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**SAFETY AND EFFICACY OF DIFFERENT
BASAL INSULIN IN TYPE 2 DIABETES
MELLITUS WITH CHRONIC KIDNEY DISEASE
IN RAMADAN**

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

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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 analogue has been recommended in fasting during Ramadan, replacing human insulin due to the benefit of lower risk of hypoglycaemia and lesser glycaemic variability. There is paucity of data on the safety and efficacy of different types of basal insulin in diabetic kidney disease populations during fasting. 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, Levemir, and Insulatard), fasted in Ramadan 2022. All continuous variables were listed as median (IQR). Hypoglycaemia profile and glycaemic variability obtained from Freestyle Libre continuous glucose monitoring were compared between insulin groups. Changes in glycated haemoglobin, fasting plasma glucose, renal profile, body weight, and waist circumference pre and post-Ramadan were evaluated. The predictors of high glycaemic variability were identified among insulin-treated patients in Ramadan.

Results: The glycaemic variability was reported 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 below range of 2.5 (13) % followed by Glargine 4(25) % and Insulatard 5(8) %; p=NS. Insulatard showed significant reduction in weight and waist circumference (0.9kg, p=0.026; 0.44 cm, p=0.008) while Levemir showed significant reduction in waist circumference (0.75cm p=0.019) post Ramadan. A higher number of low glucose event is associated with 1.29 times fold increase probability of high glycaemic variability and a higher percentage of time in range had probability of less glycaemic variability with OR of 0.90.

Conclusion: Insulatard, Levemir, and Glargine demonstrated similar safety and efficacy among those with diabetic kidney disease who fasted during Ramadan. Hypoglycaemia was identified as the clinical predictor for high glycaemic variability and time in range contribute to less glycaemic variability in Ramadan.

Keywords: Diabetic kidney disease, glycaemic variability, time below range

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INTRODUCTION

Fasting in Ramadan is an obligation for Muslims and it is the fourth pillar of Islam(1). Although Islam exempts those with chronic diseases from fasting, the majority of Muslims living with diabetes and chronic kidney disease continue to fast irrespective of knowing their high-risk status of developing complications, namely, hypoglycaemia, hyperglycaemia, diabetic ketoacidosis (DKA), dehydration, deterioration in renal function and thrombosis. 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 respectively (2, 3). It poses a management challenge for the medical practitioner to ensure safe Ramadan practise among diabetic kidney disease population (DKD). Thus, 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). In the chronic kidney disease population, those with stable kidney function between stages 1-3 are categorized under low to moderate risks, which allows them to fast with medical advice. Those with unstable kidney function of stages 1-3 (defined as rapidly declining glomerular filtration rate, presence of fluid overload, and frailty) and advanced CKD stages 4-5 are recommended to avoid fasting(5).

Type 2 diabetes mellitus (T2DM) is a metabolic disorder linked to the gradual deterioration of beta cell function. It ultimately renders oral glucose-lowering drugs ineffective, and most patients will eventually require insulin therapy for better glycaemic control. The risk of hypoglycaemia in 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 analogues, further subdivided into prandial, basal, and premixed formulations. Insulin analogues have several advantages over regular human insulin, such as lower risk of hypoglycaemia and a longer action compared to human insulin (6). Insulatard has an onset of action of 1-2 hours and duration of action of up to 12 hours (7). Conversely, Levemir and Glargine are insulin analogues with a longer duration of action of up to 24 hours and have a minimal peak, resulting in fewer hypoglycaemic episodes than human insulin.

Glycemic variability is among the factors that influence the selection of an insulin regimen. Ramadan fasting was associated with major glycaemic excursions between fasting during the day and post-*iftar* hyperglycaemia with episodes of unreported hypoglycaemia(8). Post-*iftar*

was associated with the consumption of erratic meals, making it challenging to control post-prandial hyperglycaemia. Study had shown that chronic kidney disease patients were vulnerable to high glycaemic variability as well(9). High glycaemic variability has been recognized as strong predictor of hypoglycaemia (10, 11). Furthermore, large glucose fluctuations may independently contribute to diabetes-related complications(12). Owing to the benefit of a flat pharmacokinetics profile of insulin analogues, it has been recommended to substitute human insulin in those keen to fast during Ramadan (13-18)

Deterioration in HbA1c is some dilemma encountered during fasting in Ramadan. Research has indicated that insulin analogue offer superior glycaemic control when compared to human insulin (19). However, there is still lacking data in this area during Ramadan fasting. In the real-world observational trial (ORION study), Glargine U-300 showed improved HbA1c from pre-to post-Ramadan while other Ramadan studies showed no significant change in HbA1c (15-17).

In Ramadan fasting, people must abstain from drinking and eating from pre-dawn to sunset for the entire month. Fear of dehydration, which can lead to worsening kidney functions amongst patients with diabetic kidney disease, is one of the main concerns in fasting. In the past, studies have shown deterioration in kidney function, contributed by dehydration, hyperglycaemia and worsening of renal function (20, 21). However, a more recent literature review showed promising results with no significant worsening of renal function attributed to adequate structured Ramadan counselling and advancement in diabetes treatment (22-24).

Many studies looked at the effect of fasting on different components of metabolic biomarkers as there are profound changes in dietary habits and physical activity in Ramadan. Ramadan fasting is associated with reduction in weight, BMI, and waist-hip circumference (25, 26).

In fasting, insulin analogue is generally preferred over human insulin due to lower risk of hypoglycaemia and post prandial hyperglycaemia. There is still limited data on basal insulin and the effect among chronic kidney disease patients. 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.