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Linagliptin plus insulin for hyperglycemia immediately after renal transplantation: A comparative study ☆

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ABSTRACT

Aims: Post-renal-transplanted patients frequently present hyperglycemia immediately after the procedure. The goal of this work was to evaluate the effect of linagliptin + insulin in post-renal-transplanted patients with hyperglycemia.

Methods: Retrospective comparative study in post-renal transplanted patients with hyperglycemia after transplantation who were treated with linagliptin 5 mg daily plus insulin vs insulin alone for 5 days after renal transplantation with hyperglycemia. Main outcomes were glucose levels, insulin dose and severity of hypoglycemia.

Results: There were 14 patients treated with linagliptin + insulin and 14 patients treated only with insulin. Glucose levels and insulin doses were lower in the linagliptin + insulin group in comparison with the insulin alone group, 131.0 ± 15.1 vs 191.1 ± 22.5 mg/dl (7.27 ± 0.84 vs 10.61 ± 1.25 mmol/l) and 37.5 ± 6.3 vs 24.2 ± 6.6 U, respectively ($p < 0.05$). Hypoglycemia was less severe in the linagliptin + insulin group, 65.1 ± 2.2 vs 54.2 ± 3.3 mg/dl (3.61 ± 0.12 vs 3.00 ± 3.3 ± 0.18 mmol/l), p 0.036.

Conclusions: The combination of linagliptin + insulin provided better glycemic control with a lower insulin dose and less severe hypoglycemia in comparison to insulin alone in patients with hyperglycemia immediately after renal transplantation.

1. Introduction

Hyperglycemia in hospitalized patients, defined as blood glucose equal to or greater than 140 mg/dl -(7.8 mmol/L), is a common problem, since approximately one-third of patients have blood glucose levels above 126 mg/dl (6.99 mmol/l) [1]. The treatment goals are blood glucose levels between 140 and 180 mg/dl (7.77–9.99 mmol/l) for critically ill patients and 110–140 mg/dl (6.11–7.77 mmol/l) in selected populations [2,3].

In hospitalized patients the general mortality rate has been reported to be 1.7% for normoglycemic patients, 3.0% for previously known diabetic patients, and 16–31% for new hyperglycemic patients [1].

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Variations in blood glucose levels are related to increased mortality, longer hospitalizations and increased morbidity (infections, impaired immune response and wound healing, activation of inflammatory cytokines, prothrombotic state, increased production of reactive oxygen species in the mitochondria) and are not limited to known diabetic patients [2–4].

Glucose levels between 60 and 80 mg/dl (3.33–4.44 mmol/l) had an odds ratio (OR) of 1.06 for in-hospital death, and glucose levels between 100 and 200 mg/dl (5.55–11.10 mmol/l) were associated with an odds ratio of 1.32, the relation of plasmatic glucose with mortality showed a "J" shape curve, suggesting that low or high blood glucose levels are both deleterious [5].

Mortality, length of in-hospital stay and acute kidney failure have been associated with hyperglycemia postoperatively in different studies [3,6].

Hypoglycemia is one of the main limitations for tight glycemic control. The frequency of hypoglycemia varied between 24.3 and 27.8% in glucose-controlled patients and between 72.2 and 75.6% in noncontrolled patients [6].

Similar to hyperglycemia, glycemic variability and hypoglycemia can cause damage and seems to be worse than hyperglycemia.

The mean amplitude of glycemic excursions remains almost linear (r 0.86) with the renal excretion of 8-iso prostaglandin $F_{2\alpha}$, a marker of oxidative stress [7]. Hypoglycemia itself increases C-reactive protein, proinflammatory cytokines (TNF-α, interleukin-1β, IL-6, and interleukin-8), and markers of lipid peroxidation, ROS, and leukocytosis [3].

The recommended treatment of hospitalized patients with hyperglycemia is a combination of insulin analogs, which is accomplished using some insulin analogs with slow release rates (basal insulin) and other ones with fast or very fast release rates (prandial insulin); the so-called basal bolus insulin regimen. As a general point-of-care rule, capillary glucose determinations are performed before meals to adjust the dose of prandial insulin [8].

The incidence of cardiovascular events in T2D patients is a set of adverse outcomes of interest; drugs used for the treatment of T2D need to probe that do not increase the risk of cardiovascular diseases [9].

The evaluation of DPP-4 (dipeptidyl peptidase-4) inhibitors has provided variable evidence. Most studies have proven that the use of DDP-4 inhibitors is safe regarding cardiovascular outcomes [10,11]. The odds ratio for hospitalization for heart failure (HF) in iDPP-4 users was 1.00 (95% CI 0.94 to 1.07); incident HF, 1.01 (95% CI 0.92 to 1.11); and recurrent HF, 1.02 (95% CI 0.84 to 1.22). All-cause mortality was 6% lower in iDPP-4 users ($p < 0.001$). Insulin users showed an excess of risk for any type of hospital admission (19%) and death (20%) ($p < 0.001$) [12], as well as for falls in hospitals [13].

Different studies in patients with acute coronary syndrome and high cardiovascular risk have shown a safe profile for linagliptin regarding cardiovascular and renal function [14–16].

Posttransplant renal patients have a particularly high risk of hyperglycemia (80–90%) after renal transplantation (RT). Sometimes, the patients were already diabetic prior to the transplant (but unaware); other times, they are actually new diabetes cases. Hyperglycemia in the perioperative period has been related to increased graft rejection, infections or readmission to the hospital because of infection [17].

The recommended treatment for hyperglycemia in kidney-transplanted patients is based also on insulin analogs. However, in these patients conditions may change rapidly (adjustment of immunosuppressive drugs, changes in renal function or nutrition therapy), they require intensive blood glucose monitoring and flexible and safe treatment algorithms. All these conditions create a very challenging environment for the adequate use of insulin analogs. The use of DPP-4 inhibitors in the treatment of diabetic patients who have undergone kidney transplantation is increasing. Nevertheless, few studies have assessed the efficacy and safety of these drugs in the setting of diabetic kidney-transplanted patients [17].

Although these drugs are all capable of lowering glucose, there may be some differences between them. In a population of renal-transplanted patients the mean difference between the pre- and posttreatment glycated hemoglobin (HbA1c) was −0.53 for sitagliptin, −0.38 for vildagliptin and −1.4 for linagliptin; and the average cyclosporine blood levels in the pre- and posttreatment period changed by +30.62 ng/mL in the sitagliptin group, −24.22 ng/mL in the vildagliptin group and −8.5 ng/mL in the linagliptin group [18].

The goal of this work was to evaluate the effect of combined treatment with insulin plus linagliptin in comparison with insulin alone on glucose control and hypoglycemia in hospitalized posttransplanted renal patients who present hyperglycemia during the first 24 h after RT.

2. Materials and methods

2.1. Study design and population

This retrospective comparative study was performed in a single center between 2016 and 2018 and included the data collected from 28 hospitalized post-renal-transplanted patients who presented hyperglycemia (>140 mg/dl or 7.77 mmol/l) immediately after RT (<24 h after RT). Fourteen patients were treated with linagliptin 5 mg daily plus a basal bolus insulin scheme prescribed by the Endocrinology group at the hospital, and 14 patients treated only with a basal bolus insulin scheme were randomly selected from a list of patients treated during the same period of time and by the same Endocrinology group. The linagliptin dose was 5 mg daily, and the basal bolus insulin regimen was started and adjusted according to the international guidelines; in general, patients received a starting insulin dose of approximately 0.5 U/kg/day, given half as basal insulin (NPH or Glargine) once or twice daily and half as insulin lispro divided into three equal doses before meals. The insulin dose was adjusted daily to achieve the goal of fasting glucose between 80 and 140 mg/dl (4.44–7.77 mmol/l) or random glucose levels below 180 mg/dl (9.99 mmol/l). A correction insulin dose was used before each meal, depending on the glucose measurements, starting at 1 unit for each 40 mg above 140 mg/dl (7.77 mmol/l) of glucose. Glucose levels were monitored at fasting and before each meal, as well as at bedtime according to standard clinical practice. Data regarding fasting and preprandial glucose levels, hypo-

glycemia, renal function, and immunosuppression therapy were recorded from the patient´s file during the first 5 days after RT; HbA1c levels were measured before, and 6 and 12 months after RT; fasting glucose and renal function were also recorded at 1, 6 and 12 months after RT. Patients were included if they were between 18 and 65 years of age and presented fasting hyperglycemia (>140 mg/dl or 7.77 mmol/l) during the first 24 h after RT.

The Ethical and Research Committee at the Hospital approved the study protocol with the number CEI-49-18.

Fasting glucose was measured by dry chemistry with the colorimetric method (Vitros 5600; Ortho Clinical Diagnostics), and prelunch and predinner glucose were measured by the capillary method using an Accu-Chek glucometer. Hypoglycemia was defined when glucose levels were <70 mg/dl (3.88 mmol/l). Glycated hemoglobin A_{1C} (HbA_{1C}) was determined using high-performance liquid chromatography with a DS-5 Analyzer (Drew Scientific, Inc., Miami, FL, USA). Basal prediabetes was defined when HbA_{1C} was 5.7–6.4%.

The main outcomes were glucose levels during the first 5 days in the hospital and after 6 and 12 months, insulin dose, frequency and severity of hypoglycemia, and renal function at 1, 6 and 12 months after RT.

2.2. Statistical analysis

We used an unpaired *t* test for numerical comparisons between the groups treated with linagliptin + insulin vs insulin alone and repeated measures ANOVA for intragroup comparisons with a Bonferroni post hoc test. A chi-square test was used to compare proportions between the study groups. A p value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 22 (SPSS, Chicago, IL).

3. Results

There were 28 patients with hyperglycemia post renal transplantation included in this study; 14 were treated with linagliptin 5 mg daily plus a basal bolus insulin scheme based on basal (NPH) and lispro insulin, and 14 were treated only with basal (NPH) and lispro insulin. In Table 1, we can see the general characteristics of the study population; as we can see, male patients were more prevalent in both groups (85.7%), with an average age of approximately 50 years without differences between the groups. Weight, BMI, days of hospitalization (16 vs 17), prediabetes, and previous diagnosis of

Table 1 – Characteristics of the study groups.

N = 288	Insulin + Linagliptin N = 14	Insulin N = 14	*p value*
Sex (M/F)	12/2	12/2	1.000
Age (years)	51 ± 2	49 ± 3	0.512
Previous T2D, n (%)	10 (71.4)	8 (57.1)	0.695
Prediabetes, n (%)	0 (0)	1 (7)	–
Weight (kg)	72.8 ± 4.5	72.3 ± 3.3	0.908
BMI (kg/height^2)	26.6 ± 1.1	26.2 ± 1	0.756
HbA1c (%)			
- Before RT	7.15 ± 1.46	8.05 ± 1.39	0.248
- 6 m postRT	8.30 ± 1.67 (*n* = 8)	7.69 ± 1.60 (*n* = 10)	0.428
- 12 m postRT	7.80 ± 1.75 (*n* = 8)	8.02 ± 1.70 (*n* = 10)	0.785
Fasting glucose (mg/dl)			
- 0 day	264.3 ± 36.6	245.2 ± 26.5	0.677
- 5 day	131 ± 15	191 ± 22	0.036
- Last day in hospital	135.4 ± 14.0	155.0 ± 19.0	0.418
- 1 month	160 ± 26	239 ± 43	0.143
- 6 months	131 ± 17	127 ± 16	0.879
- 12 months	99 ± 13	211 ± 32	0.008
Days in hospital	16 ± 2	17 ± 2	0.872
Hypoglycemia, n	5	5	
Creatinine levels, mg/dl			
- Before RT	7.6 ± 0.7	10.2 ± 1.0	0.044
- 1 m postRT	1.7 ± 0.2	1.7 ± 0.3	0.969
- 6 m postRT	1.9 ± 0.4	1.6 ± 0.4 (n = 13)	0.545
- 12 month postRT	1.3 ± 0.1(n = 12)	1.5 ± 0.2 (n = 12)	0.724
Methylprednisolone dose (mg/day)			
- Day 1	616 ± 95	690 ± 139	0.337
- Day 5	84 ± 11	82 ± 25	0.422
Mycophenolic acid dose (mg/day)			
- Day 1	1875 ± 125	1750 ± 250	0.936
- Day 5	1818 ± 139	1750 ± 133	0.884

diabetes were not different between the study groups (n = 10 in insulin + linagliptin vs n = 8 in insulin alone, p 0.695). HbA1c levels were 8.05 ± 1.39% in the insulin group and 7.15 ± 1.46 in the insulin + linagliptin group (p 0.248). Regarding insulin dose, there was an increase in total insulin dose only in the insulin group from day 1 to day 5, while in the insulin + linagliptin group, it remained unchanged (from 25.5 ± 5.5 to 37.5 ± 6.3 vs from 21.3 ± 2.5 to 24.2 ± 6.6 U, respectively; Fig. 1A, p 0.089); the same difference was observed in basal insulin dose (Fig. 1B, p 0.03). On the other hand, the rapid insulin dose was significantly higher in the insulin group vs the insulin + linagliptin group at days 1, 2, 4 and 5 (at day 5, it was 19.6 ± 3.9 vs 7.1 ± 4.0 U, Fig. 1C, <0.05).

Fasting and preprandial glucose levels were not different between the study groups at baseline, and as expected, they improved in both groups (FG from 191.4 ± 21.7 to 131.1 ± 15.1 mg/dl (10.62 ± 1.20 to 7.28 ± 0.84 mmol/l) and from 228.9 ± 22.6 to 191.1 ± 2.5 mg/dl (12.71 ± 1.54 to 10.61 ± 0.14 mmol/l), in the linagliptin + insulin and insulin alone group, respectively); however, fasting glucose levels showed significantly better improvement in the insulin + linagliptin group compared with the insulin group at days 3 (141.9 ± 15.3 vs 234.8 ± 28.3 mg/dl (7.88 ± 0.85 vs 13.03 ± 1.57 mmol/l), p 0.008), 4 (158.2 ± 16.5 vs 215.7 ± 21.2 mg/dl (8.78 ± 0.92 vs 11.97 ± 1.18), p 0.042) and 5 (131.1 ± 15.1 vs 191.1 ± 22.5 mg/dl (7.28 ± 0.84 vs 10.61 ± 1.25), p 0.036; Table 1, Fig. 2A).- In the insulin + linagliptin group there was a significant reduction in fasting (Fig. 2A, p 0.008) and prelunch glucose levels at day 5 vs day 1 (Fig. 2B, p 0.002), while in the insulin group there was only a significant reduction in fasting glucose levels at day 5 in comparison to day 2 to 5 (Fig. 2A, p 0.02). Predinner glucose levels tended to be lower in the insulin + linagliptin group, without reaching statistical difference between groups (Fig. 2C). HbA1c levels were similar between the study groups at 6 and 12 months (7.67 ± 1.59 vs 8.30 ± 1.67, at 6 months, and 8.02 ± 1.70 vs 7.80 ± 1.75 at 12 months in the insulin and insulin + linagliptin group, respectively, Table 1); however, fasting glucose levels were lower in the insulin + linagliptin group during the long-term follow-up, being 99 ± 13 vs 211 ± 32 mg/dl (5.50 ± 0.72 vs 11.71 ± 1.77 mmol/l), p 0.008, (Table 1) at 12 months, although only 8 patients continued with linagliptin for at least 6 months in the insulin + linagliptin group.

Notably, the incidence of hypoglycemia was equal between the study groups (5 in each group, Table 1), but the severity of hypoglycemia was worse in the insulin group (glucose levels 54.2 ± 3.3 mg/dl vs 65.1 ± 2.2 mg/dl (3.00 ± 0.18 vs 3.61 ± 0.12 mmol/L), p 0.036, Fig. 3).

Although creatinine levels were not significantly different between the study groups after 1, 6 and 12 months post renal transplantation, 3 (21.4%) patients in the insulin group and 1 (7.1%) patient in the insulin + linagliptin group had renal graft failure during the first year after RT.

The doses of methylprednisolone and mycophenolic acid, as immunosuppressive therapies were similar between the study groups during the first five days after RT (Table 1).

4. Discussion

In this retrospective and comparative analysis, we found better improvement in glucose levels, lower insulin require-

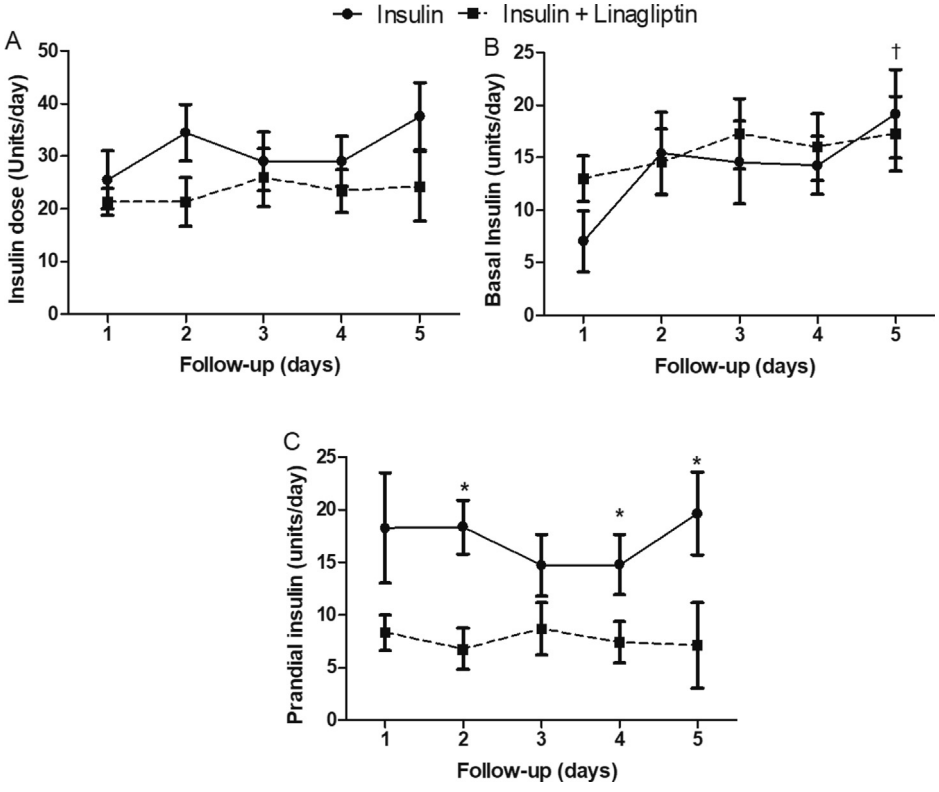

Fig. 1 – Total insulin (A), basal insulin (B), and prandial insulin (C) dose per day between the study groups * p < 0.05 between groups, † p < 0.05 vs basal intragroup for insulin treatment.

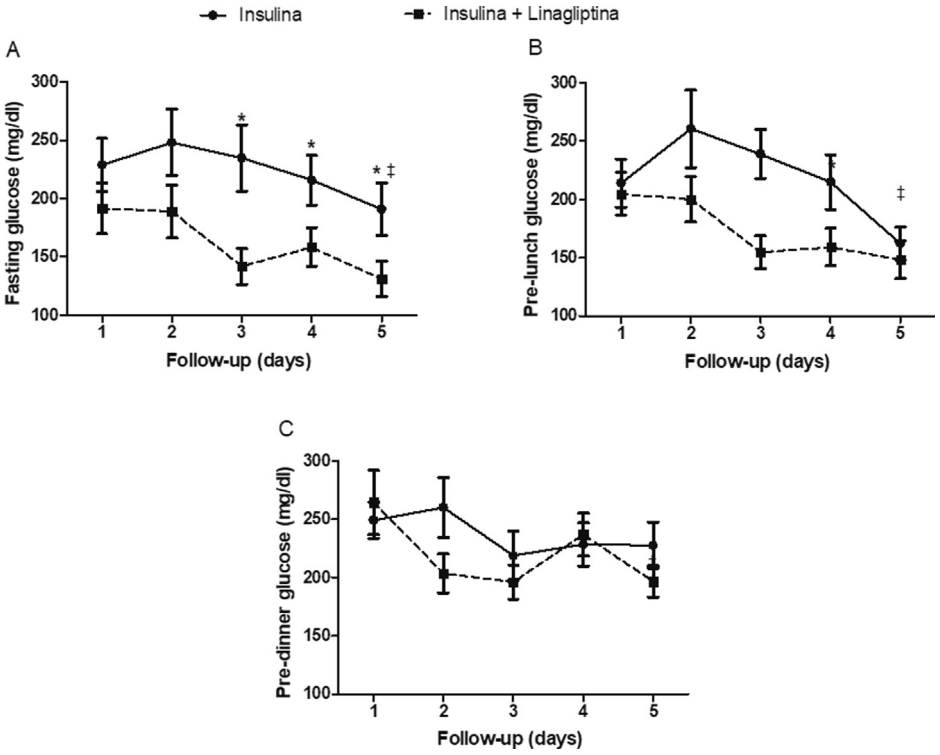

Fig. 2 – Fasting (A), prelunch (B), and predinner (C) glucose levels between the study groups. * p < 0.05 between groups, ‡ p < 0.05 vs basal intragroup for insulin + linagliptin treatment.

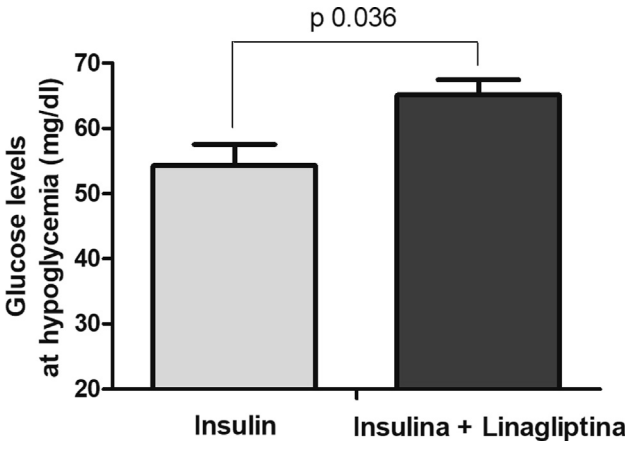

Fig. 3 – Glucose levels during the hypoglycemic events between the study groups.

ments and reduced severity of hypoglycemic events when linagliptin was added to the basal bolus insulin regimen in patients who present hyperglycemia immediately after RT in comparison to patients treated only with the basal bolus insulin regimen.

To our knowledge, this is the first study that reports the effect of a DPP-4 inhibitor, linagliptin, as an adjunctive therapy with insulin to better control glycemic imbalance presented immediately after RT in the hospital setting.

Kidney and kidney-pancreas transplantation has been shown to prolongs life and improves vascular function in patients with type 1 diabetes, highlighting the impact of a successful recovering on kidney function on patient´s life [19–21]. Posttransplant renal patients frequently present hyperglycemia immediately after RT [22,23], mainly due to the high dose of immunosuppressive therapies that they receive and the previous presence of diabetes in many cases, together with a high prevalence of risk factors and insulin resistance in these patients [23]. Hyperglycemia in the hospitalized patient has been shown to increase the risk of several micro- and macrovascular complications [5,6,24,25], and several efforts have been made to control and stabilize glucose levels in these patients. The standard treatment of hyperglycemia in hospitalized patients with or without RT is based mainly on insulin, according to international guidelines [25]; however, this kind of patient may be more sensitive to glucose variability and often presents hypoglycemia. Hypoglycemia is also a well-recognized risk factor for several complications and could be associated with renal failure in the posttransplant patient [24,26], and glycemic variability has been shown to be also a risk factor for falls in hospitalized patients [13]

In this study, we found better glycemic control and reduced severity of hypoglycemia in patients treated with linagliptin plus insulin, which implies lower glucose variability in these patients. Glucose variability has been found to be a risk factor for hypoglycemia in hospitalized T2D patients treated with basal bolus insulin regimen [24]. The lower variability in basal glycemia avoids the need to use a higher prandial insulin dose (bolus) to reach a blood glucose goal, which in turn reduces the risk of hypoglycemia.

Previous studies with DPP-4 inhibitors in hospitalized patients have found different results. When sitagliptin was used to prevent perioperative stress hyperglycemia in nondiabetic patients, there were no differences in comparison to placebo, although only patients with nontransplant surgeries and normal renal function were included [27]; in hospitalized T2D patients, sitagliptin combined with basal insulin had a similar effect on glucose control and hypoglycemia in comparison to the basal bolus insulin regimen [28], but no patients with RT were included in this study. In noncritically ill hospitalized T2D patients treated with saxagliptin, similar glucose levels were found in comparison with patients treated with the basal bolus insulin regimen and lower insulin doses, because patients treated with saxagliptin received only premeal insulin correction doses [29], although patients were excluded if they received immunosuppressive therapy with glucocorticoids.

There are few studies with linagliptin in hospitalized patients. Umpierrez et al evaluated the efficacy and safety of linagliptin in comparison with the basal bolus insulin regimen in patients with T2D undergoing noncardiac surgery [30]. Overall, they found similar glucose levels between the study groups and a lower frequency of hypoglycemia in the linagliptin group with a lower insulin dose, which was expected since these patients received only the correction premeal insulin dose. However, in the basal bolus insulin group, the total insulin dose was 29.3 ± 15.8 U/day, similar to the average insulin dose in the insulin group in our study, 31.1 ± 20 U/day; also, the basal insulin dose was similar to our study, 15.7 ± 8.1 vs 14.1 ± 13.0 U/day. As presented before, in our study, the main difference was the prandial insulin dose, besides that both groups were on the basal bolus insulin scheme. They also found a lower frequency of hypoglycemia, but we found a difference in the severity of hypoglycemia as well, being less severe in patients treated with linagliptin plus insulin.

The reports of studies with DPP-4 inhibitors tell us that DPP-4 inhibitors may not have to replace basal or prandial insulin, but they must be combined, and in the end, these patients will need lower insulin doses, with the expected lower risk of frequency or severity of hypoglycemia and similar or better glucose control. Pérez-Belmonte et al. [31] also evaluated the efficacy of a basal bolus insulin regimen in comparison with linagliptin plus basal insulin in noncritically ill noncardiac surgery patients; they found no differences in glucose levels but lower insulin dose and fewer hypoglycemic events in the linagliptin-basal insulin groups. They also reported similar total insulin doses in the basal bolus insulin group 32.5 U/day to our equivalent group 31.1/day; as mentioned before, the linagliptin-basal insulin group received only basal insulin and correction prandial insulin, which is why the authors also reported a lower total insulin dose in addition to no differences in the supplemented rapid-acting insulin doses. Notably, patients with linagliptin in our study achieved slightly lower glucose levels than those with linagliptin in these studies, which could be partially explained by the fact that both groups in our study received the basal bolus insulin regimen, and none of these two previous studies included post-renal-transplanted patients [30,31]. Interestingly, insulin use has been reported to be the main risk factor also for falls in hospitalized patients [13]

Posttransplant renal patients need more attention regarding evaluation and treatment of glucose control before, immediately after and over long-term follow-up after RT, in an effort to improve renal transplant success and reduce the risk of complications.

Linagliptin has shown cardiovascular and renal safety in patients with T2D and different degrees of renal function in several studies [15,32–34], and it could be an option in combination with insulin in posttransplant renal patients, in whom cardiovascular and renal concerns need to be carefully considered.

The main advantage of our study is that it is the first study reporting the impact of combined linagliptin plus insulin for hyperglycemia in posttransplant renal patients, since most of the previous studies have been performed in ambulatory patients or in nontransplant renal patients and since the physicians who implement in hospital hyperglycemia treatment were the same for all patients, somehow it standardizes the interventions and the follow-up of the patients. Our study has several limitations: it was not randomized, and it was a retrospective analysis; consequently, it cannot remain free of several record biases.

In conclusion, in this retrospective study, the combination of linagliptin with a basal bolus insulin regimen improved glucose levels and reduced insulin dose and hypoglycemia severity in posttransplant renal patients with hyperglycemia immediately after RT. Prospective and randomized studies are needed to better define the role of these adjunctive therapies in renal transplant patients.

5. Data Availability

The datasets generated during and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

6. Financial support

This study was supported by the Hospital Regional de Alta Especialidad del Bajío, León, Guanajuato, México.

7. Disclosure summary

The authors have nothing to disclose.

Author contribution

AAG and RGM conceived, designed, coordinated the study, performed the data analysis and wrote the manuscript; DCS designed, coordinated the study and wrote the manuscript; EGDP conceived, designed, coordinated the study and wrote the manuscript. All authors reviewed and approved the final manuscript.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107864.

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