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ORIGINAL RESEARCH

Early Conversion of Intensive Insulin Therapy to IDegLira Demonstrates Higher Efficacy and Safety in Reducing Fasting Blood Glucose and HbA1c in T2DM Patients

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Background: A short-term insulin intensive therapy is an important method used in clinical practice to control blood glucose, and a scientific post-treatment plan is key to long-term blood glucose stability control. This study aimed to investigate efficacy and safety of early conversion of intensive insulin therapy to IDegLira in T2DM patients.

Methods: This study was a prospective study, involving 80 T2DM patients finally. Patients were firstly treated with insulin for intensified therapy (Pre-IDegLira group), then switched to insulin degludec and liraglutide (IDegLira) for 3 months (IDegLira-3 months group). Data including HbA1c, fasting blood glucose, fasting C-peptide, weight, insulin dosage, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were analyzed. Correlations between fasting blood glucose and other parameters were evaluated with Pearson correlation analysis.

Results: IDegLira early conversion significantly reduced fasting blood glucose ($p<0.001$), weight ($p=0.015$), and insulin dosage ($p=0.001$) of T2DM patients compared to those of Pre-IDegLira group. HbA1c level was remarkably lower in T2DM patients underwent IDegLira early conversion compared to that in Pre-IDegLira group ($p<0.001$), with HbA1c <7% proportion of 73.75% (59/80). IDegLira early conversion significantly downregulated levels of TC ($p<0.001$), TG ($p<0.001$), LDL-C ($p<0.001$), and upregulated HDL-C level ($p=0.017$) of T2DM patients, compared to those in Pre-IDegLira group. IDegLira early conversion markedly reduced ALT ($p<0.001$) and AST ($p=0.002$) levels of T2DM patients compared to those in Pre-IDegLira group. IDegLira early conversion demonstrated a positive correlation between fasting blood glucose and HbA1c ($r=0.531$, $p<0.001$) or TG level ($r=0.336$, $p=0.002$) in T2DM patients.

Conclusion: Early conversion of intensive insulin therapy to IDegLira effectively reduced fasting blood glucose and HbA1c in T2DM patients with higher safety.

Keywords: insulin intensive therapy, IDegLira, T2DM, early conversion, safety

Introduction

In recent 30 years, the prevalence of diabetes mellitus in China has increased significantly.[1,2] The epidemiological survey of diabetes mellitus conducted by the Endocrinology Branch of the Chinese Medical Association in 31 provinces from 2015 to 2017 showed that the prevalence rate of diabetes mellitus among people aged 18 years and above in China was 11.2%, the treatment rate was 32.2%, and the control rate was 49.2%.[3] The metabolic control of type 2 diabetes (T2DM) is still a huge challenge.

The ideal treatment plan for diabetes mellitus should reduce the risk of weight gain and hypoglycemia as much as possible on the basis of effectively reducing the blood sugar level, with less adverse reactions and good compliance. Basic insulin supplements exogenous basic insulin, inhibits liver glycolysis and gluconeogenesis, reduces liver glucose output, increases skeletal muscle glucose uptake, and effectively controls fasting blood sugar.[4] The use of glucagon like

Received: 3 April 2024
Accepted: 26 July 2024
Published: 29 August 2024

peptide-1 receptor agonist (GLP-1RA) alone,[5] combined with basal insulin, can reduce the risk of hypoglycemia and weight loss.[6–8] However, both are injectable preparations, and the increased complexity of the treatment plan may reduce patient compliance.

In 2020, ADA medical diagnosis and treatment standards for diabetes recommend a compound preparation of basic insulin combined with GLP-1RA at a fixed proportion.[9] Insulin degludec and liraglutide (IDegLira) is the world's first marketed combination of basal insulin and GLP-1RA, which can exert complementary regulatory metabolic effects on multiple target organs of T2DM. It is a new choice after insulin intensive therapy. A previous study[10] has shown that after 26 weeks of treatment with IDegLira, patients have significantly improved (decreased) HbA1c and a lower risk of hypoglycemia. Therefore, IDegLira can become a new option for initiating and optimizing insulin therapy in Chinese T2DM patients.

This study investigated the efficacy and safety of early conversion of intensive insulin therapy to IDegLira in T2DM patients. After controlling blood glucose levels in patients undergoing short-term insulin intensive therapy (with a blood glucose range below 10 mmol/L), they switched to IDegLira treatment in the early stages. The effectiveness and safety compared between patients before IDegLira treatment and 3 months after IDegLira treatment.

Materials and Methods

Patients

This study was a prospective and single-arm study. This study selected 80 patients with T2DM who were hospitalized in the Endocrine Ward of our hospital as the diagnostic criteria.

This study has been approved by the Ethical Committee of YuYao People's Hospital. All patients involved in this study provided the written informed consents and approved this study.

Inclusion and Exclusion Criteria

Inclusion criteria: ① Patients met the diagnostic criteria of the World Health Organization (WHO) for T2DM in 1999. ② Gender was not limited, age ranged from 18 to 75 years old. ③ Patients who met one of the following conditions: glycosylated hemoglobin ≥9% or fasting blood glucose (FBG) ≥11.1 mmol/L (fasting for at least 8 h before collecting blood samples), or newly diagnosed T2DM patients with obvious hyperglycemia symptoms, or T2DM patients who had used multiple oral hypoglycemic drugs to treat blood glucose still significantly increased (HbA1c ≥9%).

Exclusion criteria: ① Acute complications of diabetes, including diabetic ketoacidosis, diabetic lactic acidosis, diabetic hyperosmotic hyperglycemia syndrome, etc. ② Severe infection (ie, infection combined with systemic inflammatory response syndrome and organ dysfunction). ③ End-stage renal disease (eGFR <15 mL/min). ④ Severe liver dysfunction (Child-Turcotte-Pugh score ≥7). ⑤ Previous history of pancreatitis. ⑥ Inflammatory bowel disease and diabetes gastroparesis. ⑦ History or family history of medullary thyroid carcinoma. ⑧ Pregnant or lactating women.

Therapeutic Schedule

After enrollment, 80 patients were firstly treated with insulin for intensified therapy. Degludec insulin was administered once a day in combination with pre-prandial subcutaneous injection of aspartic insulin or subcutaneous infusion of insulin with the insulin pump. After waiting for the patient's FBG to control (FBG <10 mmol/L), the above therapeutic strategy was switched to IDegLira and injected at a fixed time once a day without combining with other hypoglycemic drugs. The starting dose for IDegLira was 16 U/day. According to the titration results of the 3-day average FBG, the amount of IDegLira increased by 2 U when it was greater than 6.1 mmol/L, and decreased by 2 U when it was less than 3.9 mmol/L. In this study, the target FBG level was 3.9–6.1 mmol/L, and IDegLira was continuously used for at least 3 months. The maximum dose of IDegLira was 50 U. If the patient has already injected 50 U and their FBG was still greater than 7.0 mmol/L, they would withdraw from this study and changed their hypoglycemic regimen. The therapeutic schedule is displayed in Figure 1.

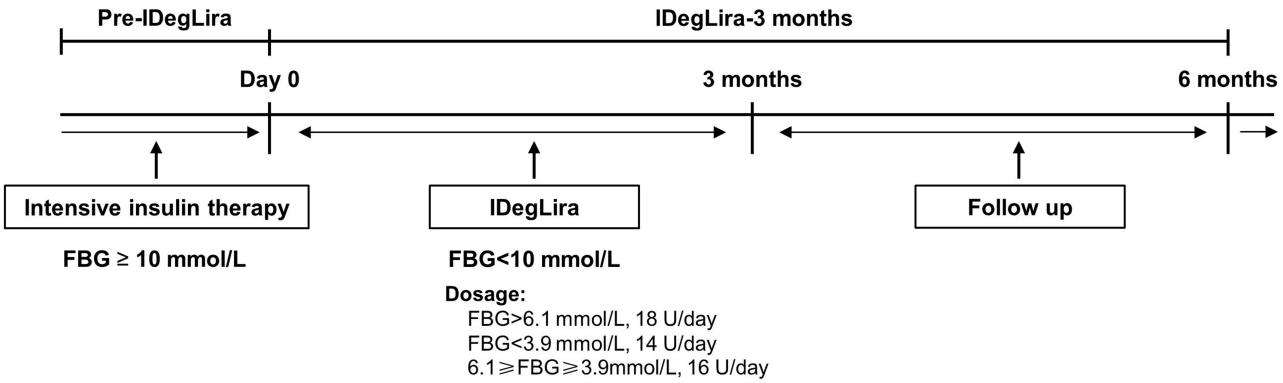

Figure 1 The therapeutic flowchart for the T2DM patients underwent early conversion of intensive insulin therapy to IDegLira therapeutic strategy.

Follow-Up

After discharge, patients would be followed up by phone once a week for a duration of 3 months. During the follow-up process, blood glucose control situation was evaluated, the number, frequency, and severity of adverse events were recorded during the drug application. Before the end of follow-up, the patient came to our Endocrine Clinic for a follow-up examination of glycated hemoglobin (HbA1c), fasting C-peptide, body weight, and average daily dosage of insulin, and developed a follow-up hypoglycemic plan based on the patient's condition.

Parameter Inspection Method

All testing items were completed at the Clinical Testing Center in Yuyao City. HbA1c was measured using high-performance liquid chromatography (Model: HLC-723G8, Dongcao Ins., Shanghai, China), fasting C-peptide was measured using chemiluminescence (Model: iFLash 3000, Yhlo Biotech., Shenzhen, China), and height and weight were measured using Omron ultrasonic height and weight meter (Model: HNH-318, Omron, Shanghai, China).

Statistical Analysis

The quantitative data, including HbA1c, fasting blood glucose, fasting C-peptide, weight, insulin dosage, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine were defined as mean ± standard deviation (SD) and analyzed using SPSS software 26.0 (IBM Corp., Armonk, NY, USA). The differences of the above data between pre-IDegLira group and IDegLira-3 months group were analyzed with the paired Student's *t*-test, and the $p<0.05$ was considered statistically significant. Adverse event incidence rate: the ratio of cases with adverse events to the total number of cases available for evaluation, expressed as a percentage (%). The correlations between fasting blood glucose and HbA1c, or fasting C-peptide, weight, insulin dosage, TC, TG, LDL-C, HDL-C were evaluated by the Pearson correlation analysis. The incidence of adverse events was the ratio of the number of cases with adverse events to the total number of evaluable adverse events, expressed as a percentage (%).

Results

IDegLira Early Conversion Reduced the Fasting Blood Glucose Levels of T2DM Patients

In this study, 103 patients with T2DM were initially included initially. During the treatment, 15 patients withdrew from the treatment group, and 8 patients had incomplete file data. Finally, a total of 80 patients were included in the data analysis. According to the statistical finding, the fasting blood glucose level was significantly lower in T2DM patients of IDegLira-3 months group (5.817 ± 1.149 mmol/L) compared to that of Pre-IDegLira group (13.704 ± 4.348 mmol/L) (Figure 2, $p<0.001$), with a reduction rate of 57.55%.

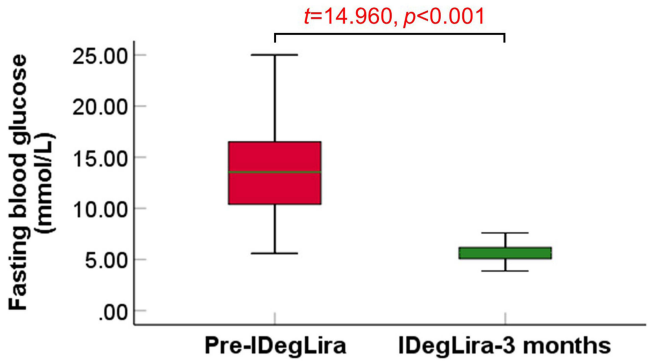

Figure 2 IDegLira early conversion reduced the fasting blood glucose level of T2DM patients. *p* value: Pre-IDegLira group vs IDegLira-3 months group.

IDegLira Early Conversion Decreased Weight and Insulin Dosage of T2DM Patients

After 3 months of IDegLira conversion, the body weight of T2DM patients in IDegLira-3 months group significantly decreased compared to that in Pre-IDegLira group (Figure 3A, p=0.015), suggesting that early conversion of intensive insulin therapy to IDegLira inhibits the increase of weight in T2DM patients. For the insulin dosage administering to T2DM patients, intensive insulin therapy indicated a dosage of 28.738 ± 19.363 U and IDegLira treatment showed a dosage of 19.950 ± 10.250 U, demonstrating a significant difference between two groups (Figure 3B, p=0.001). Therefore, IDegLira early conversion obviously decreased the dosage of insulin application in T2DM patients.

IDegLira Early Conversion Showed an Ideal HbA1c Level of T2DM Patients

For the intensive insulin therapy T2DM patients, the HbA1c level was 10.7768 ± 1.758% (Figure 3C), showing a poor controlled blood glucose level. IDegLira treatment showed a HbA1c level of 6.619 ± 1.038%, which was remarkably lower compared to that of patients in Pre-IDegLira group (Figure 3C, p<0.001). At the same time, the HbA1c of T2DM patients in IDegLira-3 months decreased by 4 percentage points (4% of HbA1c) (Figure 3C), suggesting a relatively ideal blood glucose control (<7% of HbA1c). After IDegLira early conversion for 3 months, the proportion of patients with HbA1c <7% was 73.75% (59/80), with only 2 patients of relatively poor blood glucose control (2/80, 2.5%) (Table 1).

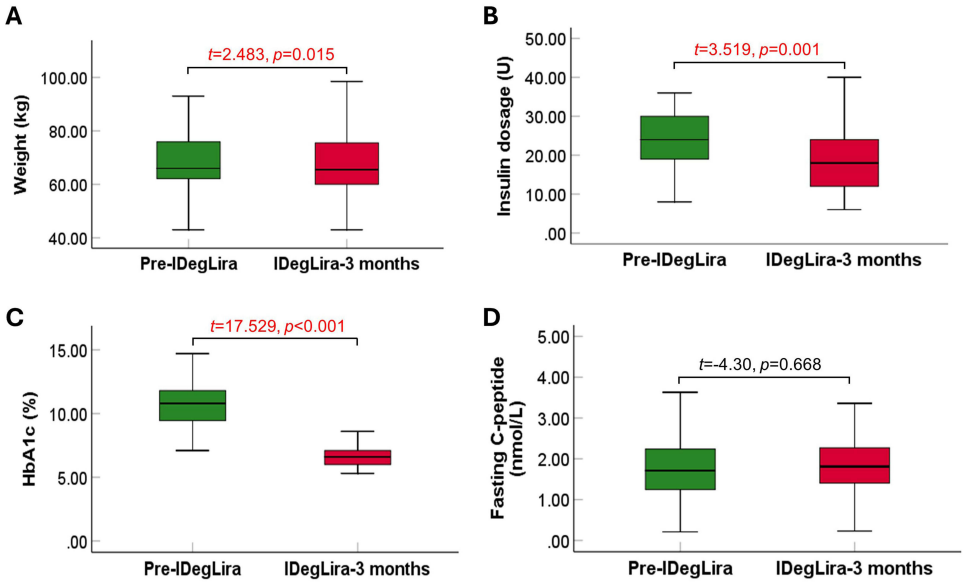

Figure 3 Effects of IDegLira early conversion on weight (**A**), insulin dosage (**B**), HbA1c (**C**), and fasting C-peptide (**D**) in T2DM patients. *p* values: Pre-IDegLira group vs IDegLira-3 months group.

Table 1 The Blood Glucose Control of T2DM Patients Undergoing IDegLira Treatment

Blood Glucose Control			
Relatively Ideal (HbA1c≤7%)	Relatively Not Ideal (7%<HbA1c≤8%)	Not Ideal (8%<HbA1c≤9%)	Relatively Poor (HbA1c>9%)
59/80	15/80	4/80	2/80
73.75%	18.75%	5%	2.5%

Furthermore, there was no obvious difference for the fasting C-peptide of T2DM patients between Pre-IDegLira group and IDegLira-3 months group (Figure 3D, p=0.688).

IDegLira Early Conversion Improved the Blood Lipid Status of T2DM Patients

The blood lipid detection results showed that IDegLira treatment (IDegLira-3 months group) significantly downregulated the levels of TC (Figure 4A, p<0.001), TG (Figure 4B, p<0.001), and LDL-C (Figure 4C, p<0.001) of T2DM patients, compared to those in the Pre-IDegLira group. However, HDL-C level was significantly upregulated in T2DM patients of IDegLira-3 months group compared to that of Pre-IDegLira group (Figure 4D, p=0.017). The above results suggest that IDegLira improved blood lipid status of T2DM patients.

IDegLira Early Conversion Reduced ALT and AST Levels of T2DM Patients

The ALT measurement results indicated that IDegLira treatment (IDegLira-3 months group) significantly reduced ALT levels (Figure 5A, p<0.001) and AST levels (Figure 5B, p=0.002) of T2DM patients, compared to those in the Pre-IDegLira group. However, there was no significant difference for the serum creatinine of T2DM patients between the Pre-IDegLira group and the IDegLira-3 months group (Figure 5C, p=0.537). These results suggest that IDegLira improved the liver function of T2DM patients but not affected the kidney function.

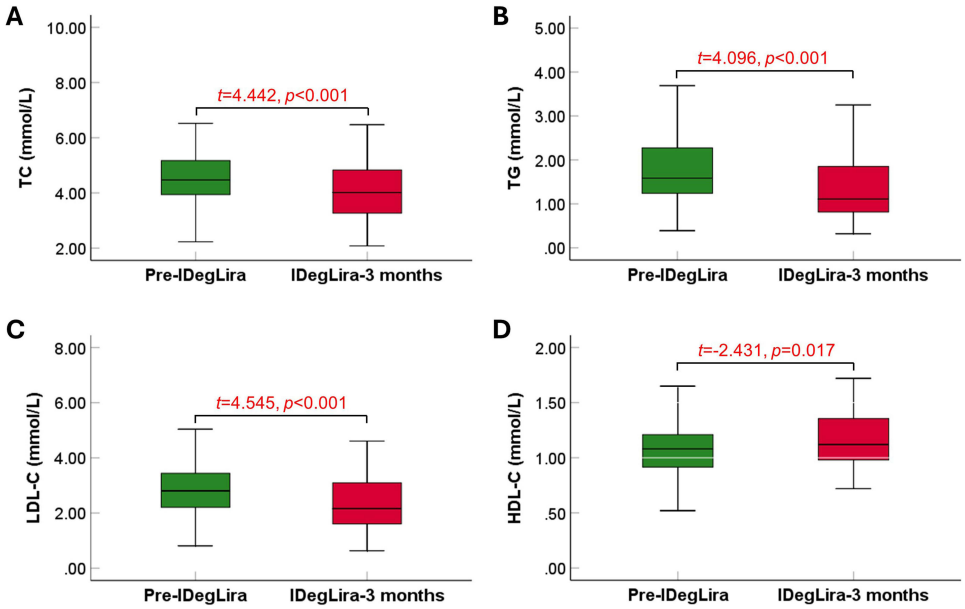

Figure 4 IDegLira early conversion modulated the blood lipid metabolism of the T2DM patients. (**A**) Statistical analysis of TC levels. (**B**) Statistical analysis of TG levels. (**C**) Statistical analysis of LDL-C levels. (**D**) Statistical analysis of HDL-C levels. p values: Pre-IDegLira group vs IDegLira-3 months group.

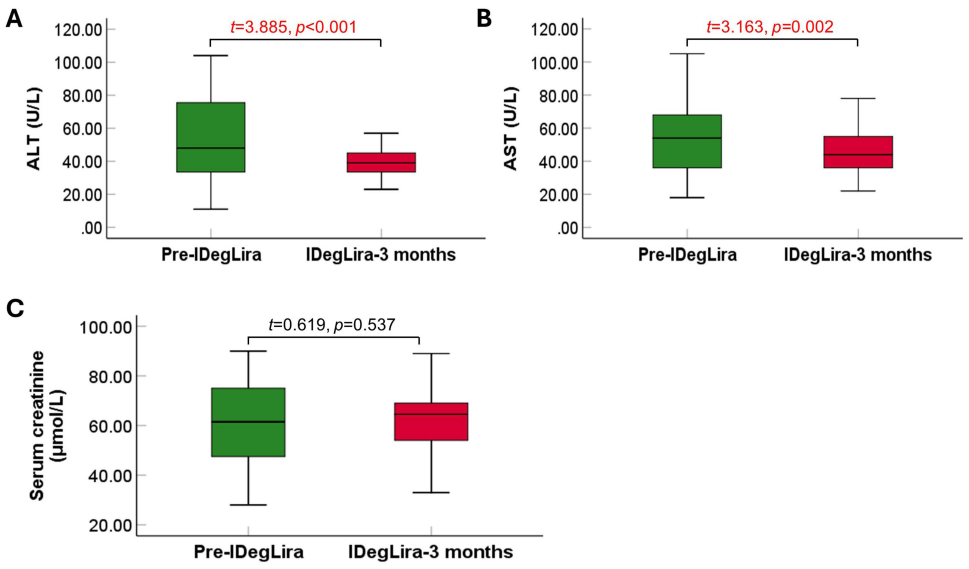

Figure 5 IDegLira early conversion reduced ALT and AST levels of T2DM patients. (**A**) Statistical analysis of ALT levels. (**B**) Statistical analysis of AST levels. (**C**) Statistical analysis of serum creatinine levels.

IDegLira Early Conversion Demonstrated a Positive Correlation Between Fasting Blood Glucose and HbA1c in T2DM Patients

According to the Pearson correlation analysis, there was no correlation between fasting blood glucose and weight (Figure 6A, p=0.814), insulin dosage (Figure 6B, p=0.918), or fasting C-peptide (Figure 6C, p=0.297) for T2DM patients underwent IDegLira treatment. However, the fasting blood glucose of IDegLira treated T2DM patients was positively correlated with HbA1c (Figure 6D, r=0.531, p<0.001).

Fasting Blood Glucose Correlated with TG Level in IDegLira Treated T2DM Patients

The fasting blood glucose of IDegLira-treated T2DM patients was not correlated with the level of TC (Figure 7A, p=0.163), LDL-C (Figure 7B, p=0.323), and HDL-C (Figure 7C, p=0.797), while IDegLira-treated T2DM patients' fasting blood glucose was positively correlated with the TG level (Figure 7D, r=0.336, p=0.002).

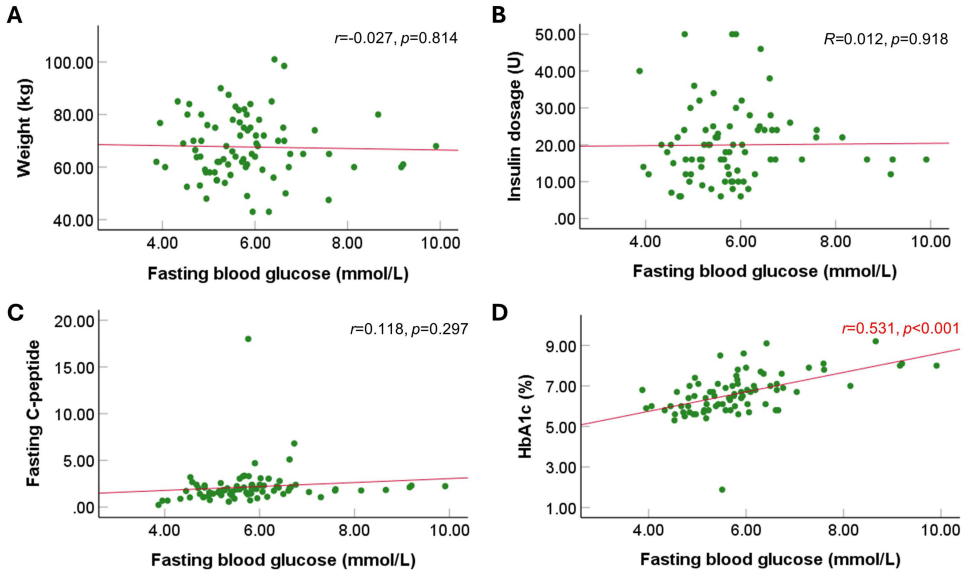

Figure 6 HbA1c was positively correlated with fasting blood glucose level in T2DM patients underwent IDegLira early conversion. Correlations between fasting blood glucose level and weight (**A**), insulin dosage (**B**), fasting C-peptide (**C**), and HbA1c (**D**) were analyzed. p values represented the significances of the correlations.

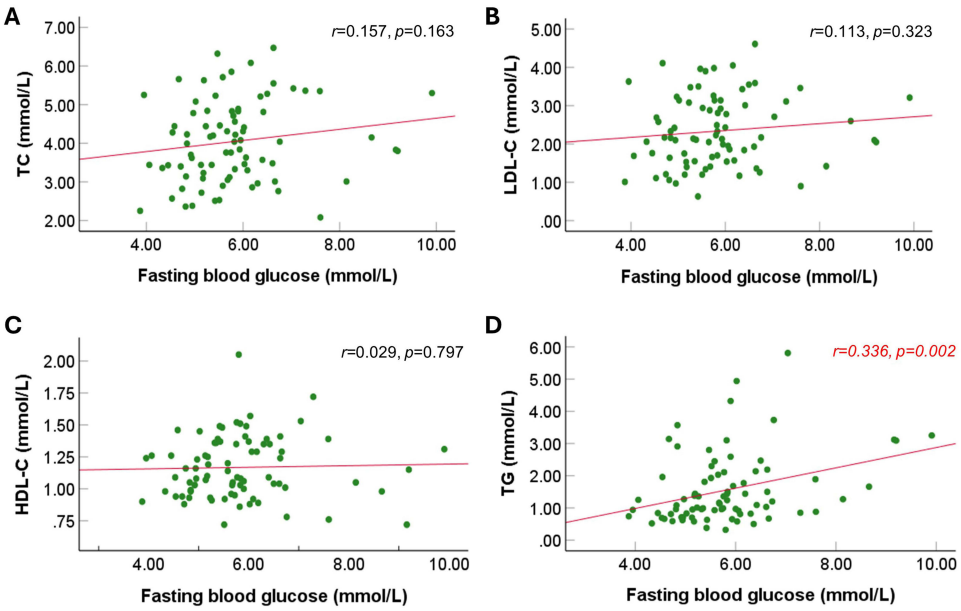

Figure 7 Correlation analyses between fasting blood glucose and TC (**A**), LDL-C (**B**), HDL-C (**C**), and TG (**D**) in T2DM patients underwent IDegLira early conversion. *p* values represented the significances of the correlations.

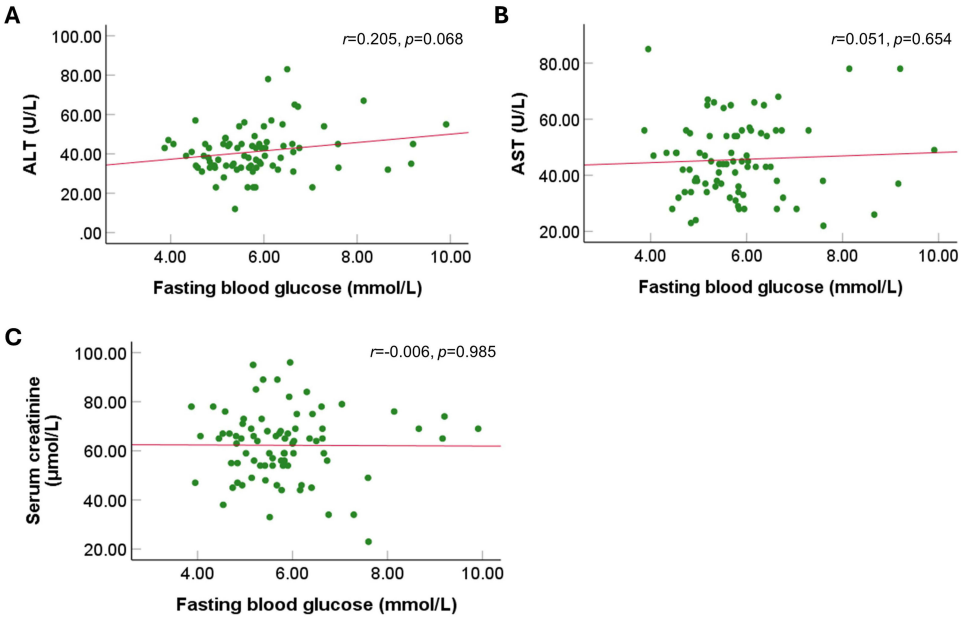

Figure 8 Correlation analyses between fasting blood glucose and ALT (**A**), AST (**B**), and serum creatinine (**C**) in T2DM patients administered with IDegLira early conversion. *p* values represented the significances of the correlations.

However, there were no correlations between fasting blood glucose and ALT (Figure 8A, p=0.068), fasting blood glucose (Figure 8B, p=0.654) and fasting blood glucose (Figure 8C, p=0.985).

IDegLira Early Conversion Was Safe and Reliable

After IDegLira early conversion, no serious adverse events occurred in all T2DM patients. Meanwhile, only 1 patient (1/80, 1.25%) reported once mild hypoglycemic event, and 1 patient (1/80, 1.25%) reported twice mild hypoglycemic events. Other patients did not experience mild or severe hypoglycemia.

Discussion

With the aging of the population, the increasing prevalence of overweight and obesity, and the genetic susceptibility of T2DM, the prevalence of diabetes mellitus in China has increased significantly in recent years.[11] The epidemiological characteristics of diabetes in China are mainly T2DM (more than 90% cases). The survey results from 2015 to 2017 showed that newly diagnosed diabetes patients accounted for 54% of the total number of diabetes,[3] and the overall rate of reaching the standard of glycosylated hemoglobin in diabetes patients was not high.

Short-term insulin intensive therapy is one of the important methods for enhancing blood glucose control, and implementing short-term insulin intensive therapy can help quickly reduce high glucose toxicity. The Expert Consensus on Short-term Intensive Insulin Treatment for Type 2 diabetes 2021 pointed out that intensive treatment can fully restore the function of B cells and insulin sensitivity.[12] Previous studies have shown that the duration of intensive treatment for newly diagnosed or short course T2DM patients ranges from 2 weeks to 3 months.[13–15] For young patients with high body mass index and certain pancreatic function, it is more suitable to switch to basal insulin combined with GLP-1RA treatment.[12] This study evaluated the efficacy and safety of early conversion of IDegLira in type 2 diabetes patients who administered the intensive insulin therapy. However, this study excluded the acute complications of diabetes, because the acute complication of diabetes is the contraindication mentioned in the instructions of IDegLira.

IDegLira early conversion significantly reduced the fasting blood glucose levels of T2DM patients compared to that in intensive insulin therapy group (Pre-IDegLira) with a reduction rate of 57.55%, suggesting that IDegLira really reduced the blood glucose levels in T2DM patients. Previous DUAL series studies have confirmed the effectiveness and safety of IDegLira in different T2DM populations, with a high HbA1c compliance rate. Regardless of previous use of oral hypoglycemic drugs (OAD), GLP-1RA, or basal insulin therapy, the average HbA1c of patients in IDegLira group decreased to below 7%, with a decrease of 1.4–2.0%[10,16–19] In the DUAL VI study, among T2DM patients who had previously been treated with OAD, the proportion of patients treated with DeGu insulin and Liraglutide injection for HbA1c <7% was as high as 89.9%.[19] The present findings showed that the HbA1c of T2DM patients underwent IDegLira administration for 3 months decreased by 4 percentage points (4% of HbA1c), with the proportion of HbA1c <7% patients of 73.75% (59/80) and 2 patients of poorly controlled (2/80, 2.5%). Therefore, IDegLira early conversion showed an ideal blood glucose control efficacy (<7% of HbA1c) in the T2DM patients. Taybani et al[19] reported that 4 months after the early conversion of intensive insulin therapy to IDegLira therapy in T2DM patients, the proportion of patients with blood glucose reaching the standard (HbA1c <7%) reached 73%, which is equal to our result of HbA1c. Furthermore, post-IDegLira early conversion, there were no serious adverse events occurred in T2DM patients, only 1 patient (1.25%) reported once mild hypoglycemic event and 1 patient (1.25%) reported twice mild hypoglycemic events. Therefore, according to the fasting blood glucose level, HbA1c level and hypoglycemic events in T2DM patients, the IDegLira is safe and reliable.

Meanwhile, IDegLira early conversion obviously decreased the body weight and insulin dosage of T2DM patients, which is consistent with the findings of some previous studies.[20,21] However, IDegLira early conversion did not trigger the changes of fasting C-peptide of T2DM patients, suggesting that the function of pancreas has not been damaged by IDegLira.[22] The IDegLira administration is correlated with the fasting lipid profile changes of the diabetes mellitus patients.[23] In this study, we found that IDegLira early conversion significantly upregulated the HDL-C level of T2DM patients, suggesting that the IDegLira improved blood lipid status of T2DM patients. However, there were no effects of IDegLira treatment on the levels of TC, TG, and LDL-C of T2DM patients. Furthermore, IDegLira early conversion also markedly reduced the ALT and AST levels, which suggests that IDegLira treatment could improve the liver functions of T2DM patients. However, IDegLira treatment did not affect the serum creatinine levels, indicating no effect on kidney functions.

Moreover, the correlations between fasting blood glucose and other diabetes mellitus associated parameters were evaluated in T2DM patients underwent IDegLira early conversion. For the IDegLira early conversion T2DM patients, the fasting blood glucose was positively correlated with the HbA1c. This result suggests that IDegLira early conversion reduced the fasting blood glucose and HbA1c, and these two parameters showed synergistic changes. Meanwhile, fasting

blood glucose correlated with TG level in IDegLira treated T2DM patients, suggesting that IDegLira could also modulate the blood lipid metabolism and may merit to the prevention of the obesity.

Compared with previous studies, this study provided evidence of the safety and effectiveness of IdegLira as a follow-up insulin regimen for some T2DM patients. At the same time, this study explored the characteristics of the population who were able to successfully converse from IdiogLira (HbA1c <7%) treatment in the early stage of insulin intensive therapy, which can provide more theoretical basis for clinical practice. Taybani and his team[19] presented the results associated with the present findings. However, Taybani et al[19] did not mention the Asian population, and he only confirmed the safety and effectiveness of IDegLira without providing suitable demographic characteristics. Meanwhile, this study confirmed the safety and effectiveness of IDegLira and explored the population characteristics suitable for diabetes patients in China. Furthermore, compared to professor Taybani's research results, our findings included data on the BMI, C-peptide, urinary protein creatinine ratio, and weight changes after 3 months.

Limitation

Although we received a few limitations, this study also has a few limitations. First, the sample size of this study is small. In the following study, we would enlarge the sample size (patients) involving in the investigations. Second, the insulin concentration and HOMA-IR have not been involved in the study parameters, because insulin is already present in IDegLira, and it might affect the HOMA-IR results.

Conclusion

Early conversion of intensive insulin therapy to IDegLira therapeutic strategy effectively reduced fasting blood glucose and HbA1c, and improved other diabetes related indexes. Therefore, IDegLira early conversion could significantly improve the blood glucose and demonstrated higher safety and reliability. The application of IDegLira early conversion would provide a reference for the development of early conversion plans for insulin intensive therapy in T2DM patients, as well as a basis for personalized precision treatment.

Data Sharing Statement

All data are available from the corresponding author.

Ethics Approval and Consent to Participate

This study has been approved by the Ethical Committee of YuYao People's Hospital. All patients involved in this study provided the written informed consents and approved this study. The present study complied with the Declaration of Helsinki.

Funding

There is no funding to report.

Disclosure

None of the authors has a personal or financial relationship with other people or organizations that could bias the content of this manuscript.

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