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Effect of exenatide twice daily according to different meal schedules on glycemic control and variability in patients with type 2 diabetes mellitus

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ABSTRACT

Objective: To assess the effect of exenatide twice daily according to different meal schedules on glycemic control and variability in patients with type 2 diabetes mellitus. **Materials and methods:** A randomized, open clinical trial was performed in 18 adults with type 2 diabetes mellitus who were overweight or obesity and inadequate glycemic control with metformin as monotherapy. Fasting glucose was < 12 mmol/l and glycated hemoglobin A1c between 7-9%. All patients received exenatide (5 µg twice daily) subcutaneously for four weeks and continued taking metformin at the same dose throughout the study. A randomized distribution of six subjects was conducted to each of the following pre-prandial times of application of exenatide: (i) breakfast and lunch, (ii) breakfast and dinner, or (iii) lunch and dinner. At the beginning and four weeks later, glucose concentrations were measured every hour during a 24-hour period. Area under the curve of glucose and glycemic variability according to the mean amplitude of glycemic excursions was calculated.

RESUMEN

Objetivo: Evaluar el efecto de exenatida aplicada 2 veces al día en diferentes horarios de ingesta de alimento, sobre variabilidad y control glucémicos en pacientes con diabetes *mellitus* tipo 2 (DM2). **Materiales y métodos:** Ensayo clínico aleatorizado, abierto, en 18 adultos con DM2, sobrepeso u obesidad e inadecuado control glucémico con metformina como monoterapia. La glucosa de ayuno fue < 12 mmol/l y la hemoglobina glucosilada A1c entre 7 y 9%. Todos los pacientes recibieron exenatida (5 µg, 2/día) subcutánea durante cuatro semanas y continuaron la metformina durante el estudio. Se distribuyeron al azar seis sujetos a cada horario de aplicación preprandial de exenatida: a) desayuno y comida; b) desayuno y cena, o c) comida y cena. Al inicio y cuatro semanas después, se midió glucosa cada hora durante 24 h. Se calcularon el área bajo la curva (ABC) de glucosa y variabilidad glucémica; esta última mediante la media de la amplitud de las excursiones de glucosa (MAEG). **Resultados**: La administración de exenatida antes del desayuno y la comida

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Results: Exenatide administration before breakfast and lunch significantly decreased fasting glucose and area under the curve of glucose after the intervention. The mean amplitude of glycemic excursions was similar in the three groups. **Conclusions:** Exenatide before breakfast and lunch appears to achieve better glycemic control. (REV MEX ENDOCRINOL METAB NUTR. 2016;3:129-36)

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Key words: Exenatida. Glycemic variability. Glycemic control. Type 2 diabetes mellitus.

disminuyó significativamente la glucosa de ayuno y ABC de glucosa. La MAEG fue similar en los tres grupos. **Conclusiónes:** Exenatida antes del desayuno y la comida parece lograr mejor control glucémico.

Palabras clave: Exenatida. Variabilidad glucémica. Control glucémico. Diabetes *mellitus* tipo 2.

INTRODUCTION

In recent years some studies have suggested that not only chronic hyperglycemia but also daily glycemic fluctuation, referred to as glycemic variability, lead to both accelerated glycation and long-term micro- and macro-vascular complications[1]. Currently, the efficacy of the therapeutics in diabetes has been to not only reduce hyperglycemia but also to avoid possible hypoglycemia[2]. There are several formulas to evaluate glycemic variability such as the mean amplitude of glycemic excursions (MAGE)[3,4].

Exenatide is a glucagon-like peptide 1 (GLP-1) receptor agonist that improves glycemic control mainly by reducing postprandial hyperglycemia, with a modest effect on fasting plasma glucose[5,6]. Immediate-release exenatide is the only GLP-1 analog recommended to be administered twice daily before the two main meals in patients with type 2 diabetes mellitus (T2DM)[7,8]. However, there is uncertainty about the best daily application schedule. A previous study reported that after 12 weeks of treatment, exenatide administration before breakfast and dinner significantly decreased glycated hemoglobin A1c (A1C), fasting plasma glucose, and the seven-point self-monitored blood glucose levels in Mexican patients. A higher percentage of patients also achieved a target A1C ≤ 7% compared to those with the administration before lunch and dinner; however, such results were not observed in a Brazilian population[9].

The aim of this study was to assess the effect of exenatide administration twice daily, according to different meal schedules, on glycemic control and variability in patients with T2DM.

MATERIALS AND METHODS

A randomized, open clinical trial was performed in 18 overweight/obese (body mass index [BMI] 25.0-39.9 kg/m^2) adults (18-55 years old) with T2DM and inadequate glycemic control with metformin as monotherapy (2,000 mg/day for at least the previous three months). Fasting glucose was < 12 mmol/l and A1C between 7-9%. All individuals were non-smokers. They had stable body weight for at least three months before the study and blood pressure < 140/90 mmHg. None of the subjects reported a personal history of hepatic, renal, or coronary artery disease. Subjects did not consume any medication known to affect gastrointestinal motility or lipid metabolism or any other antihyperglycemic agent during the study. Women who were pregnant, breast-feeding, or intended to become pregnant during the study were excluded.

At baseline and at the end of the pharmacological intervention four weeks later, weight, BMI, and systolic and diastolic blood pressure as well as fasting glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were evaluated. Additionally, all patients underwent a

24-hour inpatient stay with three previously scheduled meals. Overall macronutrient composition for the 24-hour period was 50% carbohydrate, 20% protein, and 30% fat. Similar food items for all patients were used in each respective meal. Venous blood samples were collected every hour for 24 hours for daily measurement of serum glucose. Subjects arrived at the study site at 6:00 a.m. after at least an eight-hour overnight fast.

After completion of the first inpatient period, six patients were randomized to each group according to the different meal schedules. The allocation was concealed and done by simple randomization with a closed envelope that contained a letter A, B, or C. Exenatide 5 µg (Baietta®, Eli Lilly Co., Mexico City) was administered on an outpatient basis twice daily for four weeks by subcutaneous injection within 60 minutes prior to the meals according to the different schedules: before, (i) breakfast and lunch; (ii) breakfast and dinner; or (iii) lunch and dinner. Patients were instructed on the use of the pen injection device for administration of exenatide as necessary. All patients continued taking metformin at the same dose throughout the study and received general recommendations about their medical nutritional therapy. Subjects were instructed to not modify their usual physical activity.

Height and weight without shoes were recorded by the individuals. Values were used to calculate BMI according to the following formula: weight (kg)/height (m^2). Blood pressure was evaluated by the investigator after a five-minute resting period with the individual sitting in a chair and determined using a digital sphygmomanometer.

Glucose concentration was measured by the glucose-oxidase technique (Ortho-Clinical Diagnostics, Rochester, NY, USA) with an intra- and inter-assay coefficient of variation < 1%. The A1C levels were measured using ion exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA) with an intra- and inter-assay coefficient of variation of 0.4 and 1.6%, respectively. Levels of TC, HDL-C, and TG were evaluated enzymatically. In particular, HDL-C was assessed after selective precipitation of non-HDL-C fractions. Determinations were performed with commercially available equipment (Ortho-Clinical Diagnostics) with an intra- and inter-assay coefficient of variation < 3%. Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula (LDL-C = TC – HDL-C – TG/5). Area under the curve (AUC) was calculated with the polygonal formula. MAGE was calculated as published by Service, et al.[4].

The study protocol was reviewed and approved by a local Ethics Committee. Written informed consent was obtained from all volunteers.

Sample size was calculated using a formula for mean differences[10] with a statistical confidence (CI) of 95%, statistical power of 80%, standard deviation for plasma glucose of 0.6 mmol/l[11], MAGE of 3.1 mmol/l[12], and an expected difference of 1.0 and 5.1 mmol/l, respectively, obtaining a total of six patients per group.

STATISTICAL ANALYSIS

Baseline differences among the three groups were analyzed by Kruskal-Wallis test. Fisher exact test was used for qualitative variables. Intra-group differences were determined by the Wilcoxon rank test; $p < 0.05$ was considered significant.

RESULTS

Of the 32 subjects who were possible candidates, only 18 met the entry criteria and were randomized to receive exenatide according to the different meal schedules. No patient was excluded during the intervention (Fig. 1). At baseline, the three groups of six patients each were similar according to their clinical and laboratory characteristics (Table 1).

Exenatide administration before breakfast and lunch significantly decreased fasting glucose and AUC of glucose after the intervention. No changes were observed with administration before breakfast and dinner. Meanwhile, with the administration before lunch and dinner, significant reductions in BMI, TC, and

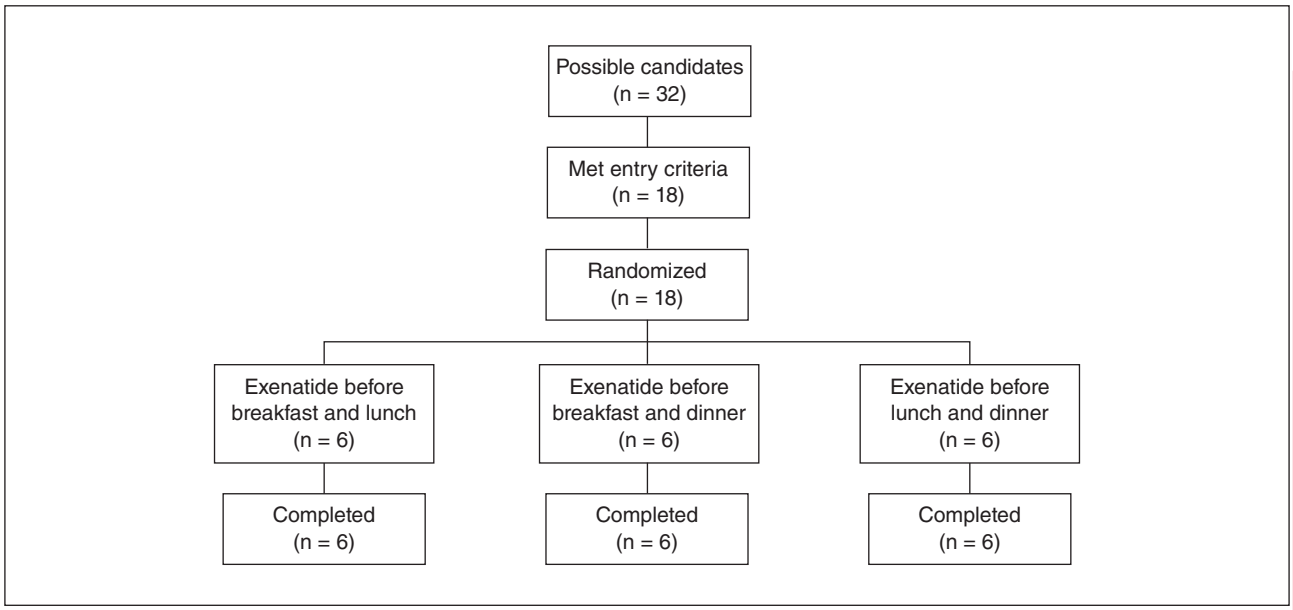

Figure 1. Study flow diagram.

Table 1. Baseline and final clinical and laboratory characteristics in the three study groups

	Breakfast/Lunch*		Breakfast/Dinner*		Lunch/Dinner*	
	Basal (n = 6)	Final (n = 6)	Basal (n = 6)	Final (n = 6)	Basal (n = 6)	Final (n = 6)
Age, years	44.6 ± 10.4		44.3 ± 6.5		49.6 ± 3.2	
Weight, kg	89.0 ± 13.9	87.6 ± 13.1	89.9 ± 20.2	89.6 ± 20.5	81.7 ± 12.5	80.6 ± 11.6
BMI, kg/m^2	33.5 ± 4.1	33.0 ± 3.7	33.9 ± 4.3	33.8 ± 4.1	32.0 ± 5.0	31.4 ± 4.8†
SBP, mm/Hg	125.3 ± 5.5	125.1 ± 11.0	129.8 ± 6.7	129.6 ± 7.0	125.5 ± 8.3	119.6 ± 15.0
DBP, mm/Hg	77.5 ± 4.0	74.1 ± 4.9	77.6 ± 4.6	80.0 ± 5.4	78.5 ± 5.2	76.1 ± 5.1
Glucose, mmol/l	8.8 ± 1.8	7.2 ± 1.2†	7.5 ± 1.7	6.6 ± 1.6	8.5 ± 1.4	7.6 ± 2.2
MAGE, mmol/l	4.5 ± 1.8	2.9 ± 1.3	2.7 ± 0.8	2.5 ± 0.7	3.9 ± 2.1	3.6 ± 1.4
AUC of glucose, mmol*h/l	225.4 ± 61.6	167.3 ± 36.3‡	202.3 ± 66.3	165.6 ± 28.1	215.4 ± 63.0	186.0 ± 46.8
TC, mmol/l	5.4 ± 0.7	5.2 ± 0.8	4.5 ± 1.0	4.3 ± 0.6	5.0 ± 0.9	4.5 ± 0.9‡
Triglycerides, mmol/l	2.7 ± 0.8	2.7 ± 1.1	2.0 ± 0.2	1.7 ± 0.4	2.2 ± 1.0	2.4 ± 0.6
HDL-C, mmol/l	1.2 ± 0.3	1.1 ± 0.3	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	0.9 ± 0.1
LDL-C, mmol/l	2.9 ± 0.7	1.3 ± 0.6	2.5 ± 0.9	0.8 ± 0.2	3.0 ± 1.0	2.4 ± 0.8†

*No significant differences between groups (Kruskal-Wallis test).
†p = 0.046, between basal and final measurement intra-group (Wilcoxon rank test).
‡p = 0.028, between basal and final measurement intra-group (Wilcoxon rank test).
AUC: area under the curve; BMI: body mass index; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MAGE: mean amplitude of glucose excursions; SBP: systolic blood pressure; TC: total cholesterol.

LDL-C were observed. MAGE after the intervention was similar among the three groups (Table 1).

As shown in figure 2, at the end of the intervention, in the group with exenatide before breakfast and lunch, AUC of glucose and 15 points of glucose values throughout the 24-hour period decreased significantly. In the groups using exenatide before breakfast and dinner and before lunch and dinner, there were no significant changes in AUC

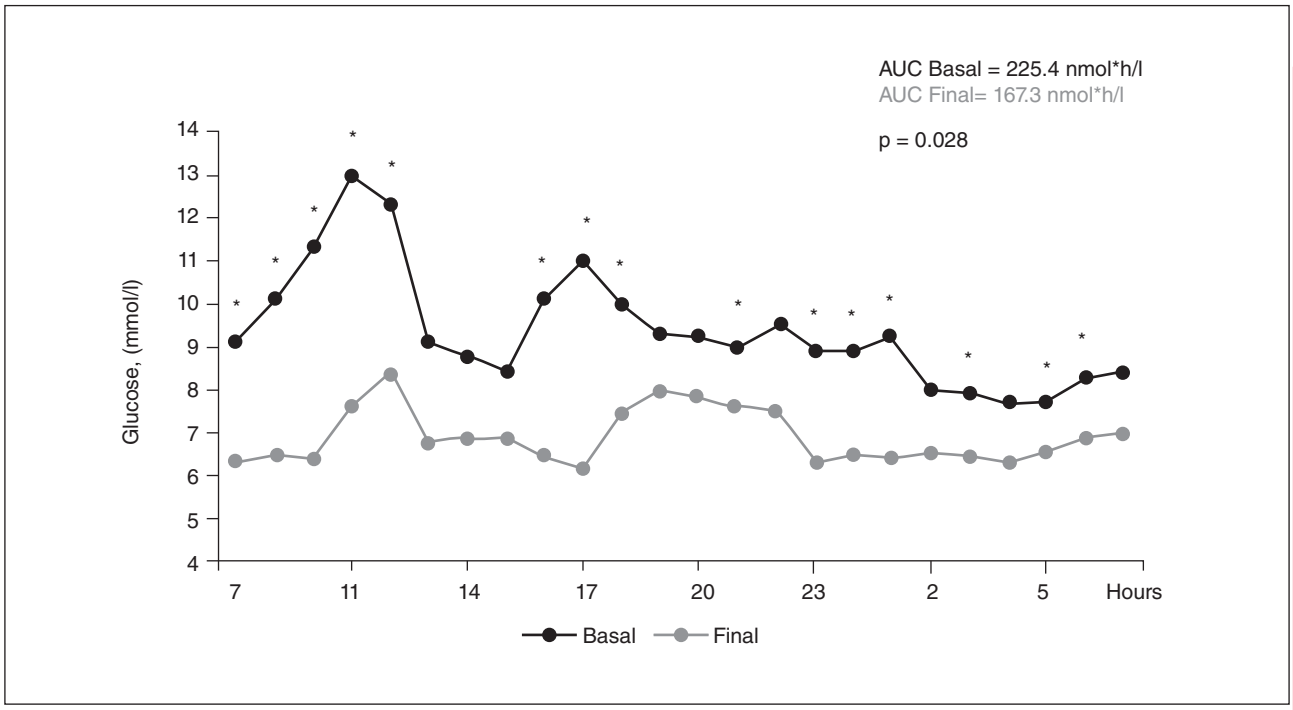

Figure 2. Behavior of glucose for 24 hours (baseline vs. final) with exenatide before breakfast and lunch. *p < 0.05 (Wilcoxon rank test). AUC: area under the curve.

of glucose; however, 8 and 6 points, respectively, of glucose values throughout the 24-hour period decreased significantly (Figs. 3 and 4).

The most common side effects with exenatide administration in the three study groups were nausea and vomiting (30%). Patients did not demonstrate hypoglycemic events. No patient withdrew from the study due to adverse effects.

DISCUSSION

Exenatide and other GLP-1 analogs have shown greater efficacy in the reduction of postprandial glucose and stabilization of glucose concentrations during the day with a low frequency of hypoglycemic events and beneficial effects in terms of weight and blood pressure reduction than other antidiabetic treatments[5-7]. According to the above-mentioned information, the contribution of exenatide could be crucial in the treatment of T2DM because increasing glucose levels (postprandial mainly) are strongly associated with cardiovascular events[1,13]. On the other hand, when the value of A1C is closer to the goal, the contribution of postprandial hyperglycemia is higher than the fasting glucose concentration[14]. In this study, exenatide administration decreased fasting glucose and the AUC of glucose including 15 points during the 24 hours evaluated when administered before breakfast and lunch, demonstrating that this schedule achieved better glycemic control.

In recent years, great value has been attributed to the fluctuations and variability of blood glucose during the day because these may play an important role in the genesis of diabetic complications by generating increased oxidative stress[1,3]. Numerous explanations are noted in regard to the fact that the hyperglycemic states trigger deleterious metabolic events through a single process: overproduction of superoxide by the mitochondrial electron-transport chain[15].

Definitions of glycemic peaks and nadirs are arbitrary or subjective and are not based on a standardized algorithm, which is the main limitation of its use[4]. MAGE is a measurement for determining glycemic variability;

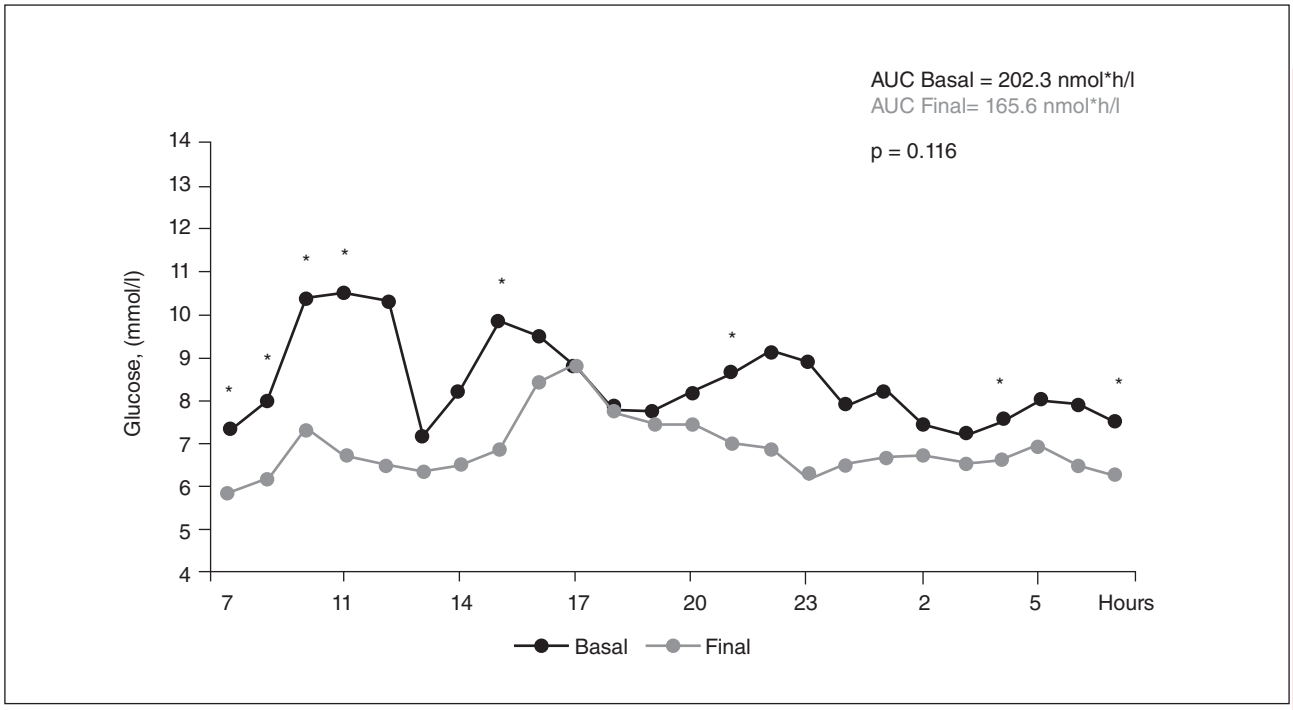

Figure 3. Behavior of glucose for 24 hours (baseline vs. final) with exenatide before breakfast and dinner. *p < 0.05 (Wilcoxon rank test). AUC: area under the curve.

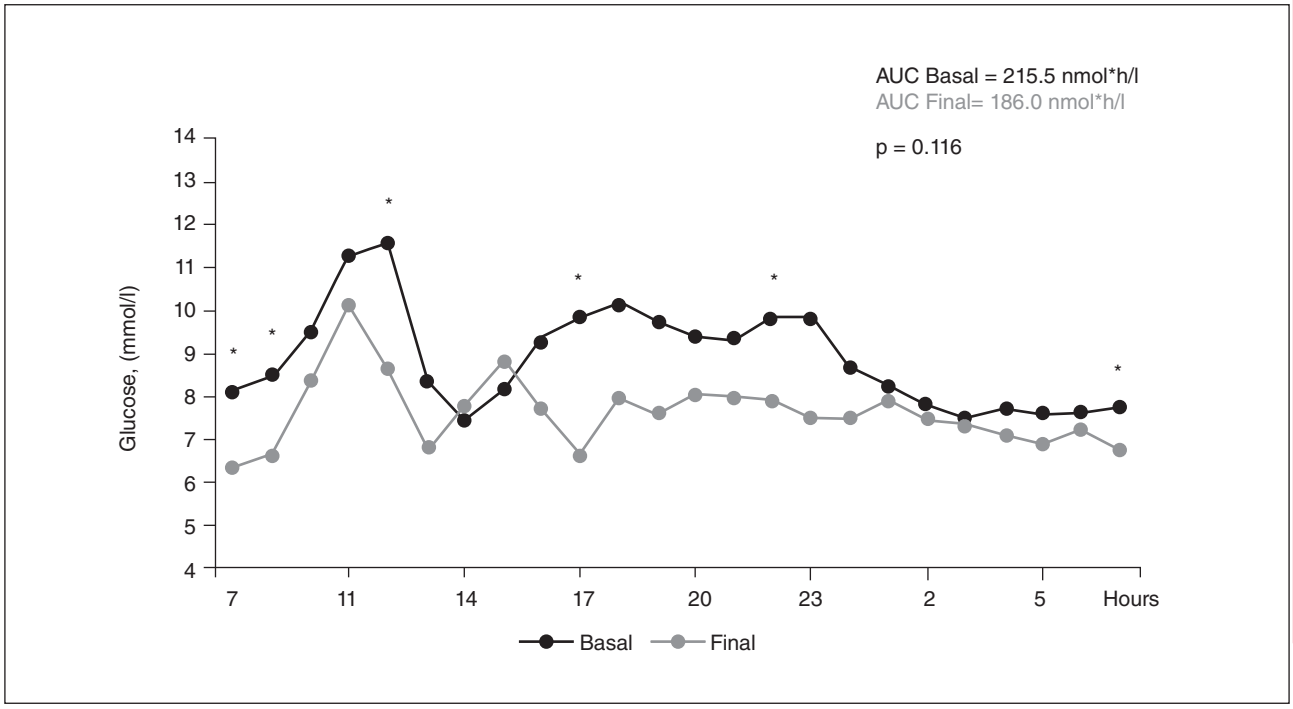

Figure 4. Behavior of glucose for 24 hours (baseline vs. final) with exenatide before lunch and dinner. *p < 0.05 (Wilcoxon rank test). AUC: area under the curve.

a higher value shows greater instability of glucose[4]. In this study, glycemic variability and assessment with MAGE showed no significant reduction according to any of the three different meal schedules, which may be due to the short period of drug intervention. Therefore, it is possible that with the dose of exenatide titrated to 10 µg twice daily and administered for a longer period of time, a greater reduction of glucose throughout the day with a decrease of A1C level as well as glycemic variability could be observed because one month is insufficient to assess A1C results. Even with the dose limitation and short intervention time, exenatide before breakfast and lunch improved glycemic control by reducing fasting glucose and AUC of glucose, including 15 points during the 24 hours evaluated. Therefore, we consider this to be the best administration schedule. However, because the purpose of this study was to assess glucose concentration and glucose behavior, the short duration should not limit the interpretation of our findings because the metabolic actions of exenatide on glucose concentrations have been demonstrated by other authors as soon as the first injection is administered[6,7,16].

The strengths of this study include randomization and the fact that patients received monotherapy with metformin at a stable dose and in an inpatient setting for laboratory assessments.

In the present study some additional effects of exenatide before lunch and dinner were observed such as reduction of TC, LDL-C, and BMI along with a statistical tendency to decreased weight and blood pressure. As observed with glycemic control results, it is possible that longer treatment and titrated doses of exenatide would have achieved significance according to these parameters in all groups. Furthermore, it should be noted that the sample size calculation does not take into account the above-mentioned variables.

In addition to the small sample size, the participation of possibly unidentified variables, such as different eating patterns in the study population, composition of individual daily meals, and use of low doses of exenatide, doses that in clinical practice are used only for purposes of achieving a major drug tolerability, make this research an exploratory or pilot study with limited results in the study population, preventing their generalization.

On the other hand, several studies have reported circadian-like patterns of GLP-1 levels in normal humans as well as a dampening of the amplitude in subjects with obesity and T2DM. Therefore, we cannot rule out that the varied observed response of exenatide at different times of administration on glycemic and metabolic variable measures may be due to the participation of different types of circadian disruption such as constant light exposure, feeding at inappropriate times, consumption of an obesogenic diet, the time period between meals and/or snacks, and the different caloric loads administered throughout the day as well as altered islet clock gene expression[17,18].

Adverse effects reported with the three different meal schedules showed no statistical significance; therefore, this aspect is not significant when making a clinical decision.

In conclusion, exenatide administration before breakfast and lunch achieved better glycemic control by reducing fasting glucose and AUC of glucose.

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DISCLOSURE OF INTEREST

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