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PRACTICAL APPROACH

Simplification of Complex Insulin Regimens with IdegLira in People with Type 2 Diabetes: Literature Review and Clinical Recommendations

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ABSTRACT

Introduction: This study developed a simple algorithm based on clinical results described in medical literature and which allows one to simplify complex insulin regimes with IdegLira to avoid adverse events related to the complexity of some insulin treatments.
Methods: We conducted a systematic review of the literature that allowed us to identify studies that evaluated the clinical result of simplifying complex insulin regimes. The authors reviewed the common factors these simpler regimes had, including the type of patients who used them.
Results: We found nine clinical studies published between 2017 and 2022, eight performed in Europe and one in Latin America. The monitoring time of the studies ranged between 3 and 18 months. The size of the study populations was between 61 and 611 patients (the latter was in five countries). In all studies, HbA1c decreased by 0.6–1.7% and the weight decreased by 0.1–3.11 kg.
Conclusions: On the basis of the findings of these studies, we made some recommendations for clinical practice to simplify treatment. The results of these studies support an algorithm that simplifies the treatment of complex insulin regimens.

Keywords: Basal insulin; Beta cell function; GLP-1 analogue; Insulin therapy; Liraglutide; Systematic review

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Key Summary Points

Simplifying complex treatment regimens in patients with type 2 diabetes mellitus (T2DM) improves treatment adherence and clinical outcomes while reducing the risk of adverse events and healthcare costs.

Multiple clinical practice guidelines exist for T2DM treatment, but they often do not address the challenges of simplifying therapy in patients who have achieved therapeutic objectives but experience adverse events.

The authors conducted a literature review to evaluate the evidence and propose a strategy to simplify complex antidiabetic treatments in patients with T2DM.

Patient selection criteria for simplified treatment regimens may include assessing beta cell reserve and considering insulin doses to achieve reasonable metabolic control without compromising glycemic outcomes.

INTRODUCTION

Evidence pointing to the need to simplify complex treatment regimens in patients with type 2 diabetes mellitus (T2DM) has increased recently [1–15]. This practice reduces the risk of adverse events, such as hypoglycemia, increases treatment adherence, and improves clinical results. The accumulated evidence of the available antidiabetic drugs makes it possible to guide the treatment of patients with T2DM on the basis of the potential benefits and risks of each group of drugs. We have observed that more straightforward treatment strategies are needed, which are helpful for health professionals who care for patients with T2DM and prescribe multiple antidiabetic medications due to the treatment inertia [16].

More complex treatments in patients with T2DM increase healthcare costs since they will need significantly more diagnostic tests to monitor clinical results and avoid adverse events [17, 18]. Therefore, if it is possible to return the patient with T2DM to primary healthcare caregivers, not only will greater comfort be obtained for the patient but it will also increase the efficiency of the health system by achieving similar results with lower costs [19, 20].

Multiple clinical practice guidelines (CPG) have been published [21–26] with different treatment strategies based on the best published evidence, which recommends the staggering use of antidiabetics to the extent that patients do not achieve the expected results. These kinds of CPGs are most valuable because they allow the rational use of medications but they lead to therapeutic inertia when adding drugs or increasing the frequency of their doses [27]. These CPGs allow for achieving therapeutic objectives. However, reaching this goal with complex treatments increases the risk of developing adverse events and decreases adherence to treatment. Furthermore, the guidelines do not usually address the clinical situation of how to treat the patient who has achieved the therapeutic objective but who, as a result of the complexity of the treatment, presents adverse events, especially hypoglycemia.

Simplifying the complex treatments received by patients with T2DM is a challenge doctors face when the patient has already achieved the proposed therapeutic objective. Therefore, these recommendations aim to present a simplification strategy for complex antidiabetic treatments by reviewing the available evidence and establishing arguments supporting the safest way to offer simpler regimens while maintaining the desired therapeutic objectives.

METHODS

Literature Review

We designed a high-sensitivity search strategy to identify all possible articles of interest and filter them in the review. We search reviews and

clinical trials in the MEDLINE, Embase, and CINAHL databases without limits on dates. The only search terms used were simplifying AND insulin, and the only search filter used was human species.

Article inclusion criteria were as follows: (1) randomized controlled trials, including open-label studies, (2) single-arm clinical trials, (3) observational studies with real-world evidence (RWE), both prospective and retrospective; and (4) revisions. In addition, two reviewers (medical epidemiologists) determined the eligibility status of each article identified by the search strategy.

Evaluation of the Evidence

The methodological evaluation of each article included in the review was carried out independently by two medical epidemiologists (JEO, Arlex Uriel Palacios (AUP)). We used the Consolidated Standards of Reporting Trials (CONSORT) [28] to evaluate randomized clinical trials, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [29] to assess observational studies, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [30] for systematic reviews. We discussed our assessment discrepancies in a meeting, and when we did not have a consensus, a third reviewer resolved any disagreement.

Although these instruments did not assess the methodological quality of the studies, they did make it possible to determine the risk of bias that the publications may have. We did not include articles with a high risk of bias because they did not fulfill several items proposed in the aforementioned evaluation guides. We sent selected papers to all authors who participated in this review, and we them to suggest any articles they felt were missing.

Characteristics of the Evidence

The articles selected for this consensus differ in the populations included, in the inclusion criteria, or the simplification strategies used, among others. That is the main challenge of this review, generating consensus recommendations in the different clinical scenarios described in the literature. The authors do not intend for these recommendations to be a definitive analysis of the evidence but rather a starting point from which continuous improvement is made on the basis of the clinical results that patients obtain from these recommendations (Table 1).

Definitions

Overtreatment

The Institute of Medicine defines overtreatment as treatment use even when the potential harms outweigh the possible benefits [31]. Its prevalence in older adults with T2DM is between 21% and 60.5% [32, 33]. The line that separates reasonable metabolic control in T2DM from overtreatment is usually very narrow [31]. There should be a special mention of patients who use insulin. These patients have the potential damage of excessive therapy, leading to a higher risk of severe hypoglycemia, weight gain, possible mortality, lower quality of life, and less adherence to treatment, especially in those on multiple-dose insulin (MDI) therapy [34]. Basal insulin overtreatment is called overbasalization and occurs when patients receive a dose > 0.5 IU/kg/day and have an HbA1c outside the target, recalling the ceiling effect of basal insulin [35]. Four of ten patients with T2DM using basal insulin have overbasalization [36].

Simplification

Simplification refers to the reduction in the complexity of a therapeutic regimen, including a lower number of administrations, a lower requirement for glucose measurement, or a reduction in the need for prandial insulin calculations about carbohydrate intake of a meal. In insulin-using patients, the term simplification includes any strategy that reduces the burden of complex insulin therapy, including lowering the insulin dose or the number of injections (especially prandial insulin) [34]. There is a direct correlation between simple treatment schemes and greater adherence by

Table 1 Main features of the clinical studies included in this review

Study	Design	Key inclusion criteria	Key exclusion criteria	*n*	Duration (months)
Ramírez-Rincón, Colombia (2022) [42]	Multicenter, retrospective, cohort study	T2DM treated with IdegLira	Pregnant women, liver insufficiency, chronic kidney disease	64	3–7
REX study, Italy (2022) [57]	Multicenter, prospective, cohort study	Age 18 years or more, T2D diagnosed at least 12 months before enrolment	Type 1 diabetes, maturity-onset diabetes of the young, latent autoimmune diabetes in adults, gestational diabetes, or any hyperglycemic state other than T2D	331	18
BEYOND trial, Naples, Italy (2021) [12]	Randomized, pragmatic, parallel-group, active-control, open-label, single-center, clinical trial	Age > 35 years, HbA1c > 7.5% (58 mmol/mol), and current use of a full BBI regimen (four injections daily)	History of diabetic ketoacidosis or pancreatitis, impaired kidney function liver insufficiency	305 102 assigned to IdegLira or LixiLan	6
Persano et al., Treviso, Italy (2021) [13]	Single-center, prospective, cohort study	Age > 18 years, C-peptide > 1 ng/ml	Type 1 DM, age > 75 years, patients naïve to insulin, pregnant women, diabetic kidney disease and glomerular filtration rate < 15 ml/min, chronic heart failure (New York Heart Association class III–IV), thyroid disease, known hepatic disease, personal or family history of medullary thyroid carcinoma, patients with multiple endocrine neoplasia syndrome type 2 or a history of pancreatitis	45	

Table 1 continued

Study	Design	Key inclusion criteria	Key exclusion criteria	*n*	Duration (months)
Zenari et al., Italy (seven diabetes centers) (2021) [14]	Multicenter, retrospective, cohort study	IDegLira therapy following the switch from prior treatments	Age < 18 years; insulin naive; concomitant or suspected malignant diseases, recent acute diseases, severe renal failure (glomerular filtration rate 15 mL/min) severe liver failure, congestive heart failure (New York Heart Association functional class IV), a high degree of fragility, chronic pancreatitis	244	12
Di Loreto et al., Perugia, Italy (2020) [7]	Single-center, retrospective, cohort study	Age > 18 years, unsatisfactory glycemic control for either hypoglycemic episodes or weight gain	Personal or family history of medullary thyroid carcinoma, or history of pancreatitis or insulin-naïve subjects	137	18
Taybani et al., Hungary (2019) [5]	Prospective, single-arm clinical trial	Age ≥ 18 years, random serum C-peptide levels > 1.1 ng/mL, HbA1c ≤ 7.5%, insulin DID < 70 IU/day and DID < 0.6 IU/kg/day	Type 1 diabetes, active cancer, anemia, and acute or chronic kidney disease	69	3
The EXTRA study, Germany, Switzerland, UK, Austria, and Sweden (2018) [3]	Multicenter, retrospective, cohort study	All patients who received at least one prescription of IDegLira	None	611 566 provided complete follow-up data	6
Sofra, Switzerland (2017) [2]	Single-center, prospective, cohort study	Poor glycemic control, (HbA1c greater than 8.0%), more than two oral antidiabetic medications and more than one injection daily, or if the patient would benefit from the addition of the liraglutide component of IDegLira for weight management	None	61 5 early discontinuation	6

Table 1 continued

Study	Baseline treatment	Daily insulin dose	Treatment transition scheme	IdegLira starting dose	IdegLira tiitration scheme	Main outcomes
Ramírez-Rincón, Colombia (2022) [42]	Basal insulin with or without simultaneous treatment with one or more AD or rapid insulin	38 (IQR 30.5) units	Stop all insulin injections and started a single daily injection of IDegLira	As recommended by the manufacturer	As suggested by the manufacturer	HbA1c change − 1.05 (CI 95% − 1.45 to − 0.65) DID change − 10 (CI 95% − 17 to − 2.5) units Weight change 0.5 (− 0.25 to 1.3) kg
REX study, Italy (2022) [57]	Basal insulin with or without simultaneous treatment with one or more AD or rapid insulin	Basal insulin 15.0 (IQR 10.0–20.0) Basal + bolus 42.0 (IQR 30.0–52.0)	NR	Basal insulin 16 (IQR 16 to 20) dose steps Basal + bolus 16 (15 to 20) dose steps	NR	Interim analysis no report of the main result at the moment of the search
BEYOND trial, Naples, Italy (2021) [12]	MDI (four injections daily) with or without metformin	NR	Stop all insulin injections and started a single daily injection of IDegLira	As recommended by the manufacturer	As suggested by the manufacturer	HbA1c change − 0.6 ± 0.8% DID change − 27.1 ± 14.2 units Weight change − 1.9 ± 4.3 DTSQ change 34.2 ± 3.7

Table 1 continued

Study	Baseline treatment	Daily insulin dose	Treatment transition scheme	IdegLira starting dose	IdegLira tiitration scheme	Main outcomes
Persano et al., Treviso, Italy (2021) [13]	MDI (four injections daily) with or without metformin	42 (IQR 30–59) units	Stop all insulin injections and started a single daily injection of IDegLira	16 dose steps	Twice weekly to reach a 90–130 mg/dl fasting glycemic target (130–160 mg/dl for weak elderly patients); adjustments were in increments of 2 dose steps at a time	HbA1c change − 0.67% Weight change − 2.4 ± 4.3 kg DTSQ change 7.5
Zenari et al., Italy (seven diabetes centers) (2021) [14]	Basal insulin with or without simultaneous treatment with one or more AD or rapid insulin	Basal insulin 21.1 ± 9.8 IU Basal + bolus 55.9 ± 26.3 IU	At the discretion of the treating physician	Basal insulin 18.7 ± 6.8 dose steps Basal + bolus 20.2 ± 7.6 dose steps	At the discretion of the treating physician	Basal HbA1c change − 1.1 ± 1.3% DID change 2.8 ± 13.4 units Weight change − 1.1 ± 4.9 kg at 6 months Basal + bolus HbA1c change − 0.2 ± 1.2% DID change − 31.6 ± 25.1 units Weight change − 2.8 ± 5.4 kg at 6 months

Table 1 continued

Study	Baseline treatment	Daily insulin dose	Treatment transition scheme	IdegLira starting dose	IdegLira tiitration scheme	Main outcomes
Di Loreto et al., Perugia, Italy (2020) [7]	Basal insulin with or without simultaneous treatment with one or more antidiabetic drug (AD) or rapid insulin	Basal insulin 0.29 (0.2) IU/kg Basal + bolus 0.62 (0.33) IU/kg	NR	NR	At the discretion of the treating physician	Basal HbA1c change − 0.9 ± 1.0% DID change 8.9 ± 9.3 units Basal + GLP1RA HbA1c change − 1.2 ± 0.4% DID change 0.3 ± 9.0 units Basal + bolus HbA1c change − 1.2 ± 1.1% DID change − 38 ± 2.8 units
Taybani et al., Hungary (2019) [5]	MDI (four injections daily) with or without metformin	43.31 (IQR 10.99) units	Stop all insulin injections and started a single daily injection of IDegLira	16 dose steps	NR	HbA1c change − 0.30 (CI 95% − 0.42 to − 0.18) DID change − 22.55 (CI 95% − 24.96 to − 20.14) units Weight change − 3.11 (CI 95% − 4.04 to − 2.18) kg Insulin requirement − 0.24 (CI 95% − 0.27 to − 0.21) IU/kg

Table 1 continued

Study	Baseline treatment	Daily insulin dose	Treatment transition scheme	IdegLira starting dose	IdegLira tiitration scheme	Main outcomes
The EXTRA study, Germany, Switzerland, UK, Austria, and Sweden (2018) [3]	AD with or without insulin 115 patients treated with basal insulin + AD, 145 with insulin + GLPRA and AD, and 161 patients treated with MDI and AD	Basal + AD 31.4 ± 21.1 units Basal + ARGLP1 44.2 ± 33.9 units MDI + AD 67.7 ± 42.5	NR	The majority (83.7%) of patients initiated on between 10 and 30 dose steps	Basal + AD Mean 8.5 dose steps at 6 months Basal + ARGLP1 Mean 6.5 dose steps at 6 months MDI + AD Mean 8.5 dose steps at 6 months	Basal + AD HbA1c change − 0.9% DID change − 1.7 units Weight change − 0.1 kg Basal + GLP1RA HbA1c change − 0.6% DID change − 2.5 units Weight change − 0.2 kg MDI + AD HbA1c change − 0.7% DID change − 20.7 units Weight change − 2.4 kg
Sofra, Switzerland (2017) [2]	Basal insulin with or without simultaneous treatment with one or more AD or rapid insulin		Stop all insulin injections and started a single daily injection of IdegLira In patients treated with 50 or more insulin units, a transition phase was included with the addition of a slow-acting insulin during titration of IDegLira	20 dose steps in insulin-treated patients and 16 dose steps in insulin-naïve patients	Four dose steps once weekly, according to individualized fasting blood glucose targets	HbA1c change − 1.7% DID change − 14.6 units Weight change − 1.9 kg

MDI multiple daily injections, *NR* not reported, *DID* daily insulin dose, *DTSQ* Diabetes Treatment Satisfaction Questionnaire, *IU* international units, *IQR* interquartile range

the patient [37], as well as between compliance and reasonable metabolic control [38]. Additionally, some evidence suggests that simplification in patients with complex insulin regimens is associated with equal or better metabolic control, less weight gain, and reduced hypoglycemia [1, 5].

Clinical Inertia

Clinical inertia is the failure of health personnel to initiate or intensify therapy when indicated. Clinical inertia comprises clinician-related factors (e.g., lack of time in care, lack of skills and confidence), patient characteristics (poor disease awareness, poor habits, fear of adverse events), and factors relating to the health system (poor communication in the care team, absence of management guidelines, or problems in the processing and delivery of medications) [39]. For example, a study in the UK that included 3185 patients treated with basal insulin with or without oral antidiabetics treated in primary care found almost 60% clinical inertia during 3 years of follow-up [40].

Reverse Clinical Inertia

Reverse clinical inertia is the lack of initiative or inability to reduce or suspend a therapy when it is no longer necessary [34]; in other words, it is the passive attitude of health personnel toward a patient with overtreatment. Contributing factors to reverse clinical inertia include the overscrupulous following of therapeutic guidelines and a lack of perception of the patient's frailty [39]. The American College of Physicians recommends de-intensifying pharmacologic therapy in patients with HbA1c < 6.5%. Simplification is necessary to avoid the risk of hypoglycemia and polypharmacy, especially in the elderly population with complex insulin regimens [34].

Patient Selection

Beta Cell Reserve

Fixed combinations of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are only approved to use in people with T2DM use. GLP-1 RAs modulate insulin release from the pancreas, so their addition to treating people with type 1 diabetes mellitus (T1DM) results in only modest reductions in HbA1c [41]. Additionally, beta cell function declines over time in people with T2DM, and it is not uncommon to add fixed combinations such as insulin degludec/liraglutide (IdegLira) in people long after diagnosis of the disease [42]. As a result, some authors have suggested different methods to identify potential patient users of a fixed combination, those without T1DM or with beta cell reserve.

Measurement of C-peptide is a widely used method to estimate beta cell function. It is a proinsulin cleavage product and is therefore produced equimolarly to insulin. However, it has a slower degradation rate and a limited, predictable metabolism after passage through the liver, making it a better predictor than insulin. On the other hand, the detection capacity of current measurement methods allows for detecting concentrations up to 500 times lower than basal concentrations in healthy individuals [43]. We can measure C-peptide after an 8–10-h fast, randomly without fasting, or stimulated by various methods. However, the recommended way to assess beta cell function is C-peptide measurement enabled either by glucagon or a mixed meal test [44].

A random C-peptide measurement of less than 0.6 ng/mL (conversion units 1 nmol/L = 1 pmol/mL = 1000 pmol/L = 3 ng/mL) has a sensitivity of 100%, a specificity of 93%, and an area under the receptor operating characteristic (ROC) curve of 0.99 to detect severe insulin insufficiency [45–47]. On the other hand, a fasting C-peptide concentration of less than 0.96 ng/mL has proven helpful in differentiating between T2DM and T1DM in insulin-treated individuals [46]. Finally, some studies associate fasting C-peptide concentrations less than 0.96 ng/mL with a poor reduction in HbA1c response in patients treated with GLP-1 RAs [47].

The DUAL V [48] and DUAL VII [49] clinical trials did not use the beta cell reserve as an inclusion criterion. However, they did have exclusion criteria to withdraw participants if they had persistent fasting hyperglycemia. Two studies report using C-peptide as a criterion to decide the initiation of IdegLira therapy. In a

single-arm clinical trial under standard clinical practice conditions, one inclusion criterion that participants had to have a randomly measured C-peptide greater than 1.1 ng/mL [5]. On the other hand, a single-cohort follow-up study evaluating the effect of switching from a multiple-dose insulin regimen to IdegLira included patients with a C-peptide measurement greater than 1 ng/mL; the authors did not specify whether the measure was randomized or after fasting. Finally, in a clinical trial conducted in Japan in patients treated with MDI, the authors randomized the patients to continue with their treatment schedule or to receive a combination of lixisenatide and insulin glargine; patients with a fasting C-peptide less than 0.5 ng/mL were excluded [4].

The effect observed with the medication in reducing blood glucose, hyperglycemic events, or hyperglycemic crises does not seem to differ between the studies that report some estimates of C-peptide as an inclusion criterion and those that do not.

The authors recommend that a fasting C-peptide measurement could be a valuable aid to the clinician when deciding to replace an MDI regimen with IdegLira, especially in those with a long-standing diagnosis of T2DM or with clinical features that suggest a different type of diabetes. We made this recommendation considering that C-peptide measurement is the method the American Diabetes Association recommended to assess beta cell function. In the same way, we can measure fasting or random C-peptide reliably and quickly. So, a fasting C-peptide value of less than 1 ng/mL is helpful to discriminate people treated with insulin with T1DM from those with T2DM. This value also correlates with a poor glycemic response to treatment with liraglutide. However, the results of multiple real-life studies that have reported IdegLira treatment in people treated with MDIs and have not included a C-peptide measurement suggest that this measurement is not always necessary. That is, it should fit the clinical criteria.

Insulin Dose

Simplifying IdegLira treatment for patients receiving MDIs implies a reduction in insulin dose at initiation and, as a result of the insulin dose limit with combination therapy, will also mean a lower final amount in some treated patients with high doses of insulin. This situation may concern clinicians because of the fear of poor glycemic control during the transition period or the impossibility of achieving reasonable metabolic control at the end of the IdegLira titration. However, patients treated with insulin in DUAL VII [49] and DUAL VIII [50] trials only had the basal component; these clinical trials do not fully answer this question.

Multiple observational studies and those carried out in routine clinical practice, as well as a clinical trial, have addressed the situation of simplification from an MDI scheme. The BEYOND clinical trial [12] evaluated the effect of simplification from an MDI regimen. One of its arms included fixed combinations of GLP-1 RAs. Inclusion criteria did not include insulin or exclusion of a maximum dose of insulin before inclusion in the study. The average insulin daily dose (IDD) of the group assigned to the fixed combination was 0.59 units/kg/day.

One clinical trial without a control group defined an inclusion criterion for a "low" daily insulin dose as an IDD of less than 70 units/day or 0.6 units/kg/day. However, patients who had experienced multiple hypoglycemia episodes were allowed an IDD between 0.6 and 0.8 units/kg/day without exceeding 70 units/day. The mean IDD at the beginning of the study was 0.47 ± 0.13 units/kg/day. Finally, an observational study reported the results of the follow-up of patients in whom the simplification was made on the basis of an institutional protocol. In this previous study, the patients with an IDD greater than 50 units had a transition phase that added a second dose of long-acting insulin during the IdegLira titration; the average initial insulin dose was 0.57 units/kg/day [2].

The DUAL VII clinical trial [49] demonstrated that escalation from a basal insulin regimen to a fixed-combination regimen is effective and safe. Four weeks after starting therapy, the difference in fasting glucose was 11.16 mg/dL (95% CI 5.04–17.5) lower in the IdegLira group, highlighting that hyperglycemia should not be a concern with proper drug titration. In the treatment simplification

of the BEYOND trial, simplification was performed without fear in patients with an IDD close to 0.6 units/kg/day. Studies conducted under usual clinical practice conditions have used strategies such as establishing a limit on the IDD at which a patient is not a candidate for treatment or transition phases with an additional insulin dose. This group considers that the current evidence is insufficient to recommend an IDD from which not to feel a patient is a candidate for therapy. However, the authors believe that an IDD of 0.6 units/kg/day is a sensible cutoff point to consider differential approaches to simplification, as proposed in the algorithm (Fig. 1).

Initial Dose

In the DUAL series of clinical trials, the initial dose of formulation with IdegLira is estimated on the basis of previous antidiabetic treatment. It means that are two scenarios: if the patient is taking oral antidiabetics, the initial amount will be 10 units, and if the patient is being treated with GLP-1 RAs or with basal insulin (BI), the initial dose will be 16 units [48–51]. This scheme has two pathways. The first is the initial dose of GLP-1 RAs (liraglutide), given the basal doses tested in clinical trials with monocomponent [52], which start with 0.6 mg/day. The second one, the initial amounts of the second-generation insulin analogue (insulin degludec), is also based on the titration algorithms previously explored as a monocomponent [53–56]. Given this context, it is intuitive to contemplate finding similar scenarios in RWE studies.

In the scenario that concerns this review (ongoing basal insulin or MDI), the authors found a basal starting dose of 16 units in different clinical studies [5, 7, 12–14]. In a study in Colombia, the authors specified the initial amount, but they followed the titration processes of the DUAL trials; that is, it is implicit that the initial dose was 16 units [42]. On the other hand, the REX study group describes initial amounts of 20 units with an interquartile range of 16–20 units [52], and Sofra [2] reports initial doses of 20 units. No study reported a starting amount of 10 units if the patient came from BI or MDI.

Studies such as the one published by the EXTRA study group with results from five European countries (Germany, Switzerland, the UK, Austria, and Sweden) propose broader

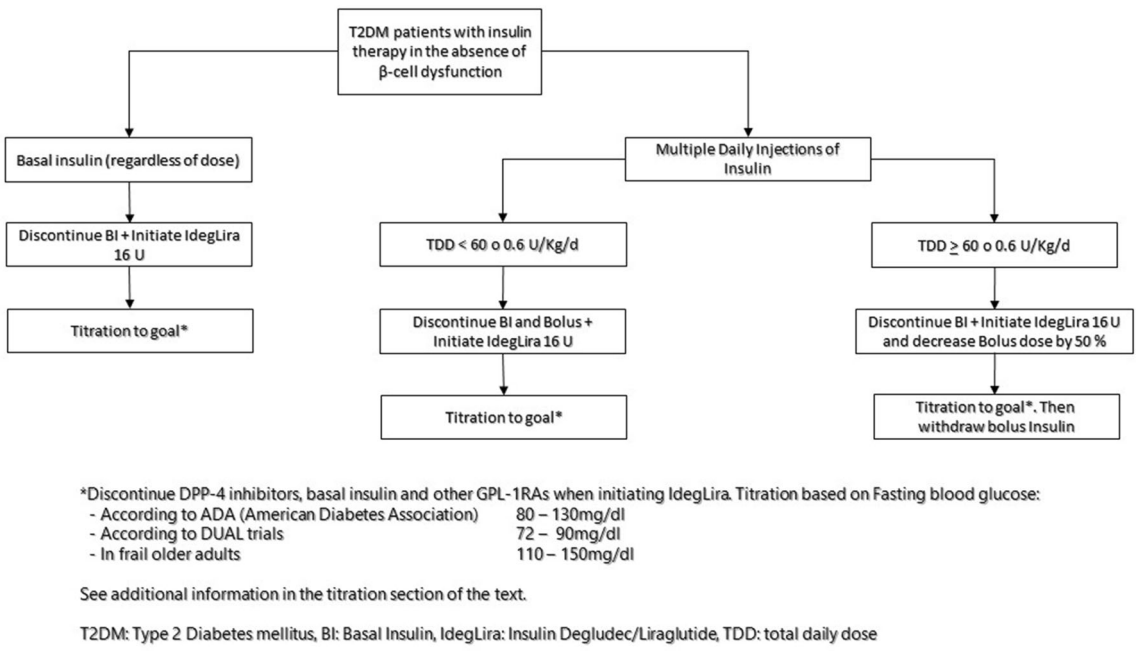

Fig. 1 Simplification algorithm of complex insulin regimens with IdegLira in patients with type 2 diabetes mellitus

ranges [3]. They started with initial doses from 10 units to more than 50 units per day. The average initial amount from oral antidiabetics was 17.2 units. If the patient came with GLP-1 RAs with or without oral antidiabetics, the average dose was 16.8 units. On the other hand, if, before the study, the patients received insulin + GLP-1 RAs with or without oral antidiabetics, the mean dose was 30.9 units. If they only had BI with or without oral antidiabetic drugs, it was 20 units. Finally, if they received MDI with or without oral antidiabetic drugs, the average dose was 21.2 units. Likewise, Di Loreto et al. [7] describe a mean amount of 16.2 units (SD 2.2) if patients were receiving BIs and oral antidiabetics; if they received GLP-1 RAs, the dose was 27 units (SD 12.2), and if they were receiving MDI treatment, the amount was 17 units (SD 4.3).

On the basis of the above and the literature review results, the authors recommend starting a dose of 20 units of IdegLira in patients receiving GLP-1 RAs with or without BIs with or without oral antidiabetics. Likewise, suppose patients receive BIs with or without oral antidiabetics or MDI with or without oral antidiabetics. In that case, the initial dose will be 16 units of IdegLira, insisting on the importance of dose titration as a fundamental strategy to achieve individualized therapeutic goals.

Titration

Regarding the titration component, the studies tended toward homogeneity. For example, five studies of RWE [5, 7, 12–14] recommend carrying out a titration as per the essential studies of IdegLira in the DUAL program [48], i.e., twice a week (every 3 days) with an average of three consecutive days and increments of 2 units per time [5, 7, 12–14, 42]. On the other hand, three studies do not specify the titration scheme. However, discussion items state that the manufacturer's suggestions were followed [3, 7, 57], and only one study reports titration once a week [2]. On the basis of this argument, the authors recommend that the titration scheme for the therapeutic simplification process be twice a week (every 3 days), with an average of three consecutive days and increments of 2 units per time.

Goals

The basal glucose goal to guide the titration proposed in the DUAL study program is 72–90 mg/dL [48]. The argument for such a strict objective is to seek better metabolic control with the safety offered by a second-generation insulin analogue such as degludec insulin. The results of monocomponent studies are convincing compared to those of a first-generation insulin analogue [53–56]; however, the real-life clinical landscape includes other considerations, which is why different studies have considerable heterogeneity.

Three studies included in this review do not specify the basal glucose goal [3, 12, 57]; however, in different sections, they argue that the treating clinician had the power to individualize the goal. On the other hand, only one study indicates that its goal is the same as that of the DUAL series of clinical trials, i.e., 72–90 mg/dL [14]. Taybani et al. set a goal of 5–6 mmol/L, corresponding to 90–108 mg/dL [5]; any other study does not assume this goal. Sofra adheres to the goals of the European Association for the Study of Diabetes, which, when publishing these recommendations, are consistent with those of the American Diabetes Association in 2022, i.e., 80–130 mg/dL [2]. An Italian study sets two goals, a common goal between 90 and 130 mg/dL and another of 130–160 mg/dL in "frail elderly." However, this last term has no definition in the text since the choice of one or the other goal was made only on clinical grounds [13]. Ramírez-Rincón et al. did not have a single standard goal orientation. Given that in this study, every physician assumed their criteria, some patients were oriented on the basis of the goal established in the DUAL clinical trials (72–90 mg/dL), while others attempted to meet the ADA goal (80–130 mg/dL).

When performing a specific search in the population over 65, insulin simplification schemes set goals as lax as 90–150 mg/dL [1], an essential element to consider. Thus, the authors

recommend that the treating clinician be the one to make a personalized decision according to the age and the specific clinical and social conditions of each patient, taking as a reference framework one of the following options:

- Fasting blood glucose between 72 and 90 mg/dL [48, 49, 54]
- Fasting blood glucose between 80 and 130 mg/dL [58]
- Fasting blood glucose between 90 and 150 in older adults [1]

Although the REX [57] and Di Loreto [7] studies did not report transition schedules, we have included them in this review for the following reasons. The REX study says that the authors chose the therapy as a simplification strategy in two-thirds of the patients, which is why we have included it. In the study by Di Loreto et al. [7], the authors included outcomes due to changing therapy. Although both studies do not indicate how the change was made, the authors consider that the clinical results reported by both studies should not be ruled out, so we have included them in our review.

Limitations

The main limitation of this study is the heterogeneity of the types of studies included in this review. The authors know it is difficult to form conclusions from different studies, with varying observation periods and sometimes various outcome measures. Not many studies have evaluated the clinical results of the simplification of insulin treatment with IdegLira, so the challenge for the study was how these results could support a simplification process. Table 1 of the study presents the summary of the main clinical characteristics of each of the studies, as well as their clinical results so that the reader can identify the differences between the studies, which, in turn, allow supporting the treatment simplification process such as IdegLira as a strategy that makes it easier for the patient to achieve their treatment goals.

CONCLUSION

The purpose of this review is to propose a simplification scheme based on the available evidence from IdegLira. The chronic and progressive nature of diabetes gradually increases the complexity of therapeutic strategies, which aim to achieve specific goals. Unfortunately, this process is accompanied by greater patient demand, negatively impacting their quality of life. That is why implementing strategies that simplify treatment has the potential to be very important. Therefore, we carried out a literature review to contribute to constructing a scheme that meets this objective. Besides, we describe some definitions, pathophysiological principles, and technical scrutiny of the real-life studies' specifications. In this order, we propose simplifying complex insulinization regimens with IDegLira in patients living with T2D, with elements of a logical sequence to promote the construction of an algorithm. Thus, constructing the process in question allows us to visualize the co-formulation with IDegLira for simplification as a simple, versatile, safe, and effective therapeutic tool.

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Declarations

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