Effect of Insulin Degludec Versus Insulin Glargine on Glycemic Variability in Patients With Renal Transplantation with Pre-existing Type 2 Diabetes Mellitus; A 1-year, Randomized, Treat-to-Target Pilot Trial

Amin R Soliman,[1] Haytham Soliman,[2] Rabab M. Ahmed[1]

[1]Department of Internal Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt
[2]House Officer, Faculty of Medicine, Cairo University, Cairo, Egypt

Keywords. insulin degludec, kidney transplantation, hypoglycemia, insulin glargine

Introduction. This study hypothesized that the insulin Degludec may have benefit if used in management of diabetes mellitus after renal transplantation to achieve better control at the critical time of adjustment of immunosuppressive regimens during the first year post transplant.
Methods. Fifty patients with Type 2 diabetes Mellitus after renal transplantation with stable serum creatinine with glycosylated hemoglobin (HbA1C) 7 to 11% were included in the study to receive either Insulin Degludec or Insulin Glargine. Fasting blood glucose, 2 hour post-prandial levels and (HbA1c), were measured at 12, 16, 26, 40, and 52 weeks after renal transplantation also hypoglycemic episodes were documented all through the study.
Results. Despite both groups are matched as regards demographic and metabolic data, FPG, and 2h PPG were lower in insulin Degludec group all through the study. HbA1c most pronounced decline, occurred at 52th week of treatment in both groups. The most important clinically relevant finding in our study was that; the overall confirmed hypoglycemia rates and the rate of nocturnal confirmed hypoglycemia was significantly lower with Degludec treated group ($P < .001$).
Conclusion. Insulin Degludec provides optimum glycemic control in in the first year post-renal transplant patients with significantly lower rate of hypoglycemia.

IJKD 2021;15:385-90
www.ijkd.org
DOI: 10.52547/ijkd.6131

Original Paper

INTRODUCTION

High doses and long-term usage of steroid and different immunosuppressive agents and tapering modality, iatrogenic weight gain may cause fluctuations in glucose level in renal transplant recipients, which can negatively affect graft function and survival as well as on the ability of the immunocompromised host to fight infections.[1]

No strict guidelines for management of post-transplant hyperglycemia, it just follow the same management of type 2 diabetes. However, different Insulin types and regimen were recommend in most published data as first line therapy which can be accompanied by oral hypoglycemic drugs after immunosuppressive drug dosage stabilization.[1]

Long-acting insulin has showed stable glucose profile in type 2 diabetes patients. Some researchers compared Insulin Degludec and insulin Glargine in those patients and the results are in favor of Insulin Degludec as regards the fewer hypoglycemic

events.[2-5]

We hypothesized that the insulin Degludec may have the same benefit if used in management of diabetes mellitus after renal transplantation to achieve better control at the critical time of adjustment of immunosuppressive regimens during first year of therapy.

MATERIALS AND METHODS

A double blind, randomized, parallel group clinical trial was carried out. The sample size was calculated using the formula for clinical trials of mean differences with a minimum number of 25 patients per group was obtained. Patients between 30 and 60 years of age were included with T2DM after a successful renal transplantation with serum creatinine less than 1.6 mg/dL, A1C 7 to 11%.

In our study, all donors are living donors. Inclusion criteria included also stable immunosuppressive medications and stable weight during first 3 months of the study. Both groups are matched in type, dose, tapering modality of immunosuppressive drugs and in anti-glycemic agent.

Groups were assigned randomly by sealed envelope either to receive insulin Degludec SC, or insulin Glargine SC. Eligible participants were randomized to receive once daily Degludec (100 U/mL, 3 mL PDS; Novo Nordisk, Bagsværd, Denmark) or Glargine (Lantus, 100 U/mL, 3 mL SoloStar; Sanofi-Aventis, Paris, France). They were given every 24 hours and were followed up for one year.

Dose individually adjusted according to insert company protocol. The starting dose for both insulins was 10 units. In the subsequent 52 treatment weeks, each participant's insulin dose was adjusted ensuring titration toward pre breakfast plasma glucose of 100 mg/dL.

Participants measured blood glucose with calibrated glucose meter with strips. Frequent visit scheduled for first 6 months and treat-to-target approach were chosen to ensure optimal titration. Participants are allowed to receive short acting insulins and different oral hypoglycemic drugs and were reported.

The clinical findings and laboratory tests were registered at baseline. Body weight, body mass index and blood pressure were performed during the initial visit. Also, plasma glucose concentrations both fasting (FBG) and 2 hour post Prandial (2-PPG) levels and glycosylated haemoglobin (HbA1c), were measured at 12, 16, 26, 40, and 52 weeks after renal transplantation which served to assess the glycemic variability during the first year of transplantation.

The primary outcome was to compare changes from baseline in HbA1c. Adverse events and adherence to treatment were documented. Also Metabolic study at baseline included serum LDL-cholesterol, HDL-cholesterol, triglycerides in addition to serum creatinine levels. In addition, diabetic complications at inclusion till termination of study were also counted including number of treatment emergent confirmed hypoglycaemic episodes. Hypoglycemic episodes are defined as: 1) Mild: any measured Capillary blood glucose (CBG) 54 to 72 mg/dL, 2) Severe: any episode of hypoglycemia with a measured CBG < 54 mg/dL, or which the subject is not able to recognize and treat without the direct (substantial) intervention of a professional caregiver, nurse or physician (e.g. intravenous dextrose or intramuscular glucagon).

Exclusion criteria included major postoperative complications following the transplant surgery, significant GI discomfort with nausea or vomiting, inability to learn continuous glucose monitoring, those with fasting triglycerides of > 400 mg/dL, impaired liver function, defined as ALAT (alanine aminotransferase) above or equal to 2.5 times upper normal range, serum creatinine above or equal to 1.6 mg/dL at the beginning and during the study, Occurrence of rejection, those with breast feeding and patients with untreated thyroid disease.

Ethics Statements

All participants provide written consent. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Statistical Analysis

Data were coded and entered using the statistical package SPSS version 23. Data were summarized using mean and standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables while non-parametrical

Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables. For comparing categorical data, Chi-square (c2) test was performed. An exact test was used instead when the expected frequency is less than 5. Correlations between quantitative variables were done using Spearman correlation coefficient. *P* values less than .05 were considered as statistically significant.

RESULTS

As can be seen from Table 1, 62 patients with renal transplant who met the inclusion criteria were included in the study, and they divided into two groups. Group 1 included 37 patients will receive Insulin Degludec and Group 2 included 25 patients will to receive Insulin Glargine. Only Fifty patients of them (28 patients in group 1 and 22 in group 2) subjected to completed the 52 weeks of study after withdrawal of 12 patients due to various reasons mentioned in same Table.

Baseline characteristics, metabolic and laboratory data were generally comparable between the two groups studied (Table 1, 2, and 3).

Based on the cut off values for hyperglycemia and dyslipidemia it is also noted that; both groups had uncontrolled diabetes and significant dyslipidemia (Table 2). Other anti-glycemic drugs used as adjuvant therapy to adequately control patients` glycemic profile are reported in Table 4.

None statistically significance difference between both groups as regarding the diabetic complications Table 5.

Comparable decrease in FPG, 2h PPG, and HbA1c from baseline to the end of the study in both groups. FPG and 2h PPG were lower in insulin Degludec group all through the study as noticed from Table 6.

Table 2. Baseline Laboratory Data Before Study in Both Groups

Parameter	Insulin Degludec	Insulin Glargine	*P*
FBS, mg/dL	205 ± 16.7	210 ± 15.4	> .05
A1c (%)	8.1 ± 0.7	8.2 ± 0.5	> .05
LDL-cholesterol, mg/dL	137 ± 8.6	138 ± 7.5	> .05
HDL- cholesterol, mg/dL	39.5 ± 3.8	38.8 ± 4.1	> .05
Triglycerides, mg/dL	190 ± 0.63	205 ± 0.21	> .05
Serum creatinine, mg/dL	1.3 ± 0.28	1.3 ± 0.31	> .05
BUN, mg/dL	20 ± 9	24 ± 5	> .05
AST, U/L	39 ± 5	39 ± 6	> .05
ALT, U/L	55 ± 9	57 ± 5	> .05

Table 3. Baseline Laboratory Data During Study in Both Groups

Parameter	Insulin Degludec	Insulin Glargine	*P*
Serum Creatinine, mg/dL	1.4 ± 0.27	1.3 ± 0.51	> .05
BUN, mg/dL	22 ± 8	23 ± 4	> .05
AST, U/L	40 ± 2	39 ± 4	> .05
ALT, U/L	56 ± 6	55 ± 11	> .05

Table 1. Baseline Data of Both Groups Studied

Parameter	Insulin Degludec	Insulin Glargine	*P*
Patients Included in the Study	37	25	
Patients Withdrawn Before Treatment	3	0	
Patients Subjected to Treatment	34	25	
Patients Withdrawn After Treatment	6	3	
-Non-compliance	1	1	
-Financial	4	1	
-Side Effects	1	1	
Patients Completing Treatment	28	22	
Sex Ratio (n)			
Male	17	14	> .05
Female	11	8	
Age, y	38 ± 8.7	39.2 ± 8.4	> .05
BMI, kg/m^2	31.5 ± 4.1	30.5 ± 5.2	> .05
Duration of Diabetes, y	8.3 ± 5.5	10.5 ± 6.3	> .05
Hypertension			
Systolic	128.3 ± 14.5	131.2 ± 10.6	> .05
Diastolic	75.5 ± 9.5	78.1 ± 8.4	
Donors (Living)	100%	100%	> .05
Related	22 (78.6%)	17 (77.3)	> .05
Unrelated	6 (21.4%)	5 (22.7%)	> .05

Table 4. Anti-diabetic Medications at Screening in Patients Completed the Study

Parameter	Insulin Degludec (n = 28)	Insulin Glargine (n = 22)
Sulfonylureas (n)	4	3
DPP-4 Inhibitor (n)	6	3
Vildagliptin	3	2
Sitagliptin	3	1
Metformin (n)	10	9
Insulins (n)	18	18
Short-acting	11	12
Intermediate-acting	7	6

Abbreviations: DPP-4, dipeptidyl peptidase-4.

Table 5. Diabetic Complications of Patients Completed the Study at Inclusion

Parameter	Insulin Degludec	Insulin Glargine	*P*
Hypertension	21	17	> .05
Arteriosclerosis	2	2	> .05
Retinopathy	5	4	> .05
Neuropathy	12	10	> .05

Table 6. Blood Sugar (mg/dL) in Relation to Time

Time	Fasting ID Fasting IG	Prandial ID Prandial IG	A1c ID A1c IG
12 Weeks	125 ± 15.5 130 ± 10.5	162 ± 10.5 170 ± 11	7.51 ± 0.8 7.48 ± 0.7
16 Weeks	126 ± 11.5 128 ± 11.6	150 ± 11.5 158 ± 11.5	7.22 ± 0.9 7.21 ± 0.8
26 Weeks	110 ± 10.1 116 ± 9.5	155 ± 9.9 160 ± 15.6	7.1 ± 0.7 7.08 ± 0.6
40 Weeks	105 ± 10.5 108 ± 10.3	156 ± 9.6 160 ± 10.5	7.03 ± 0.8 7.00 ± 0.9
52 Weeks	102 ± 11.1 105 ± 8.5	150 ± 10.8 162 ± 11.6	6.9 ± 0.6 6.9 ± 0.8

Abbreviations: ID, insulin degludec; IG, insulin glargine; A1c, HbA1c.

As regarding HbA1c most pronounced decline, occurred at 52th week of treatment in both groups and this indicates that Degludec is non-inferior to glargine (Table 6).

The number of overall confirmed hypoglycemia rates and the rate of nocturnal confirmed hypoglycemia all through the study was significantly lower with Degludec treated group and this was statistically significant ($P < .001$) as shown in Table 7.

DISCUSSION

Diabetes always received considerable attention in medical field due to evident metabolic and vital organs damage accompanied its progression.[6-8]

It is not rare that even non-diabetic patients may developed post-transplant diabetes mellitus (PTDM) up to 25% due to numerous of causes which reported in many reviews.[9]

Nephrologists fall in trouble when they confront the sophisticated immunosuppressive (IS) regimen against the risk of rejection with inadequate immunosuppression and against the associated significant higher rates of cardiovascular disease and infection with uncontrolled glycemic profile.[10-13]

Because of the relative shortage of available transplantable organs versus a growing end-stage kidney disease population, glycemic profile should managed carefully to maintain adequate allografts function but unfortunately, the rationale for treating patients with NODAT is obtained from studies of non-transplanted patients.[14-15]

Basal-bolus insulin mimics normal insulin release and one of the most important events in this field is FDA Approval of Ultra-Long-Acting Basal insulin Degludec at beginning 0f 2016.

After its spreading to the market, studies began to compare it to insulin glargine in type 1 and type 2 DM. Almost all the studies demonstrate that; Degludec is associated with equivalent HbA1c control and significantly lower nocturnal hypoglycemia rates.[16-19]

Very little was found in the literature about Insulin Degludec in renal patients. Istvan Kiss *et al.* mentioned that no difference in Pharmacokinetics of Insulin Degludec in study included normal patients, CKD patients with different GFR and even in ESRD patients and they found also no need for

Table 7. Confirmed Reported Hypoglycemic Episodes

Numbers of Hypoglycemic Episodes	12 week	16 week	26 week	40 week	52 week	*P*
Overall Episodes						
Insulin Degludec	2	3	2	2	2	< .001
Insulin Glargine	3	3	4	5	5	
Nocturnal Episodes						
Insulin Degludec	1	1	1	1	1	< .001
Insulin Glargine	1	1	3	3	4	

dose adjustments in patients with impaired renal function but unfortunately this study assess single dose only of insulin degludec.[20]

Recent study by Debmalya Sanyal *et al.* included 61 post-kidney transplant diabetic patients to evaluate glycemic parameters after receiving insulin Degludec. They found Degludec is tolerated, safe and effective in those patients.[21] The differences between our study and Sanyal *et al.* study are: our study compare the two commonly used forms of basal insulin and we follow up the patients for one year but in their study, they only used Degludec and the patients is followed up only for 3 months.

Binayak Sinha *et al.* which publish a case of uncontrolled T2DM, post renal transplantation with burning at the site of glargine injection, her glycemic parameters improved 1 week later after switching to Degludec at the same dose.[22]

In addition, in an indirect way, Miyako *et al.* reported poor glycemic control in case using steroids for rheumatic polymyalgia until Glargine was switched to Degludec. This change helps to attain postprandial hyperglycemia control.[23]

In our study, despite that 100% of patients in both groups had uncontrolled diabetes and use other anti-glycemic drugs as adjuvant therapy to control their glycemic profile; FPG, 2h PPG and HbA1c decreased from baseline to the end of the study in both groups indicating that both drugs are effective. However, FPG and 2h PPG are lower in insulin Degludec group than in insulin Glargine group all through the study. The numbers of the overall confirmed hypoglycemia rates and the rate of nocturnal confirmed hypoglycemia was significantly lower with Degludec treated group all through the study and this was statistically significant.

Importantly, our study was conducted on diabetic renal transplant patients with very limited published data about this. However, the small size of sampling is considered as limitation of the study. Future studies on the current topic are recommended as caring for transplant patients is a complex lifelong process that requires a multidisciplinary team approach.

CONCLUSION

Insulin Degludec provides optimum glycemic control in in the first year post renal transplant patients with significantly lower rate of hypoglycemia.

CONFLICT OF INTEREST

None.

ACKNOWLEDGMENT

None.

SOURCE(S) OF SUPPORT

None.

REFERENCES

1. Tahseen A Chowdhury. Post-transplant diabetes mellitus. Clin Med (Lond). 2019 Sep; 19(5): 392–395.
2. Jonassen I, Havelund S, Hoeg-Jensen T, et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long acting basal insulin. Pharm Res 2012; 29: 2104–2114.
3. Zinman B, Fulcher G, Rao PV, et al. Insulin Degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomized, open-label, phase 2 trial. Lancet 2011; 377: 924–931.
4. Heller S, Buse J, Fisher M, et al. BEGIN Basal-Bolus Type 1 Trial Investigators Insulin Degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3 randomized, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379: 1489–1497.
5. Garber AJ, King AB, Del Prato S, et al. NN1250-3582 (BEGIN BB T2D) Trial Investigators Insulin Degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomized, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379:1498–1507.
6. Diabetes. World Health Organization, Geneva, 2016.
7. Sarwar N, Gao P, Seshasai SR, et al.Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Emerging Risk Factors Collaboration. Lancet. 2010; 26; 375:2215-2222.
8. Hailing Yang, Dede Lian, Xiaofei Zhang, Hongjun Li, Guangda Xin. Key Genes and Signaling Pathways Contribute to the Pathogensis of Diabetic Nephropathy. IJKD 2019;13:87-97.
9. Peev V, Reiser J, Alachkar N. Diabetes mellitus in the transplanted kidney. Front Endocrinol (Lausanne) 5: 2014.
10. Thomusch O, Wiesener M, Opgenoorth M, et al. Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomized controlled trial. Lancet 2017; 388:3006.
11. Cole E., Prasad G., Cardella C., et al. A pilot study of reduced dose cyclosporine and corticosteroids to reduce new onset diabetes mellitus and acute rejection in kidney transplant recipients. Transplant Res 2: 1 (2013) PMID: 23369458. DOI: .10.1186/2047144021.
12. Israni A., Snyder J., Skeans M., Kasiske B. Clinical

diagnosis of metabolic syndrome: predicting new-onset diabetes, coronary heart disease, and allograft failure late after kidney transplantation, Transplant Int (2012) 25: 748–757.

13. Cosio FG, Pesavento TE, Kim S, et al. Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. Kidney Int 2002; 62:1440.
14. Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. Transplantation 2003; 75:SS3.
15. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. 2009; (4):1121–1127.
16. Ghosal S, Sinha B, Gangopadhyay KK. Insulin glargine versus insulin Degludec in patients failing on oral therapy in type 2 diabetes: A retrospective real world comparative data from India.nDiabetes Metab Syndr. 2016 Jul-Sep; 10(3): 161-5.
17. Russell-Jones D, Gall MA, Niemeyer M, Diamant M, Del Prato S. Insulin Degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials. Nutr Metab Cardiovasc Dis. 2015 Oct; 25(10): 898-905.
18. Rodbard HW, Gough S, Lane W, Korsholm L, Bretler DM, Handelsman Y. Reduced risk of hypoglycemia with insulin Degludec versus insulin glargine in patients with type 2 diabetes requiring high doses of basal insulin: a meta-analysis of 5 randomized begin trials. Endocr Pract. 2014 Apr; 20(4): 285-92.
19. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, et al. NN1250-3579 (BEGIN Once Long) Trial Investigators.) Insulin Degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care. 2012 Dec; 35(12): 2464-71.
20. Kiss I, Arold G, Roepstorff C, Bøttcher SG, Klim S, Haahr H. Insulin Degludec: pharmacokinetics in patients with renal impairment. Clin Pharmacokinet. 2014 Feb; 53(2): 175-83.
21. Debmalya Sanyal, Soumyabrata Roy Chaudhuri, Anirban Majumder. Efficacy and safety of insulin degludec in renal transplant recipients with pre-existing diabetes. Endocrine and Metabolic Science 2 (2021) 100071.
22. Binayak Sinha, Kalyan Kumar Gangopadhyay, and Samit Ghosal. Is insulin Degludec a more effective treatment for patients using high doses of insulin glargine but not attaining euglycemia? Some case reports from India. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2014 Volume 2014:7 Pages 225—228.
23. Miyako Kishimoto and Mitsuhiko Noda. Verification of glycemic profiles using continuous glucose monitoring :cases with steroid use, liver cirrhosis, enteral nutrition, or late dumping syndrome. J Med Invest. 2015; 62(1-2): 1-10.

Correspondence to:
Rabab Mahmoud Ahmed Mahmoud, MD
Internal Medicine department, Cairo University, Egypt
Tel: 002 01 060 139 196
E-mail: ruby_mahmoud_555@cu.edu.eg

Received May 2021
Revised July 2021
Accepted August 2021