

Original article

# Effectiveness of IDegLira in Type-2 Diabetes Patients During the COVID-19 Pandemic: A Teleconsultation Follow-up

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## Abstract

**Introduction:** The current management of type 2 diabetes mellitus (T2D) requires a comprehensive approach to achieve goals, emphasizing treatment compliance through periodic surveillance.

**Objective:** The purpose of this study was to determine the effectiveness of insulin degludec/liraglutide therapy (IDegLira) on glycemic control in adults with T2D in a real-world setting, with follow-up care provided via teleconsultation during the COVID-19 pandemic.

**Materials and methods:** Analysis of a real-world anonymized database of patients with T2D, treated in a specialized medical institution between March 2020 and March 2021. HbA1c levels and fasting blood glucose were evaluated at three and six months of follow-up.


**Results:** We included 61 patients between the age of 43 and 94 years. Most of the patients used oral antidiabetics (75.41%), 85.25% had insulin formulations (basal or basal-bolus), and half of the subjects (55.74%) had insulin-combined formulations. From an average level of HbA1c at baseline of 8.44% (SD 1.4), significant reductions were observed at three months (-0.48%, CI -0.10 to -0.86) and six months (-0.94%, CI -0.55 to -1.33), consistent with a decrease in fasting glycemia (-37.80 mg/dL, CI -21.62 to -53.97 at six months) and with an increase in the proportion of patients achieving glycemic goals. Insulin requirements (total daily dose) decreased on average 11.3 U (CI -6.59 to -16.01, p 0.00). No episodes of significant hypoglycemia were reported.

**Conclusions:** In the real world, IDegLira generated significant changes towards glycemic control in adults with T2D, with no reports of hypoglycemia for up to 6 months in the context of virtual medical care.

**Keywords:** Insulin degludec, IDegLira, liraglutide, type-2 diabetes.

## Highlights:

- A notable aspect of this study concerns the optimal glycemic control response in a virtual care and monitoring environment, and in this regard, several studies have documented telemedicine support for glycemic control.
- Real-world studies have reported reductions in HbA1c with IDegLira in a range of 0.3% to 2.2%, showing a more significant effect if baseline glycemic control is poor.
- No significant hypoglycemia events were reported in this follow-up, as is expected due to the mechanisms of action of insulin degludec and GLP1a, in accordance with the lower incidence of this adverse event compared with the insulin regimens.

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# Efectividad de IDegLira para el manejo de la diabetes tipo 2 durante la pandemia Covid -19: un seguimiento a través de teleconsulta

## Resumen

**Introducción:** El manejo actual de la diabetes mellitus tipo 2 (DT2) requiere un abordaje integral para el logro de los objetivos, enfatizando en el cumplimiento del tratamiento a través de la vigilancia periódica.

**Objetivo:** El propósito de este estudio fue determinar la efectividad de la terapia con insulina degludec/liraglutida (IDegLira) en el control glucémico en adultos con DT2, en un entorno real con atención de seguimiento proporcionada por teleconsulta durante la pandemia de COVID-19.

**Materiales y métodos:** Análisis de una base de datos anonimizada del mundo real, de pacientes con DT2 tratados en una institución médica especializada entre marzo de 2020 y marzo de 2021. Se evaluaron los niveles de HbA1c y la glucosa en sangre en ayunas a los tres y seis meses de seguimiento.

**Resultados:** Se incluyeron 61 pacientes entre 43 y 94 años. La mayoría de los pacientes usaban antidiabéticos orales (75,41%), el 85,25% tenían formulaciones de insulina (basal o basal-bolo) y la mitad de los sujetos (55,74%) tenían formulaciones de insulina combinada. A partir de un nivel medio de HbA1c al inicio del 8,44 % (DE 1,4), se observaron reducciones significativas a los tres meses (-0,48 %, IC -0,10 a -0,86) y a los seis meses (0,94 %, IC -0,55 a -1,33), consistente con una disminución de la glucemia en ayunas (-37,80 mg/dL, IC -21,62 a -53,97 a los seis meses) y con un aumento en la proporción de pacientes que alcanzan los objetivos glucémicos. Los requerimientos de insulina (dosis diaria total) disminuyeron en promedio 11,3 U (IC -6,59 a -16,01, p 0,00). No se informaron episodios de hipoglucemia significativa.

**Conclusiones:** En el mundo real, IDegLira generó cambios significativos hacia el control glucémico en adultos con DM2, sin reportes de hipoglucemia hasta por 6 meses en el contexto de atención médica virtual.

**Palabras clave:** insulina degludec, IDegLira, liraglutida, diabetes tipo 2.

## Destacados

- Un aspecto importante de este estudio, hace referencia a la respuesta óptima del control glucémico en un entorno virtual de atención y monitoreo, se debe tener en cuenta que varios estudios han documentado el apoyo de la telemedicina para el control glucémico.
- Los estudios del mundo real informaron reducciones en HbA1c con IdegLira, en un rango de 0.3% a 2.2%, mostrando un efecto más significativo si el control glucémico inicial es deficiente.
- No se reportaron eventos significativos de hipoglucemia en este seguimiento, como era de esperar por los mecanismos de acción de la insulina degludec y GLP1a, de acuerdo con la menor incidencia de este evento adverso en comparación con los regímenes de insulina.

## Introduction

Type 2 diabetes mellitus (T2D) is a chronic disease with a growing prevalence and increased premature mortality associated (1). The burden of this disease implies a deterioration of health-related quality of life, complications and comorbidities, and a substantial socioeconomic burden with increased use of health care resources and costs (2).

Clinically, glycosylated hemoglobin (HbA1c)  $\leq 7\%$  is associated with reducing the risk of micro and macrovascular complications, and potentially lowering the risk of related mortality (3). Therapeutic adherence plays a critical role in the success of glycemic control. Non-adherence and

non-persistence with therapies and interventions, have been barriers to achieving goals in T2D. Observational studies report adherence rates between 38% and 93% (4), with the persistence of 56% and treatment interruptions in approximately one-third of patients (5), depending on the type of pharmacological therapy.

During the COVID-19 pandemic, ensuring medication intake at prescribed doses, intervals, and frequency, and the compliance of complementary interventions in T2D, has been challenging. Self-care and patient adherence with therapy have required follow-up in less traditional care settings such as teleconsultations. Remote care activities are part of a recently promoted strategy to provide efficient, timely, and continuous health

and medical care to the population, particularly those with chronic diseases (6).

New modalities of outpatient care in T2D seem more convenient today; however, the results of disease management in virtual settings vary according to patients' therapeutic needs. The complexity of treatment regimens, the perception of benefit, the occurrence of adverse events, and the cost of medication, influence the adherence to treatment and, consequently, the scope of glycemic control (7). New dual formulations of anti-diabetics in more favorable regimens have shown improved results against the efficacy and safety of their single components. The combination of second-generation long-acting insulin (Degludec), with a glucagon-like peptide-1 receptor agonist (aGLP1) (Liraglutide), has been extensively evaluated in several populations of patients with T2D as part of phase 3 DUAL clinical trial program. Therefore, showing benefits in the decline of the HbA1c and the weight with a lower risk of hypoglycemia, and a significantly lower requirement of insulin (8–11).

The purpose of this study was to evaluate the effectiveness of insulin degludec/liraglutide (IDegLira) therapy on glycemic control in adults with T2D in a real-world setting with follow-up care provided via teleconsultation.

## Materials and Methods

An observational, real-world retrospective study was conducted, based on secondary data from an institutional database. We included adult patients with T2D being treated with IDegLira standard management between March 2020 and March 2021, with at least three months of follow-up. Pregnant women and patients with diabetic gastroparesis were excluded. The Institutional Ethics committee approved the study protocol.

The primary outcome, was the change in glycated hemoglobin (HbA1c) level at three and six months follow-up. Secondary outcomes included changes in fasting glycemia, triglycerides, LDL levels, insulin dose, and self-reported hypoglycemia events during treatment with IDegLira.

The study drug, IDegLira, was prescribed (dose and titration) according to individualized medical criteria. (12) Regarding the dose, for patients who were not managed with insulin, the dose used was standard (it started with 15 units), and in those patients who were managed with insulin, what was done was a decrease of 50% of the total dose of insulin, and from there the titration begins.

The clinical information was extracted from institutional anonymized electronic records stored in a validated electronic database. Demographic variables (age and sex); previous anti-diabetic medication (doses, insulin type, and other therapies for diabetes); clinical and paraclinical variables used to evaluate therapy, such as weight (in kilograms), HbA1c, fasting glycemia, cholesterol, triglycerides, were recorded; as well as hypoglycemic events.

The follow-up of the patients was carried out by teleconsultation. During this, patients were given information on the correct use of the medication, in addition, diet and exercise recommendations were given, as in the face-to-face consultations carried out prior to the COVID-19 pandemic.

Central tendency and dispersion measures were calculated for quantitative variables according to their distribution (Shapiro Wilks test), qualitative variables were represented as absolute and relative frequencies with confidence intervals. To estimate the mean or median differences, we used the Kruskal Wallis test, and for qualitative variables, we used the Chi2 test, with an alpha of 0.05. The data was analyzed using the Stata v. 15 statistical software.

## Results

Sixty-one adult patients with T2D treated with IDegLira who met the selection criteria were included. Only complete follow-up of HbA1c from 47 to 3 months and 44 to 6 months. Demographic and baseline clinical and paraclinical characteristics of patients are described in Table 1. Most participants were women, and the average age was  $66.6 \pm 9.3$  years. About 85.25% of the patients were insulin users, and 75.41% received oral antidiabetics (OAD), mainly metformin and

DPP4 inhibitors. More than half of the patients were receiving combined OAD and insulin therapy (55.74%). The daily insulin dose used before treatment with IDegLira was 41.18 units  $\pm$  20.40

(range 12 to 95 U). Regarding baseline laboratory measurements, the average fasting glycemia was 149.15 mg/dL  $\pm$  56.15, and the mean HbA1c at the beginning was 8.44%  $\pm$  1.45%.

**Table 1.** Baseline characteristics of patients in this study

	<b>Overall</b>
	<b>n=61</b>
Sex, female, n (%)	36 (59,02)
Age (y), Mean [Range]	66,6 [43 to 94]
Body weight (kg), mean [SD]	76,11 [11,45]
Fasting glycemia (mg/dL), mean [SD]	149,15 [56,15]
HbA1c (%), mean [SD]	8,44 [1,45]
Total cholesterol, mean [SD]	159,53 [44,91]
Triglycerides, mean [SD]	204,05 [108,84]
Basal LDL, mean [SD]	79,92 [38,74]
Basal HDL, mean [SD]	39,7 [11,13]
<b>Previous medication</b>	
Oral antidiabetics, n (%)	
None	15 (24,59)
1	28 (45,9)
2	18 (29,51)
Metformin, n (%)	22 (36,07)
DPP4 inhibitors, n (%)	13 (21,31)
SGLT2 inhibitor, n (%)	12 (19,67)
GLP1a, n (%)	8 (13,11)
Sulfonylureas, n (%)	0 (0)
Insulin, n (%)	52 (85,24)
Oral antidiabetics + insulin, n (%)	34 (55,74)
Basal insulin, n (%)	33 (54,1)
Basal bolus insulin, n (%)	15 (24,59)

Note: DPP4 Dipeptidyl Peptidase-4, GLP1-RA Glucagon-like peptide-1 agonists, SGLT2 sodium-glucose cotransporter type 2

**Source:** The authors

Outcomes at three and six months are presented in Tables 2 and 3, respectively. At the 3-month follow-up, a statistically significant decrease in HbA1c levels was recorded (-0.48%, CI -0.10 to -0.86), a trend that continued at six months (-0.94%, CI -0.55 to -1.33). Similarly, fasting glycemia had a significant decrease at both

three- and six-months follow-up (-17.17 mg/dL [-0.83 to -33.51] and -37.80 mg/dL [-21.62 to -53.97], respectively). Before treatment with IDegLira, 10% of the patients had reached Hb1Ac targets (Hb1Ac <7%). At the three- and six-month treatment with this drug, 19.15% and 43.18% of patients reached this target.

**Table 2.** Change in clinical and biochemical parameters at three months of treatment with IDegLira

Characteristics	N	At baseline	At 3 months	Mean difference (CI 95%)	p value
HbA1c (%), [SD]	47	8.26 [1.2]	7.78 [0.99]	-0.48 (-0.10 to -0.86)	0.0139
Fasting glycemia (mg/dL), Mean [SD]	41	142.26 [45.4]	125.1 [33.76]	-17.17 (-0.83 to -33.51)	0.0400
HbA1c < 7%		10%	19%		0.1761

Note: CI confidence interval, N number of patients in each subgroup

Source: The authors

**Table 3.** Change in clinical and biochemical parameters at six months of treatment with IDegLira

Characteristics	N	At baseline	At 6 months	Mean difference (CI 95%)	p value
HbA1c (%), [SD]	44	8.35 [1.34]	7.42 [0.92]	-0.94 (-0.55 to -1.33)	0.0039
Fasting glycemia (mg/dL), Mean [SD]	39	146.4 [45.4]	108.6 [36.42]	-37.80 (-21.62 to -53.97)	0.0000
Total daily insulin dose (units), [SD]	53	38,43 [22.33]	27.13 [11.87]	- 11.3 (-6.59 to -16.01)	0.0000
HbA1c < 7%		10%	43%		0.0001

Note: CI confidence interval, IQR interquartile range, N number of patients in each subgroup

Source: The authors

After six months of treatment with IDegLira, the insulin requirement decreased by an average of 11.3 U (CI -6.59 to -16.01) of TDD (total daily dose) ( $p < 0.00$ ). Reductions in weight, total cholesterol, triglycerides, and LDL levels were also observed. However, more than 50% of the data from these variables were missing and therefore, not included. At the end of the follow-up (six months), 59 patients continued treatment IDegLira with an average dose of 26.54 units ( $\pm 11.5$ ), ranging doses from 10 to 70 units.

Only one patient reported hypoglycemia (blood sugar test of 70 mg/dL), and no patients reported significant hypoglycemia (less than 54 mg/dL).

## Discussion

There is substantial evidence on the benefit of optimizing metabolic control in T2D to reduce the risk of disease-related micro and macrovascular complications. The lack of initiation or intensification of therapy when indicated, known as clinical inertia, has a high burden on the effectiveness of care in T2D (13). Although clinical practice guidelines recommend monitoring HbA1c levels every three months, and intensifying drug therapies to achieve glycemic targets, real-world studies show that glycemic control in patients with diabetes is usually inadequate with high clinical inertia rates reported in the treatment of T2D. Studies have found that two out of three patients with poor glycemic control (HbA1c  $> 7\%$ ), do not receive early treatment intensification (e.g., increased dose or addition of oral anti-diabetic agents, the addition of GLP1a, or the addition of insulin) within six months of the failure of oral anti-diabetic agents (14,15). A recent systematic review found that, after a HbA1c measurement above the target, the median time to treatment intensification was one year or more (16).

The suboptimal management of diabetes evidenced in practice, requires compliance with evidence-based indications for pharmacological treatment, and a broad understanding of the therapeutic arsenal available; particularly the advantages that the latest therapeutic classes and combinations can offer to achieve the

appropriate glycemic objective on each individual. Recently, the GLP1a has been highlighted for its results in glycemic control, weight reduction, and cardiovascular benefits. Studies of liraglutide (17) have shown significant reductions in the incidence of major cardiovascular events (MACE) and cardiovascular death, encouraging its use in patients with poor metabolic control despite other therapeutic strategies. IDegLira combines degludec (a second-generation long-acting insulin analog) and liraglutide (a long-acting GLP1a) in a single formulation to enhance its components' effectiveness with complementary mechanisms of action (18).

The DUAL clinical trial program evaluated the safety and efficacy of IDegLira in patients with T2D in different clinical and therapeutic conditions. The DUAL V study (19), compared it with insulin glargine alone, finding a significant decrease in HbA1c, and weight loss with a lower risk of hypoglycemia using IDegLira. The DUAL VII (20) study, compared the use of basal-bolus insulin versus IDegLira, showing the non-inferiority of the latter in decreasing HbA1c, with a lower risk of hypoglycemia and, significant weight loss in contrast to weight gain in the basal-bolus group, in addition to a significantly lower insulin requirement (TDD) in the intervention arm (40 IU versus 84 IU, mean difference -44.5, CI95% -48.3, -40.7). Similarly, the DUAL VIII (21) study compared IDegLira response duration to that of insulin glargine in patients with uncontrolled T2D receiving OAD, finding that injectable therapy resulted in fewer patients requiring intensification of treatment, a longer duration of the glycemic control effect and, a 44% decrease in the rate of hypoglycemia. All in all, suggesting a potential reduction in the burden of disease and improvement of long-term outcomes.

Real-world studies have reported reductions in HbA1c with IDegLira in a range of 0.3% to 2.2% (22), showing a more significant effect if baseline glycemic control is poor. These results are consistent with our findings, where the mean reduction from an average level of Hb1Ac of 8.4% was 0.5%. Farther, IDegLira studies have also shown changes in insulin requirements. Hence, our study highlights the total daily dose reduction

(mean 11.3 U, CI -6.59 to -16.01,  $p < 0.00$ ).

A favorable effect on the weight of T2D patients treated with IDegLira, has been observed with reductions between 0.7 and 6.76 kg (23,24). Weight changes were not evaluated in our study due to the modality of care, but we assumed, based on the evidence, that subjects might have shown a reduction in weight due to the integral metabolic management given.

No significant hypoglycemia events were reported in this follow-up, as is expected due to the mechanisms of action of insulin degludec and GLP1a, in accordance with the lower incidence of this adverse event compared with the insulin regimens, both in clinical trials and observational studies (25).

Another notable aspect of this study, concerns the optimal glycemic control response in a virtual care and monitoring environment, and in this regard, several studies have documented telemedicine support for glycemic control (26). A meta-analysis was conducted to evaluate the effectiveness of telemedicine (teleconsultation and telemonitoring), compared to usual care in patients with diabetes (27). From 42 randomized trials with information from 6,170 participants (3,042 in the intervention), a significantly higher average reduction of HbA1c was reported in telemedicine groups, especially in patients with T2D (g Hedges -0.48,  $p < 0.001$ ), compared to patients with type 1 diabetes. Telemedicine results were higher in older patients (> 50 years of age) and with a longer duration of therapy (>6 months). These findings are particularly relevant, along with what has been stated in this study, as they suggest that, in a restrictive interaction scenario such as the COVID-19 pandemic, teleconsultations can be very useful for people with T2D.

As previously mentioned, in many patients with diabetes, glycemic control remains suboptimal despite the introduction of hypoglycemic therapies that are effective. In order to address this problem, in addition to therapeutic inertia, aspects of health care services and other related to patients, must be considered. In a telemedicine

context, barriers must be widely considered in terms of therapeutic adherence, self-management of the disease, and complementary interventions in patients with diabetes to achieve the integral goals required in the disease, and thus, maintain them in virtual care settings.

This study has limitations inherent to an observational follow-up of a single care center with a small sample size. Due to the remote nature of monitoring, some variables of interest were not considered or not adequately evaluated, limiting a comprehensive analysis of results or the inclusion of potential confounding or bias factors. However, the findings here are considered relevant in addition to evidence of glycemic control, in particularly challenging settings of care in chronically difficult-to-control patients.

## Conclusions

The results of this study confirm the efficacy of IDegLira in patients with T2D who require intensification of therapy to achieve therapeutic objectives, demonstrating advances towards glycemic control, reduction of insulin requirements, and absence of episodes of significant hypoglycemia. All this is in the context of virtual attention and monitoring. One of our concerns was that, being a follow-up by teleconsultation, the results were underestimated, but our study shows that during the pandemic it was possible to carry out an effective virtual follow-up and, in that scenery, IDeglira showed effective results that are compatible with other studies carried out.

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## Conflict of interest

None reported by the authors.

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