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Effect of deprescribing in elderly patients with type 2 diabetes: iDegLira might improve quality of life

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ABSTRACT

Older people with type 2 diabetes (T2D) often have several comorbidities and take multiple drugs. This study tested a deprescribing strategy in older T2D patients, replacing a hypoglycemic therapeutic scheme with a single drug combination (iDegLira). In this 6-month, real-world, single-arm, open interventional study, we enrolled patients ≥ 75 years with T2D taking ≥ 2 medications for diabetes. Patients on a basal-bolus insulin regimen (n = 13), on a basal-insulin regimen plus oral glucose-lowering drugs (n = 9), and those on oral glucose-lowering drugs (n = 18) were switched to daily iDegLira. The primary clinical endpoint of the study was an improvement in CASP-19 and/or DTSQ score after 6 months. We also evaluated changes in glucose metabolism, depression, cognitive function, level of independence, and markers of inflammation. Thirty-five patients (12 women, mean age=81.4 y) completed the protocol. Results shown here are given as estimated mean difference (95%CI). DTSQ score improved [11.08 (7.13/15.02); p = 0.0001], whereas CASP-19 did not after 6 months of iDegLira treatment. We observed reductions in BMI [− 0.81 (− 1.27/0.35); p < 0.001], fasting glucose [− 52.07 (− 77.26/26.88); p < 0.001], HbA1c [− 0.58 (− 1.08/0.08); p < 0.05], and TNF-α [− 1.83 (− 3.12/− 0.54); p = 0.007]. Activities of daily living and cognitive function score increased [p = 0.006 and p = 0.02], whereas depression score significantly decreased [p = 0.02]. Notably, no patient reported episodes of severe hypoglycemia after initiation of iDegLira treatment. Among older patients with T2D, deprescribing using a single dose of iDegLira resulted in a greater likelihood of improving health and quality of life. Although our data indicate the effectiveness and safety of this approach, it must be confirmed in larger studies.

1. Introduction

Older adults with type 2 diabetes often suffer numerous coexisting medical problems requiring multiple prescription medications. Diabetes, hypertension, cardiovascular diseases, neurodegenerative diseases, and digestive and respiratory disorders are common in older people and tend to coexist. Unfortunately, the complex therapy of these diseases increases the risk of adverse drug events [1]. Furthermore, there is marked heterogeneity in health status and functional capacity in older patients with type 2 diabetes, often making prescribing decisions complex and challenging [2]. However, despite the use of many medicines, undertreatment is also frequently present in the elderly, and the probability of underprescribing increases significantly with the number of medicines [3,4]. Both conditions have a detrimental effect on quality of life (QoL) of elderly individuals, increasing the risk of disability and death [5]. Therefore, older people would greatly benefit from a simplification of drug regimens and a reduction in pill burden, as well as better explanations of the need for each prescription [6]. In fact, the evidence base for deprescribing in older people is growing [7,8]. Accordingly, the World Health Organization launched the third global patient safety challenge, "Medication Without Harm," [9] which highlights the need to reduce unnecessary polypharmacy. However, there is limited evidence available for the deprescribing of antihyperglycemic medications in the elderly [10]. For this purpose, specific clinical studies with adequate clinical outcomes are required to support evidence-based decision-making in this patient population.

iDegLira is a combination of insulin degludec (100 units/mL) and liraglutide (3.6 mg/mL). It was approved in 2014 for the treatment of type 2 diabetes inadequately controlled with oral glucose-lowering agents alone or in combination with a glucagon-like peptide 1 (GLP-1) receptor agonist or basal insulin (European indication). Randomized clinical trials and real-world evidence have provided insights into its

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effectiveness and safety in routine clinical practice [11,12]. However, beyond its known metabolic efficacy, iDegLira has a very low hypoglycemic rate [13,14], with a single daily and flexible in time administration dose and a very good safety profile that makes it suitable for older or frail patients with diabetes.

To investigate whether simplification of a diabetes drug regimen may improve patients' QoL, we performed a pilot clinical study in a group of older and frail diabetic patients (age $\geq$ 75 y) taking 2 or more medications for diabetes, including or not insulin. We replaced the pre-existing hypoglycemic therapy with a single daily dose of iDegLira, with the aim of improving QoL and simplifying therapy in these patients without lessening their diabetes control. We report here the results after 6 months of iDegLira therapy. Our results may help to fill the knowledge gap on deprescribing of hypoglycemic medications, providing a possible strategy through the use of a single, safe drug combination in older individuals with diabetes.

2. Methods

This study was an open, single-arm interventional study conducted in a real-world setting lasting 6 months. All study procedures were performed in compliance with ethical standards for human clinical trials (institutional and national) and with the Declaration of Helsinki of 1964, as revised in 2013. This clinical study was approved by the University Hospital Committee of "Tor Vergata" University (protocol number: 141/18) and consequently registered (ClinicalTrials.gov ID: NCT04190160). All participants provided written informed consent before they were included in the study.

We screened a group of very old patients with type 2 diabetes (n = 56) who were referred to our outpatient clinic between March and December 2019. To determine patient eligibility, we used the following inclusion criteria: [1] informed consent obtained before screening and every procedure performed during the protocol; and [2] aged 75 years or older patients affected by type 2 diabetes, taking 2 or more tablets of any oral hypoglycemic agent and/or doses of insulin. The exclusion criteria were [1] estimated glomerular filtration rate (e-GFR) $<$ 15 mL/min [1.73 m]$^{-2}$ (according to the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula); [2] involved in an experimental clinical trial or taking any experimental drug during the 6 months prior to the beginning of this study; [3] any known or suspected allergic reaction or intolerance to degludec or any GLP-1 receptor agonist; [4] any known contraindication to use of iDegLira as described in the prescribing information; [5] a recent cancer diagnosis ($<$ 3 y) or active radio- or chemotherapy (a cancer diagnosis $>$ 3 y before the start of the study was allowed).

2.1. Replacement of previous hypoglycemic therapies with iDegLira

We invited eligible patients to replace their pre-existing hypoglycemic therapeutic scheme, whatever it was, with or without insulin, with a single daily and flexible in time administration of iDegLira. A single unit of iDegLira contains 1 unit of insulin degludec and 0.036 mg of liraglutide; therefore, to accomplish replacement, we used the following scheme: [1] patients on a basal bolus insulin regimen (n = 13) switched to daily iDegLira at the same dose of any type of pre-existing basal insulin plus 4 units; [2] patients on a basal insulin plus oral glucose-lowering drugs regimen (n = 9) switched to the same dose of any pre-existing basal insulin plus 2 units; [3] patients on oral glucose-lowering drugs (n = 18) switched to iDegLira at a dose of 0.15 units/kg. Of note, the protocol did not include any clinical visits or telephone contact for iDegLira titration. Moreover, we applied a categorical classification of therapy simplification, based on the hypoglycemic therapy before starting iDegLira, as follows: patients previously treated with up to 2 oral glucose-lowering drugs were included in the "low level of therapy simplification" group, and all others were included in the "high level of therapy simplification" group.

2.2. Study endpoints

The primary clinical endpoint of the study was a composite outcome at 6 months. This outcome was defined as an improvement in QoL as determined by increases in the Control, Autonomy, Self-Realization and Pleasure-19 (CASP-19) scale and/or Diabetes Treatment Satisfaction Questionnaire (DTSQ) score with respect to baseline. CASP-19 is designed to explore factors that affect QoL at an older age, whereas DTSQ, which is relevant for studies involving a clinical intervention, evaluates self-reported satisfaction related to a change in diabetes therapy. The secondary study endpoints were [1] glycemic control evaluated by treatment-related modification of fasting glucose and glycated hemoglobin (HbA1c); [2] change in depression evaluated by the Geriatric Depression Scale (GDS); [3] change in cognitive function evaluated by Mini Mental State Examination (MMSE); [4] change in level of independence as assessed by activities of daily living (ADL) and by instrumental activities of daily living (IADL).

To address these goals, the clinical protocol included 2 ambulatory visits, at the beginning of the study (V0), and 6 months after switching therapy to iDegLira (V1). During each visit, each participant completed the above-described battery of tests.

2.3. Clinical and biochemical protocol

At each visit, and following 12 h of fasting, participants underwent a complete clinical evaluation. BMI was calculated by dividing the weight (in kilograms) by the square of height (in meters). Waist circumference was measured in the midpoint between the lower rib and upper margin of the iliac crest. Blood pressure was acquired in the dominant arm in the sitting position with a standard appropriately sized sphygmomanometer cuff. Between 8:00 and 9:00 AM after an overnight fast, urine, fecal, and blood samples were obtained from all patients. Biological samples were divided into multiple aliquots and stored at − 80 °C until analysis. Every sample was thawed only once. About 8 mL of whole blood underwent centrifugation for serum sampling. Cytokine expression levels were determined in serum using Simple Plex, an integrated immunoassay system for the rapid and sensitive detection of up to 4 targeted protein antigens across multiple biological sources. Simple Plex assays consist of a disposable microfluidic cartridge and an automated analyzer (the Ella instrument) and were performed according to the manufacturer's instructions (ProteinSimple, San Jose, CA, USA).

Briefly, human serum samples were diluted 1:2 for interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) in sample diluent SD13; diluted samples, quality control samples, and buffer were loaded into each cartridge. A barcode scanner was used to identify the cartridge and automatically load lot-specific factory-calibrated standard curves that are embedded in each cartridge barcode. Sample identities and dilution factors were input using SimplePlex Runner software. At the conclusion of the assay, triplicate results (one per glass nano-reactor) for every analyte in each sample were automatically displayed. Raw (background-subtracted) signal levels are reported in relative fluorescence units (RFU) for each individual glass nano-reactor, and mean RFU signal values, standard deviation, and coefficient of variation are provided for triplicate glass nano-reactors. The RFU values were automatically back-fit to barcode-embedded standard curves, and back-fit concentrations were multiplied by user-defined dilution factors to provide calculated concentrations in picograms per milliliter for each analyte and every sample.

2.4. Sample power calculation of clinical protocol

For the composite primary clinical end point, we calculated that 34 participants would allow us to estimate an effect size of 0.5 for changes in quality of life/satisfaction scores with a statistical power of 80% (α = 0.05). Similarly, the same sample size would allow us to detect a reduction in HbA1c level of 0.5% (3.1 mmol/mol), assuming a baseline

standard deviation of 1.0.

2.5. Statistical methods

Descriptive data are summarized as mean ± standard deviation, minimum, and maximum for continuous variables and as absolute frequencies (percentages) for categorical variables. Longitudinal linear models were applied to longitudinal end points (both primary and secondary). The results are reported as estimated mean difference (EMD) from baseline to 6 months with 95% CI. Statistical significance was declared if $p < 0.05$.

The effect size was also estimated to measure the clinical relevance of significant differences. According to Cohen's d value, cut-offs of 0.2, 0.5, and 0.8 can be used to represent small, medium, and large effect sizes, respectively [15]. SAS software (release 9.4; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

3. Results

The clinical protocol for the study is presented as a flowchart in Fig. 1. Of the 57 screened patients, 11 were excluded because of an e-GFR < 15 mL/min and 6 were excluded for reported intolerance to GLP-1 receptor agonists. Therefore, 40 participants [12 women, 28 men, mean age = 81.2 y (range 75–90 y)] met inclusion and exclusion criteria and were enrolled. One participant died of acute respiratory failure 14 days after the beginning of the study. Another patient stopped iDegLira administration after 48 h following admittance to the intensive care unit because of a severe hemorrhagic stroke. We excluded 3 participants because of very low compliance with the study protocol. The remaining 35 patients (12 women, 23 men, mean age=81.4 y) discontinued all previous treatments for diabetes and took iDegLira from V0 to V1 (6 months).

Table 1 summarizes the concomitant chronic comorbidities and related pharmacological therapies. The patients followed several different therapeutic regimens, confirming the intricate clinical heterogeneity of the participants. Notably, more than half ($n = 20$, 57.1%) of the enrolled patients had 4 or more comorbidities. Table 2 shows the hypoglycemic therapies taken by participants before commencing the trial. Of note, 19 participants were taking 4 or 5 hypoglycemic drugs daily. Consequently, in 28 cases (80% of the study population), the level of therapy simplification was classified as "high." The mean prescribed dose of iDegLira was 20.6 ± 12.1 IU in patients previously treated with basal insulin and 10.9 ± 4.5 IU in insulin-naive patients.

3.1. Study outcomes

Table 3 shows 6-month changes in anthropometric, clinical, biochemical and questionnaire scores data of study participants on iDegLira.

DTSQ improved [EMD 11.08 (95% CI, 7.13–15.02); $p = 0.0001$], whereas CASP-19 did not change [EMD − 1.02 (95% CI, −3.42 to 1.37); $p = 0.39$] after 6 months of iDegLira treatment. With respect to baseline, participants at V1 showed a significant reduction in BMI [EMD − 0.81 (95% CI, −1.27 to −0.35); $p < 0.001$], a marked decrease in fasting glucose [EMD − 52.07 (95% CI, −77.26 to −26.88); $p < 0.001$] and a lowering of HbA1c [EMD − 0.58 (95% CI, −1.08 to −0.08); $p < 0.05$], without severe hypoglycemic episodes. Moreover, we observed a decrease in total cholesterol level [EMD − 8.4 (95% CI, −14.74 to −2.07); $p = 0.01$] and in circulating levels of TNF-α [EMD − 1.83 (95% CI, −3.12 to −0.54); $p = 0.007$]. We documented numeric, but not significant, reductions in waist circumference [EMD − 1.46; 95% CI, − 2.99–0.07; $p = 0.06$] and in circulating IL-1β [EMD − 0.15 (95% CI, −0.36 to 0.06); $p = 0.16$], whereas IL-6 levels, systolic and diastolic blood pressure, and creatinine remained similar to baseline values. Interestingly, ADL score improved [EMD 0.39 (95% CI, 0.12–0.66); $p = 0.006$] as did MMSE score [EMD 0.39 (95% CI, 0.12–0.66); $p = 0.02$], whereas GDS score decreased [EMD − 1.28 (95% CI, −2.32 to −0.25); $p = 0.02$]. No other significant changes were detected. As shown in Table 3, based on the effect size, changes in BMI, TNF-α, and total cholesterol were considered of small clinical relevance; changes in

Table 1
Baseline characteristics of enrolled patients.

Variables	Enrolled patients ($n = 40$)
Age, years (mean ± SD)	81.2 ± 4.4
Sex (male/female)	28/12
Diabetes duration, years (mean ± SD)	16 ± 8.4
Diabetes treatment, *n* (%)	
Oral hypoglycemic agents (OHAs)	16 (40)
Insulin and OHAs	10 (25)
Insulin only	14 (35)
Comorbidities, *n* (%)	
Any	38 (95)
> 4 concomitant diseases	23 (57.5)
Anemia	2 (5)
Arrhythmia	9 (22.5)
Benign prostatic hypertrophy (BPH)	4 (10)
Chronic obstructive pulmonary disease (COPD)	4 (10)
Coronary artery disease	10 (22.5)
Dementia	2 (5)
Depression	5 (12.5)
Dyslipidemia	15 (37.5)
Heart failure	11 (27.5)
Hypertension	25 (62.5)
End-stage renal disease	4 (10)
Inflammatory bowel disease	1 (2.5)
Hearing/vision loss	2 (5)
Liver disease	1 (2.5)
Osteoporosis	5 (12.5)
Other blood disease	3 (7.5)
Peripheral artery disease	14 (35)
History of cancer	6 (15)
Thyroid disease	4 (10)
Mean number of comorbidities (± SD)	3.0 ± 1.4
Concomitant treatments, *n* (%)	
ACE inhibitor and/or angiotensin receptor blocker	26 (65)
Anticoagulant	10 (25)
Antidepressant	7 (17.5)
Anti-platelets	27 (67.5)
α-Blocker	3 (7.5)
β-Blocker	18 (45)
BPH drugs	4 (10)
COPD therapy	1 (2.5)
Calcium antagonist	7 (17.5)
Constipation therapy	2 (2.5)
Dementia drug	2 (2.5)
Diuretic	19 (47.5)
Fibrate	1 (2.5)
Omega-3	5 (12.5)
Osteoporosis drug	4 (10)
Other antihypertensive	5 (12.5)
Proton pump inhibitor	21 (52.5)
Pain therapy	6 (15)
Parkinson therapy	3 (7.5)
Statin	18 (45)
Thyroid hormone	4 (10)
Vitamin D	8 (20)

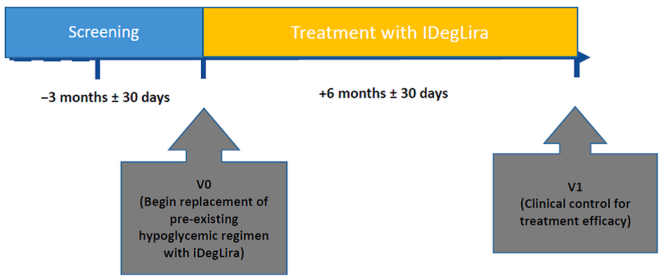

Fig. 1. Flowchart describing the study protocol.

Table 2
Diabetes therapy in the study population before initiation of iDegLira.

Previous therapy	
Classes of drugs prescribed before iDegLira initiation, *n* (%)	
Metformin	17 (42.5)
Sulfonylurea	5 (12.5)
Glinides	8 (20)
Thiazolidinedione	2 (5)
Dipeptidyl peptidase IV inhibitor (DPP-IV-i)	10 (20)
Sodium-glucose cotransporter inhibitor (SGLT2-i)	3 (7.5)
Basal insulin	21 (52.5)
Short-acting insulin	17 (42.5)
Doses of insulin, IU (±SD)	
Basal insulin mean dose	17.9 ± 10.2
Short-acting insulin mean dose	35.6 ± 11.7
Total insulin mean dose	40.2 ± 28.9
Treatment scheme, n (%)	
Oral hypoglycemic agents (OHA)	16 (40)
Basal Insulin and Oral Antihyperglycemic Therapy (BOT)	9 (22.5)
Basal Bolus (BB) ± OHA	15 (37.5)
Mean classes of drugs, n (±SD)	
Overall population	2.1 ± 0.8
Distribution of patients by number no. of daily administration of antihyperglycemic drugs, n (%)	
2	8 (20)
3	13 (32.5)
4	14 (35)
> =5	5 (12.5)
Distribution of patients by level of therapy simplification, n (%)	
Low	8 (20)
High	32 (80)
Mean dose (IU) of IDegLira	
All patients	15.3 ± 9.9
Insulin-Naive patients	10.9 ± 4.5
Patients with previous basal Insulin treatment	20.6 ± 12.1

HbA1c level and ADL, MMSE, and GDS scores were of moderate clinical relevance; and changes in fasting glucose and DTSQ score were of high clinical relevance.

The change in fasting glucose from V0 to V1 was significantly correlated with improvement in MMSE ($r = -0.415$; $p = 0.025$), and the decrease in GDS score (depression) in elderly patients was correlated with reductions in TNF-α ($r = 0.247$; $p = 0.050$) and HbA1c ($r = 0.382$; $p = 0.041$) (Table 4) but not with changes in IL-1β or IL-6. No patient reported episodes of severe hypoglycemia after initiation of iDegLira treatment.

4. Discussion

In this study, we demonstrated that therapy deprescribing in elderly and frail patients with type 2 diabetes is feasible. In fact, we found that replacing the existing hypoglycemic therapy with a single daily administration of iDegLira led to markedly improved DTSQ score. The DTSQ is a widely used instrument that has recently been used to assess gratification with many novel therapies for type 2 diabetes [16] and to evaluate the quality of diabetes care in clinical settings [17]. The large effect size of 1.4 achieved here showed that our strategy led to broadly perceived satisfaction, probably because of increased self-efficacy and adherence to therapy in older, frail patients with comorbid type 2 diabetes. Furthermore, patients showed improvements in activities of daily living, in cognitive function, and depression symptoms (ADL, MMSE, and GDS scores, respectively). Together, these results indicate that iDegLira may be a useful and effective therapeutic option for deprescribing. Of note, improvement in activities of daily living is a critical result because this can prevent cognitive impairments, dementia, and mortality in older adults [18].

Notably, our strategy was shown to be safe because no severe hypoglycemic events occurred during the 6 months of the study, despite the underlying frailty of the study participants. On the other hand, the CASP-19 score was unchanged after 6 months, perhaps suggesting that a generic and multi-dimensional measure of QoL is unlikely to be influenced solely by a change in diabetes therapy.

Furthermore, in this pilot study, we report some significant and clinically relevant improvements in metabolic control, cardiovascular risk factors, and inflammatory markers. We documented a 0.5-point reduction (−3.1 mmol/mol) in the HbA1c level, a reduction in fasting glucose of approximately 50 mg/dL, a decrease in total cholesterol of about 10 mg/dL, and a 1-point reduction in BMI. These results were unexpected because they were achieved despite a high level of deprescribing in 80% of the patients and because the therapeutic simplification was performed independently of the existing glycemic control. However, it is possible that our findings reflect in part the simultaneous administration of degludec and liraglutide (iDegLira) rather than only on the deprescribing per se. In fact, degludec can target fasting and postabsorptive glucose control, and liraglutide reduces postprandial glycemic excursion by inhibiting gastric emptying, stimulating glucose-dependent insulin secretion, and suppressing hyperglucagonemia [19]. However, in addition to the metabolic improvements, we also observed an amelioration of cognitive and depression symptoms. It is known that the brain consumes glucose at a high rate, and glucose utilization in patients with cognitive impairment is decreased in areas of the brain that are directly related to cognitive function, such as the hippocampus and cerebral cortex. Intriguingly, both central administration of insulin and subcutaneous delivery of GLP-1 are reported to alleviate learning and memory dysfunction in patients with Alzheimer disease [20]. Notably, both insulin and GLP-1 agonists cross the blood–brain barrier [21], whereas insulin receptors are highly expressed in the hypothalamus and in the hippocampal and GLP-1 receptors are expressed in the thalamus, hypothalamus, and cortical brain areas [22], structures relevant for metabolic regulation and the forming of analytical memory contents [23]. Furthermore, innovative investigations are focused on the availability of insulin in the central nervous system aimed at preventing or delaying Alzheimer disease and related disorders [24]. Of note, in animal models, liraglutide treatment has been shown to significantly modulate metabolites involved in NAD metabolism [25], such as taurine, creatinine, and trigonelline, which are reported to be affected in depression and cognitive dysfunction [26,27]. Moreover, adults with Alzheimer disease and diabetes who are treated with insulin and hypoglycemic medications, including GLP-1 receptor agonists, are known to have reduced amyloid pathology compared with adults without Alzheimer disease or diabetes [28].

Given our preliminary results, we hypothesize that the simultaneous administration of degludec and liraglutide (iDegLira) may positively modulate the critical control of brain metabolism. Moreover, our findings might also reflect modulation of the gut microbiota. Recent studies have shown that liraglutide may influence the gut microbiome, suggesting a relationship between gastrointestinal tract microbes, diabetes, and GLP-1 agonism [29]. Similarly, there is support for the involvement of the microbiota in depression, cognitive impairment, and type 2 diabetes, all typical diseases of aging [30]. A relationship between intestinal microbial destabilization in type 2 diabetes and reversal of dysbiosis via antidiabetic treatment remains unclear [31]. Therefore, we cannot exclude a modification of bacterial community in elderly patients taking iDegLira and any association with changes in QoL.

Another important study finding was the significant reduction of BMI from 28.9 to 27.9, even though the mean age of our study population was greater than 80 years and no diet indications were provided. We also reported reduced levels of TNF-α (but not IL-1β or IL-6) 6 months after beginning administration of iDegLira. These results were consistent with previous studies indicating that administration of both GLP-1 receptor agonists and insulin to animals or humans with type 2 diabetes or obesity was associated with a reduction in local or systemic inflammation [31,32].

This study has several limitations that should be considered when interpreting the results. The major limitation is the small sample size, which increases the risk that the results, although significant, occurred due to chance. Other limitations are the lack of a randomized control

Table 3
Changes in estimated mean levels of continuous clinical parameters and questionnaire scores from baseline (V0) to 6 months (V1).

Parameter	Visit	Estimated mean (95% CI)	Estimated mean difference (95% CI) from baseline	Within-group *P* value	Effect size
HbA1c	V0	[7.72 (7.37–8.06) %] or [61 (57–65) mmol/mol]			
	V1	[7.14 (6.77–7.5) %] or [55 (50–58) mmol/mol]	− 0.58 (−1.08 to −0.08) or − 4 (−9.5 to −0.64)	**0.019**	**0.6**
Fasting glucose	V0	180.06 (155.83–204.29)			
	V1	127.99 (115.88–140.09)	− 52.07 (−77.26 to −26.88)	**0.0002**	**0.9**
BMI	V0	28.53 (27.03–30.04)			
	V1	27.72 (26.38–29.06)	− 0.81 (−1.27 to −0.35)	**0.001**	**0.2**
Waist circumference	V0	102.59 (97.68–107.49)			
	V1	101.13 (96.83–105.43)	− 1.46 (−2.99 to 0.07)	0.06	
Systolic blood pressure	V0	128.68 (122.66–134.69)			
	V1	129.83 (122.25–137.41)	1.15 (−4.95 to 7.25)	0.70	
Diastolic blood pressure	V0	74.21 (71.18–77.24)			
	V1	70.93 (67.89–73.98)	− 3.27 (−7.22 to 0.67)	0.10	
Total cholesterol	V0	164.56 (153.11–176.01)			
	V1	156.16 (144.25–168.06)	− 8.4 (−14.74 to −2.07)	**0.010**	**0.2**
Creatinine	V0	1.15 (1.02–1.27)			
	V1	1.17 (1.06–1.27)	0.02 (−0.06 to 0.09)	0.641	
e-GFR	V0	57.75 (51.29–64.22)			
	V1	55.66 (49.52–61.8)	− 2.09 (−6.01 to 1.83)	0.282	
IL-1β	V0	0.29 (0.08–0.49)			
	V1	0.14 (0.09–0.19)	− 0.15 (−0.36 to 0.06)	0.163	
IL-6	V0	6.14 (2.93–9.34)			
	V1	6.45 (2.54–10.36)	0.31 (−1.12 to 1.75)	0.664	
TNF-α	V0	15.9 (14.01–17.79)			
	V1	14.07 (12.57–15.57)	− 1.83 (−3.12 to −0.54)	**0.007**	**0.4**
CASP-19	V0	43.59 (41.02–46.16)			
	V1	42.56 (40.04–45.09)	− 1.02 (−3.42 to 1.37)	0.395	
DTSQs	V0	23.82 (20.45–27.2)			
	V1	34.9 (33.2–36.6)	11.08 (7.13–15.02)	**< 0.0001**	**1.4**
ADL	V0	4.94 (4.56–5.32)			
	V1	5.33 (5.05–5.61)	0.39 (0.12–0.66)	**0.006**	**0.4**
IADL	V0	6.29 (5.44–7.15)			
	V1	6.27 (5.44–7.11)	− 0.02 (−0.34 to 0.3)	0.906	
MMSE	V0	23.33 (22.14–24.52)			
	V1	24.52 (23.46–25.57)	0.39 (0.12–0.66)	**0.020**	**0.4**
GDS	V0	5.26 (3.98–6.55)			
	V1	3.98 (2.83–5.14)	− 1.28 (−2.32 to −0.25)	**0.021**	**0.4**

Values in bold are statistically significant. HbA1c, glycated hemoglobin; e-GFR, estimated glomerular filtration rate; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; CASP-19, Control, Autonomy, Self-Realization and Pleasure-19; DTSQs, Diabetes Treatment Satisfaction Questionnaire score; ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini Mental State Exam; GDS, Geriatric Depression Scale.

Table 4
Significant correlations among study variables.

	V0 to V1 MMSE changing	V0 to V1 TNF-α changing	V0 to V1 HbA1c changing
V0 to V1 glucose changing	r = −0.415; $p = 0.025$		
V0 to V1 GDS changing		r = 0.247; $p = 0.05$	r = 0.382; $p = 0.041$

group and the lack of information about mild or symptomatic hypoglycemia in the study population. However, the definitive major strength is the novelty of data in an elderly and frail population undergoing underprescribing because of a high pill burden. In fact, although increasing QoL is an important target for older people in the real world, it is rarely included in health evaluations. Therefore, considering patients' experiences is particularly important in chronic diseases. Consequently, effective, safe, and easy to manage diabetes treatments represent a great opportunity to improve health and QoL of elderly people. The reduction in the use of drugs, self-monitoring of blood glucose, and access to emergency rooms for hypoglycemic episodes have not only clinical but also economic implications. Finally, larger studies are needed to assess the efficacy, safety, and cost-effectiveness of iDegLira in these populations.

CRediT authorship contribution statement

S.R. contributed to study concept and design of data. S.R. and M.F. contributed to drafting of the manuscript, to interpretation of data, to statistical analysis and to critical revision of the manuscript for important intellectual content. S.R., M.M, R.T., G.P., A.N. and S.L. contributed to acquisition of data. All authors read and approved the final manuscript. S.R. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement

All the authors declare no relevant conflicts of interest among them and with the work. The editorial assistance was provided by CORESEARCH SRL through a Novo Nordisk S.p.A. unconditional grant. Novo Nordisk S.p.A. did not influence and has not been involved in the data interpretation presented in the manuscript.

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Duality of Interest

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