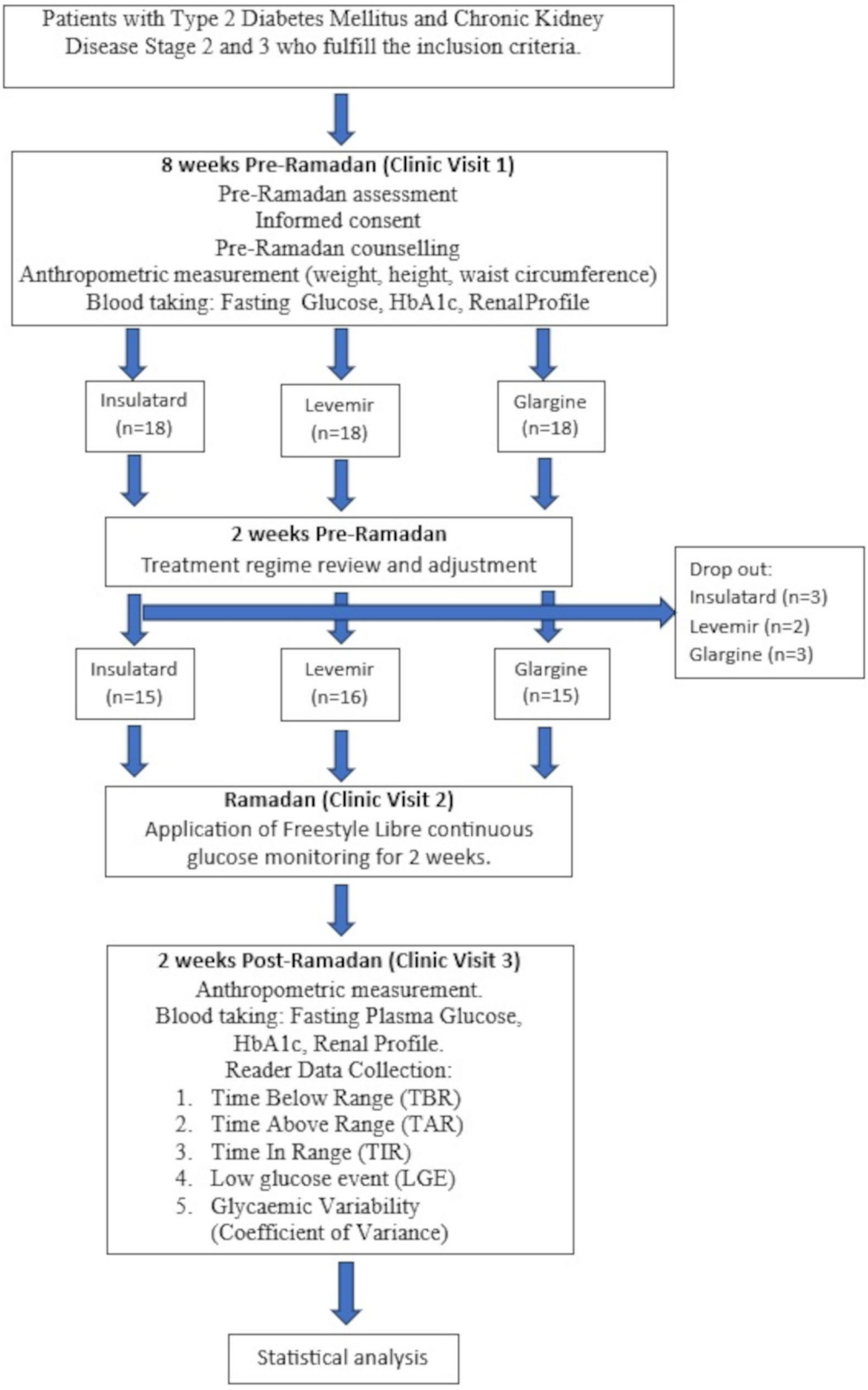

Fig. 1 Study flowchart

estimated glomerular filtration rate (eGFR) of 60–89 mL/min/1.73 m^2 while CKD stage 3 is defined as eGFR of 30–59 mL/min/1.73 m^2.

Based on the International Consensus Use of CGM, the number of low glucose events are defined as glucose below the target range (≤3.9mmol/l) for at least 15 min or more [28]. The time below range is defined as the percentage of time a person spends with their blood glucose level ≤3.9mmol/l. Time in range is defined as the percentage of time a person spends with their blood glucose level 4–10 mmol/l. The time above range is defined as the percentage of time a person spends with their blood glucose level ≥10 mmol/l. Glycaemic variability is the measurement of the degree of fluctuations of glucose readings over a given time, and, in this study, we are using the coefficient of variant with CV ≥ 36%, which indicates an unstable glycaemic variability.

Statistical analysis

Data in this study were analyzed using the Statistical Package for the Social Science (SPSS) version 26.0 (IBM). Categorical variables were expressed in number (%) and continuous variables were expressed as median (interquartile range). Data were checked for normality before analysis by the Kolmogorov–Smirnov test and by examining normality plots. The results were not normally distributed hence non-parametric statistical analysis was chosen.

Kruskal Wallis test was used to compare the three insulin groups on hypoglycaemic profile and glycaemic variability. For each group of insulin, changes in HbA1c, fasting blood sugar, plasma creatinine, EGFR, weight, and waist circumference pre and post-Ramadan were analyzed using the Wilcoxon Sign Ranked test while the change in differences across all data sets were analyzed using the Kruskal-Wallis test. Statistical significance was defined as p-value < 0.05.

Results

General characteristics

A total of 46 patients were recruited in the study. The sociodemographic and clinical characteristics of the patients were shown in Table 1. While there were more men within the Insulatard group, all three groups showed similar median age, duration of diabetes, diabetic complications, and use of oral medications. Two-thirds of the patients were obese; all three groups demonstrated a median waist circumference above 90 cm. All three groups had a median HbA1c of above 8% and similar fasting glucose of 6.8 to 7.7 mmol/L. 60% of the patients in the Insulatard and Glargine group and 56% in the Levemir group had chronic kidney disease stage 2, while the rest were in stage 3. The total basal and prandial insulin daily doses were similar between the three groups, but the total insulin daily dose was numerically higher in those who received insulin Levemir, followed by Glargine and Insulatard [0.85 (0.62), 0.56 (0.63), 0.35(0.72) unit/kg/day, respectively, p=0.079]. According to the risk stratification of fasting in Ramadan, 60% of the patients in Insulatard and Glargine and 50% of Levemir were from a high-risk category based on IDF-DAR guidelines.

Hypoglycaemic profile

In terms of hypoglycaemic profile, there was no significant difference in the time below range across the three basal insulin. Numerically, Levemir had the lowest TBR of 2.5 (13)%, followed by Glargine 4 (25)% and Insulatard 5 (8)% (Table 2). Despite reporting the lowest TBR, Levemir showed a higher number of low glucose events than Glargine and Insulatard, but it was statistically insignificant. There was also no significant difference in TAR and TIR across the three basal insulin (Table 2).

Glycaemic variability

The median GV between the three groups was statistically non-significant. However, numerically, Levemir reported the lowest GV of 34.45 (14.8) %, followed by Glargine 36.80 (18.2) % in comparison to insulatard 37.20 (9.80) % (Table 3). From this study, we could see that in the Levemir group, more than 50% of the patients had stable GV (< 36%) compared to Glargine and Insulatard. On the other hand, the insulatard group showed more than 50% of the patients had unstable glycaemic variability (GV ≥ 36%) compared to Levemir and Glargine, albeit with no statistical difference.

Change in HbA1c, fasting plasma glucose, plasma creatinine, eGFR

The changes in HbA1c observed between pre- to post post-Ramadan were not statistically significant in all insulin groups. All three basal insulin demonstrated a rise in fasting plasma glucose at the end of the study post-Ramadan, but the result was only significant among Insulatard-treated patients (0.90mmol/L, p=0.050). There was a trend towards a rise in serum creatinine in the Insulatard and Glargine groups and an opposing decline in the Levemir group, but these results were not statistically significant (Table 4).

Change in body weight, BMI, and waist circumference

The changes seen in body weight and waist circumference were not significant when compared between the three basal insulin. However, individually, the Insulatard group demonstrated a significant reduction in body weight and waist circumference (0.9 kg, p=0.026; 0.44 cm, p=0.008, respectively), while the Levemir group demonstrated a reduction in waist circumference of (0.75 cm, p=0.019).

Table 1 Baseline characteristics

	Insulatard (*n* = 15)	Levemir (*n* = 16)	Glargine (*n* = 15)	*p*-value
Sociodemographic detail				
Age (years)	66 (7)	57 (14)	62 (6)	0.149
Gender *n* (%)				
Male/Female	12(80.0)	10(62.5)	5(33.3)	0.032
Female	3(20.0)	6(37.5)	10(66.7)	
Diabetes Background				
Duration of diabetes (years)	15.0 (9)	18.5 (13)	16.0 (12)	0.812
Weight (kg)	75.3 (10.5)	76.8 (28.4)	69.0 (34.8)	0.864
BMI (kg/m^2)	29.7(4.54)	29.4(7.34)	28.4(11.37)	0.954
Waist circumference (cm)	91.4 (13)	93.2(14.38)	90.0(28.50)	0.678
HbA1c (mmol/mol)	8.2 (1.70)	8.1(1.95)	8.4(1.00)	0.700
Fasting Plasma Glucose (mmol/l)	7.7 (2.40)	6.8 (3.85)	7.5 (3.60)	0.543
Creatinine (umol/L)	103.0 (25)	107.5 (34.50)	88.0 (66)	0.368
EGFR (mL/min/1.73 m^2)	61 (10)	60 (21)	60(38)	0.944
CKD staging upon recruitment; *n* (%)				
CKD 2	9 (60.0)	9 (56.3)	9 (60.0)	0.970
CKD 3	6 (40.0)	7 (43.8)	6 (40.0)	
Diabetic Complications				
Retinopathy; *n* (%)	6(40.0)	7(43.75)	3(20.0)	0.334
Neuropathy; *n* (%)	5(33.3)	6(37.5)	8(53.3)	0.501
Macrovascular; *n* (%)	7(46.7)	5(31.25)	8(53.3)	0.443
Diabetic Treatment at Screening				
Biguanides; *n* (%)	7(46.7)	5(31.3)	6(40.0)	0.697
Sulphonylurea; *n* (%)	6(40.0)	1(6.3)	2(13.3)	0.049
DPP4-I; *n* (%)	0(0.0)	1(6.3)	1(6.7)	0.602
SGLT2; *n* (%)	7(46.7)	10(62.5)	9(60.0)	0.638
Biguanides + DPP4-I; *n* (%)	6(40)	10(62.5)	6(40.0)	0.347
GLP 1 agonist; *n* (%)	0(0.0)	1(6.3)	0(0.0)	0.384
Actrapid; *n* (%)	8(53.3)	9(56.3)	6(40.0)	0.632
Novorapid; *n* (%)	1(6.8)	4(25.0)	4(26.7)	0.306
Fasting Risk Category				
Risk level associated with fasting; *n* (%)				
Moderate risk	6(40%)	8(50%)	6(40%)	0.809
High risk	9(60%)	8(50%)	9(60%)	
Insulin Requirement				
Prandial; (unit/kg/day)	0.22(0.44)	0.43(0.28)	0.26(0.46)	0.193
Basal insulin; (unit/kg/day)	0.22(0.27)	0.39(0.33)	0.15(0.30)	0.099
Total insulin; (unit/kg/day)	0.35(0.72)	0.85(0.62)	0.56(0.63)	0.079

Data are presented as median (IQR) for continuous variables and number (percentage) for categorical variables. *p*-value are results of the non-parametric Kruskal Wallis test for both continuous and categorical variables between three groups of insulin. BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; DPP4-I, dipeptidyl peptidase IV inhibitor; SGLT2, sodium-glucose cotransporter-2 inhibitor; GLP-1, glucagon-like peptide 1 agonist

Table 2 Hypoglycaemic Profile

	Insulatard (*n* = 15)	Levemir (*n* = 16)	Glargine (*n* = 15)	*p*-value
Low glucose event; (n)	5 (11)	6.50 (12)	4.0 (14)	0.900
Proportion of pre-iftar hypoglycaemia; *n* (%)	7 (33.3)	4 (19.0)	10 (47.6)	0.070
Glucose time below range; (%)	5(8)	2.5(13)	4(25)	0.625
Glucose time above range; (%)	23 (21)	27 (36)	25 (26)	0.744
Glucose time in range; (%)	69 (19)	65.50 (30)	69 (30)	0.804

Data are presented as median (IQR) for continuous variables. *p*-value are results of the non-parametric Kruskal Wallis test for both continuous variables between three groups of insulin

Table 3 Glycaemic variability

	Insulatard (*n* = 15)	Levemir (*n* = 16)	Glargine (*n* = 15)	*p*-value
Glycaemic variability; (%)	37.20 (9.8)	34.45 (14.8)	36.80 (18.2)	0.988
Glycaemic variability; *n* (%)				
Good variability	6 (27.3)	9 (40.9)	7 (31.8)	0.666
Poor variability	9 (37.5)	7 (29.2)	8 (33.3)	

Data are presented as median (IQR) for continuous variables and number (percentage) for categorical variables. *p*-value are results of the non-parametric Kruskal Wallis test for both continuous and categorical variables between three groups of insulin. CV ≥ 36% indicates high glycaemic variability

Table 4 Comparison of differences in HbA1c, fasting plasma glucose, plasma creatinine, and estimated glomerular filtration rate pre and Post-ramadan

	Insulatard (*n* = 15)	Levemir (*n* = 16)	Glargine (*n* = 15)	**p*-value
HbA1c(mmol/mol)				
Pre Ramadan	8.20 (1.7)	8.10 (1.9)	8.40 (1.0)	0.809
Post Ramadan	8.00 (1.6)	8.15 (2.0)	8.20 (1.9)	
Difference	-0.20	0.05	-0.20	
#*p*-value	0.314	0.737	0.842	
FPG (mmol/l)				
Pre Ramadan	7.70 (2.4)	6.80 (3.90)	7.50 (3.6)	0.265
Post Ramadan	8.60 (4.4)	7.85 (5.2)	7.90 (3.5)	
Difference	0.90	1.05	0.40	
#*p*-value	0.050	0.326	0.975	
Plasma Creatinine (umol/L)				
Pre Ramadan	103.00 (25)	107.50 (34.5)	88.00 (66)	0.695
Post Ramadan	105.00 (33)	104.00 (48.3)	90.00 (73)	
Difference	2.0	-3.50	2.0	
#*p*-value	0.320	0.842	0.132	
EGFR (mL/min/1.73 m^2)				
Pre Ramadan	63.00 (14.1)	60.00 (20.8)	60.00 (37.7)	0.773
Post Ramadan	64.00 (18)	65.20 (23)	59.00 (38)	
Difference	1.0	5.20	-1.0	
#*p*-value	0.477	0.959	0.281	

Data are presented as median (IQR) for continuous variables. #*p*-value is the result of the non-parametric Wilcoxon sign rank test for individual insulin and * *p*-value are result of the non-parametric Kruskal Wallis test for between insulin groups. FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate

Otherwise, there was no change in all three parameters in the Glargine group (Table 5).

Discussion

To the best of our knowledge, this is the first study that compared the safety and efficacy of three types of basal insulin (Insulatard, Levemir, and Glargine U-100) in type 2 diabetes mellitus with mild to moderate chronic kidney disease during fasting in the one month of Ramadan.

Hypoglycaemia is a major barrier in a fasting month and is a primary determining factor for risk assessment in Ramadan fasting. This study found that all three basal insulin caused hypoglycaemia in Ramadan but the number of the low glucose event and time below range were not statistically significant when compared between groups. We observed that insulin analogues (Levemir, Glargine U-100) numerically showed a lower percentage of time spent during hypoglycaemia than human insulin (Insulatard). When comparing Levemir with Glargine, Levemir reported the lowest percentage of time spent during hypoglycaemia with most patients did not report pre-iftar hypoglycaemia despite the result was not statistically significant. Despite the higher dosage of insulin requirement in the Levemir group, the percentage of time spent during hypoglycaemia remains the lowest as compared to the other two basal insulin groups and this aligns with the results of a previous Ramadan study [29]. Studies had shown that the highest proportion of hypoglycaemia occurs during the late fasting periods. In this study, we spotted that Levemir showed the lowest percentage of pre-iftar hypoglycaemia compared to others. The pharmacokinetics and pharmacodynamics of the respective insulin analogues most likely contributed to this. In the clamp study, it showed that Levemir had a similar effect with Glargine in the first 12 h in glucose infusion rate, whereby this effect was lower in the next 12–14 h, thus reducing the duration of hypoglycaemia with Levemir [30]. The same plausible explanation may also support the findings that although the Levemir group demonstrated the highest number of low glucose events, the same group recorded the lowest time below range, albeit insignificant. The low glucose event seen among Levemir-treated patients was observed most of the time during morning and mid-day. The higher

Table 5 Comparison of differences in weight, body mass index (BMI), and waist circumference pre and Post-ramadan

	Insulatard (*n* = 15)	Levemir (*n* = 16)	Glargine (*n* = 15)	**p*-value
Body weight (kg)				
Pre Ramadan	75.30 (10.5)	76.80 (28.40)	69.10 (34.80)	0.614
Post Ramadan	74.40 (11.5)	75.95 (30.1)	67.15 (32.30)	
Difference	-0.90	-0.85	-1.95	
#*p*-value	0.026	0.352	0.570	
BMI (kg/m^2)				
Pre Ramadan	29.70 (4.51)	29.48 (7.3)	28.47 (11.4)	0.653
Post Ramadan	29.10 (12.50)	28.96 (8.0)	27.57 (12.50)	
Difference	-0.60	-0.52	-0.90	
#*p*-value	0.048	0.278	0.426	
Waist Circumference (cm)				
Pre Ramadan	91.44 (13)	93.25 (14.4)	90.00 (28.50)	0.834
Post Ramadan	93.25 (14.4)	92.50 (13.80)	90.00 (27)	
Difference	-0.44	-0.75	0	
#*p*-value	0.008	0.019	0.119	

Data are presented as median (IQR) for continuous variables. #*p*-value is the result of the non-parametric Wilcoxon sign rank test for individual insulin and * *p*-value are result of the non-parametric Kruskal Wallis test for in-between insulin groups. BMI, body mass index

number of low glucose events could be possibly related to the higher percentage of prandial insulin in comparison to Glargine and Insulatard. Despite the study was not able to demonstrate statistically significant outcomes, these findings suggest a potential clinical significance, particularly for patients who experience frequent hypoglycaemia events within the final four hours pre-iftar, in which future similar studies should further confirm.

Glycaemic variability denotes the oscillations of blood glucose levels over a given period and has become increasingly clinically relevant in determining glycaemic control, as well as its association with increased risk of microvascular and macrovascular complications [12]. In Ramadan, a significant difference was observed in the mean CGM curve, with a glucose fall during fasting hours followed by a rapid rise of glucose post-Iftar [31]. It is crucial to identify the appropriate insulin regime to minimize these blood glucose fluctuations throughout the fasting and post-iftar hours. Studies have shown that in comparison to a non-fasting state, there was no significant difference in the glycaemic variability. However, looking into the period of Ramadan itself, a study observed a transient increase in glycaemic variability in early Ramadan which subsequently returned to pre-Ramadan level [8]. Currently, no data have been published concerning the impact of GV among basal insulins in Ramadan involving diabetic kidney disease patients. Numerically, we could see that Levemir-treated patients had stable glycaemic variability despite the results was not statistically significant. The shorter duration of time spent during hypoglycaemia may contribute to less variability seen in the Levemir group. We would expect that Levemir and Glargine would have lesser variability in Ramadan, but our results were not statistically significant. Despite receiving dietary counselling during the pre-Ramadan assessment, the elevated post-prandial glucose levels observed suggest a lack of adherence to the proposed controlled diet. HbA1c levels have traditionally been the gold standard in accessing glycaemic control and treatment efficacy. In this present study, the changes in HbA1c observed pre and post-Ramadan were not significant, and it is consistent with findings in multiple studies on basal insulin in Ramadan [13, 17]. Fasting can be challenging in patients with Diabetes Mellitus and CKD, with a duration of fasting of up to 15 h in Malaysia. There is a concern regarding risks of dehydration, worsening kidney function, and electrolyte imbalance. In our study, we can conclude that across three basal insulin, there were no significant changes in the renal profile. Therefore, this group of patients with CKD stages 2 and 3 can fast with a reasonable degree of safety in Ramadan, supported by several studies [22–24].

Studies have also revealed that fasting has been shown to improve health outcomes. A reduction in weight and fat mass with is mainly seen in people who are overweight and obese [32]. In our study, reductions in weight and waist circumference were found across all three basal insulin groups. Those in the Insulatard reported significant weight loss, which could have been attributed to an increment in fasting blood sugar observed post-Ramadan. A plausible explanation would be the hyperosmolar symptoms resulting in osmotic diuresis and subsequent fluid loss, and subsequent weight loss. Among the three basal insulin, we would expect significant improvement in the anthropometric measurement in the Levemir group as Levemir is known to have a weight-lowering effect [33]. However, in this study, a significant reduction was seen only in the waist circumference parameter.

In accordance with the IDF-DAR guideline, high risk patients should not fast in Ramadan. The majority of our patients were in the high-risk group with remaining in the moderate-risk group. With the use of CGM in

our study, we observed numerous hypoglycaemic events and unstable glycaemic variability among our patients. Despite the results were not statistically significant, it is worth highlighting that patient using the insulin analogues group had numerically lower glucose time below range and stable glycaemic variability than the human insulin group. Nevertheless, these findings should be corroborated by larger-scale studies in the future to justify that this high-risk patient should be changed to a much safer regime of insulin which should include insulin analogues.

This study had limitations, particularly with the small sample size. Although we managed to reach the calculated sample size, the dropout rate was significantly higher, partially contributed by the residual effects of the COVID-19 epidemic. Furthermore, this was a non-interventional, observational study with some population and sample bias. A randomized controlled clinical trial with a larger sample size is therefore ideal. In addition, the use of continuous glucose monitoring especially the glycaemic variability measurement was an exciting new outcome to be studied. The limitation of sensors and readers for CGM has contributed to the shortened duration of usage to only 2 weeks in Ramadan instead of one whole month.

Conclusion

In conclusion, this study found that Insulatard, Levemir, and Glargine demonstrated similar safety and efficacy among patients with T2DM and CKD who fasted in the month of Ramadan.

Abbreviations

BMI	Body mass index
CKD	Chronic kidney disease
CGM	Continuous glucose monitoring
DKD	Diabetic kidney disease
DPP4-1	Dipeptidyl Peptidase IV inhibitor
EGFR	Estimated glomerular infiltration rate
GV	Glycaemic variability
FPG	Fasting plasma glucose
GLP-1	Glucagon like peptide 1
IDF DAR	International Diabetes Federation and the Diabetes and Ramadan International Alliance
IQR	Interquartile range
SGLT-2	Sodium-glucose transport protein 2 inhibitor
TIR	Time in range
TAR	Time above range
TBR	Time below range
T2DM	Type 2 diabetes mellitus

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Author contributions

N.H. conducted the study. R.A.G, S.F, N.A edited and reviewed the manuscript critically. All authors have read and agreed to the published version of the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was conducted according to the ethical guidelines of the Helsinki Declaration. The study protocol was approved by the Research Ethics Committee of University Technology MARA (REC no: REC/01/2022 (PG/FB/7). Written informed consent was obtained from each participant before data collection.

Consent of application

Not applicable.

Competing interests

The authors declare no competing interests.

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