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Comparative Study of Liraglutide and Insulin Glargine on Glycemic Control and Pancreatic β-Cell Function in db/db Mice

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Background: The aim of this study was to compare the effects of liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, and insulin glargine, a long-acting insulin analog, on glycemic control and pancreatic β-cell function in db/db mice.

Material/Methods: Eight-week-old male db/db mice (n=40) were divided into five groups: the vehicle-treated group (VG) (n=8); the insulin glargine-treated group (GG) (dose, 450 mg/kg) (n=8), the low-dose liraglutide-treated group (LLG) (dose, 75 μg/kg) (n=8), the mid-dose liraglutide-treated group (MLG) (150 μg/kg) (n=8), and the high-dose liraglutide-treated group (HLG) (300 μg/kg) (n=8), treated with subcutaneous injection once daily, from 8–14 weeks-of-age. Body weight, pancreatic weight, levels of blood glucose, triacylglycerol, C-peptide, and the intraperitoneal glucose tolerance test (IPGTT) were used. Expression levels of the *INS1* gene were measured using reverse transcription polymerase chain reaction (RT-PCR), and pancreatic and duodenal homeobox 1 (Pdx1), paired box 4 (Pax4), and paired box 6 (Pax6) mRNA expression were measured.

Results: Both insulin glargine and liraglutide improved glycemic control of db/db mice when compared with vehicle. The following were significantly increased in the HLG compared with the GG: the receiver operating characteristic (ROC) area under the curve (AUC) for the IPGTT; C-peptide levels; the pancreas to body weight coefficient; expression levels of the *INS1* gene and pancreatic transcription factors Pdx1, Pax4 and Pax6. Liraglutide treatment was without hypoglycemic effects.

Conclusions: Liraglutide acted in a dose-dependent manner on glycemic control of db/db mice, and was more effective than insulin glargine, when administered at a high dose.

MeSH Keywords: Diabetes Mellitus • Glucagon-Like Peptide 1 • Insulin • Insulin-Secreting Cells

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Background

Currently, the prevalence of diabetes mellitus is increasing worldwide, and it is now considered to be a pandemic non-communicable disease. Up to 95% of patients suffer from type 2 diabetes mellitus (T2DM), which is characterized by insulin resistance and β-cell dysfunction [1]. Currently, several hypoglycemic agents have been developed for the treatment of T2DM, including insulin analogs, insulin-sensitizing agents, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SLG2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists [2]. Previous studies on the treatment of diabetes mellitus have shown that long-acting GLP-1 receptor agonists protect pancreatic β-cell function [2,3]. Furthermore, GLP-1 receptor agonists and insulin analogs have shown hypoglycemic effects [3]. Short-term intensive insulin therapy can improve and recover β-cell function in newly diagnosed T2DM [4,5]. Currently, both GLP-1 receptor agonists and insulin analogs have been widely used to control blood glucose.

GLP-1 is an incretin hormone secreted by intestinal cells in response to orally ingested food, which reduces glucagon secretion, delays gastric emptying, reduces appetite, and promotes pancreatic β-cell proliferation and differentiation. The spectrum of effects in diabetes mellitus gives GLP-1 a unique physiological and pharmacological profile that has been the basis for the development of a hypoglycemic agent for T2DM. However, GLP-1, which is a substrate of dipeptidyl peptidase IV (DPP-IV), is rapidly degraded by DPP-IV and cleared from the plasma, giving the biologically active peptide a half-life of less than two minutes after intravenous administration, and of between one and two hours after subcutaneous administration. Therefore, native GLP-1 is not optimal for therapeutic use because of its pharmacokinetic profile, but the development of GLP-1 receptor agonists provide a new approach to the treatment of T2DM [6].

Previous studies have shown that GLP-1 receptor agonists have pleiotropic effects that may enhance their therapeutic effect in patients with T2DM, including glycemic control, improving lipid metabolism, lowering blood pressure, reducing cardiovascular risk factors, and reducing the levels of inflammatory mediators [7,8]. Liraglutide is a long-acting GLP-1 receptor agonist, which permits 24-hour glycemic control with a once-daily injection [3,9]. Although the effects of the GLP-1 receptor agonist, liraglutide, and the insulin analog, insulin glargine, on glycemic control have been studied clinically, it remains unclear whether there are differences between the insulin analog, insulin glargine and the GLP-1 receptor agonist, liraglutide, regarding the effects on glucose control and preservation of β-cell function *in vivo*.

The aim of this study was to compare the effects of liraglutide, a long-acting GLP-1 receptor agonist, and insulin glargine, a long-acting insulin analog, on glycemic control and pancreatic β-cell function in db/db mice.

Material and Methods

Treatment of animals

Seven-week-old male db/db mice (between 35–40 gm) were obtained from the National Resource Center for Mutant Mice (Nanjing, China, SCXK-2010-0001). To minimize the stress due to handling, all animals were accustomed to blood sampling and dosing procedures for one week before the start of the experiments. Liraglutide was obtained from Novo Nordisk, Denmark.

Eight-week-old male db/db mice (n=40) were divided into five groups: the vehicle-treated group (VG), treated with phosphate-buffered saline (PBS) injection (n=8); the insulin glargine-treated group (GG) (dose, 450 mg/kg) (n=8), the low-dose liraglutide-treated group (LLG) (dose, 75 μg/kg) (n=8), the mid-dose liraglutide-treated group (MLG) (150 μg/kg) (n=8), and the high-dose liraglutide-treated group (HLG) (300 μg/kg) (n=8). Liraglutide and insulin glargine were given once daily via subcutaneous injection to mice between 8–16 weeks-of-age. All animals were housed in an environmentally controlled room at 25°C with a 12-hour light and 12-hour darkness cycle, and fed with a normal diet and with free access to water throughout the experimental period. All experimental animal procedures were approved by the Animal Care and Use Committee of the Second Affiliated Hospital of Nanchang University and were conducted in compliance with Guide of the Care and Use of Laboratory Animals, according to the National Institutes of Health (NIH) publication (No. 86-23, revised 1996).

Assays for metabolic components

Random blood glucose levels were measured using the Accu-Check Advantage glucose meter (Roche Diagnostics Ltd) with blood obtained from a tail vein. Serum triacylglycerol was measured using a mouse triacylglycerol enzyme-linked immunosorbent assay kit (Biovision, USA) according to the manufacturer's protocol. Body weight, blood glucose, and serum triacylglycerol levels were measured on days 1, 5, 9, 11, 15, 22, 29, 36 and 43 during the six-week study period.

Intraperitoneal glucose tolerance test (IPGTT) and serum C-peptide levels

Intraperitoneal glucose tolerance test (IPGTT) was performed at the end of the treatment period. Mice were injected intraperitoneally with glucose (0.5 gm/kg body weight) after an

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Table 1. Oligonucleotide sequences for quantitative reverse transcription- polymerase chain reaction (qRT-PCR) analysis.

Gene symbol	Forward primer	Reverse primer
β-actin	GCAGAAGGAGATTACTGCTCT	GCTGATCCACATCTGCTGGAA
Pax4	GCCTATCTCCAACCCTACTGG	GCCAGGCAAATTCCACATA
Pax6	TACCAGTGTCTACCAGCCAAT	TGCACGAGTATGAGGAGGTCT
Ins1	GCTTCTTCTACACACCCATGTC	AGCACTGATCTACAATGCCAC
Pdx1	CCCCAGTTTACAAGCTCGCT	CTCGGTTCCATTCGGGAAAGG

Pax4 – paired box gene 4; Pax6 – paired box gene 6; Pdx1 – pancreatic and duodenal homeobox 1; Ins1 – Insulin1.

overnight fast, and blood samples were taken from tail veins at 0, 30, 60, and 120 minutes for measurement of blood glucose. The area under the curve (AUC) of IPGTT was calculated by the trapezoid formula. Serum C-peptide levels, at 120 minutes following glucose injection, were measured using a mouse C-peptide enzyme-linked immunosorbent assay (ELISA) (ALPCO, Salem, NH, USA).

Pancreas to body weight coefficient

At the end of the treatment period, the mice were sacrificed by decapitation during CO_2 anesthesia, and the pancreas was removed and weighed for each mouse. An index of the pancreas to body weight was calculated.

RNA extraction and real-time polymerase chain reaction (RT-PCR)

Total RNA was extracted from pancreas using RNeasy Mini Kit (Qiagen, Valencia, CA, USA). Real-time polymerase chain reaction (RT-PCR) was performed using a Reverse Transcription System Kit (Invitrogen, USA) in a LightCycler 480 high-throughput PCR platform (Roche). The primers were designed using Applied Biosystems (Foster City, CA, USA) Primer Express design software. The sequences of the primers are listed in Table 1. RT-PCR was performed using the LightCycler 480 System (Roche) using SYBR Green Supermix (Takara). Data were normalized to the housekeeping gene, β-Actin.

Statistical analysis

All data were presented as the mean ± standard error of the mean (SEM). Statistical analysis was performed with one-way analysis of variance (ANOVA) with Bonferroni pairwise corrections and the Student's t-test. P-values <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 11.0 software (SPSS, Inc, Chicago, IL, USA).

Results

Effect of liraglutide and insulin glargine on body weight and blood glucose in db/db mice

The db/db mice (n=40) were divided into five groups: the vehicle-treated group (VG) (n=8); the insulin glargine-treated group (GG) (n=8), the low-dose liraglutide-treated group (LLG) (n=8), the mid-dose liraglutide-treated group (MLG) (n=8), and the high-dose liraglutide-treated group (HLG) (n=8), treated from 8–14 weeks-of-age. The body weight of the db/db mice was significantly reduced following different doses of liraglutide injection, with a maximal effect in the HLG compared with the VG at day 36 ($P<0.05$) and at day 43 ($P<0.01$) (Figure 1A). Also, the body weight of the HLG was significantly lower than the GG at day 36 and day 43 ($P<0.005$ and $P<0.001$, respectively).

The blood glucose levels of the mice in the GG, the LLG, the MLG, and the HLG were significantly reduced when compared with the VG ($P<0.05$). Also, blood glucose levels of the mice in the HLG were significantly reduced compared with the GG at days 22–43 ($P<0.05$) (Figure 1B). However, no statistical differences were observed in serum triacylglycerol levels between the treatment groups (Figure 1C). These results showed that liraglutide and insulin glargine treatment effectively controlled glucose levels rather than lipid metabolism in db/db mice.

High-dose liraglutide treatment had a more effective anti-diabetic effect than insulin glargine in db/db mice

Glucose tolerance was significantly improved in the GG, the LLG, the MLG and the HLG compared with the VG at the end of the six-week treatment period in db/db mice ($P<0.001$) (Figure 2A). The reduction of blood glucose levels after intraperitoneal glucose tolerance test (IPGTT) was significantly greater in the HLG compared with the GG ($P<0.001$) (Figure 2A). The HLG showed receiver operating characteristic (ROC) maximum area under the curve (AUC) of glucose tolerance ($P<0.001$) (Figure 2B). Also, the serum C-peptide of the db/db mice at the end of

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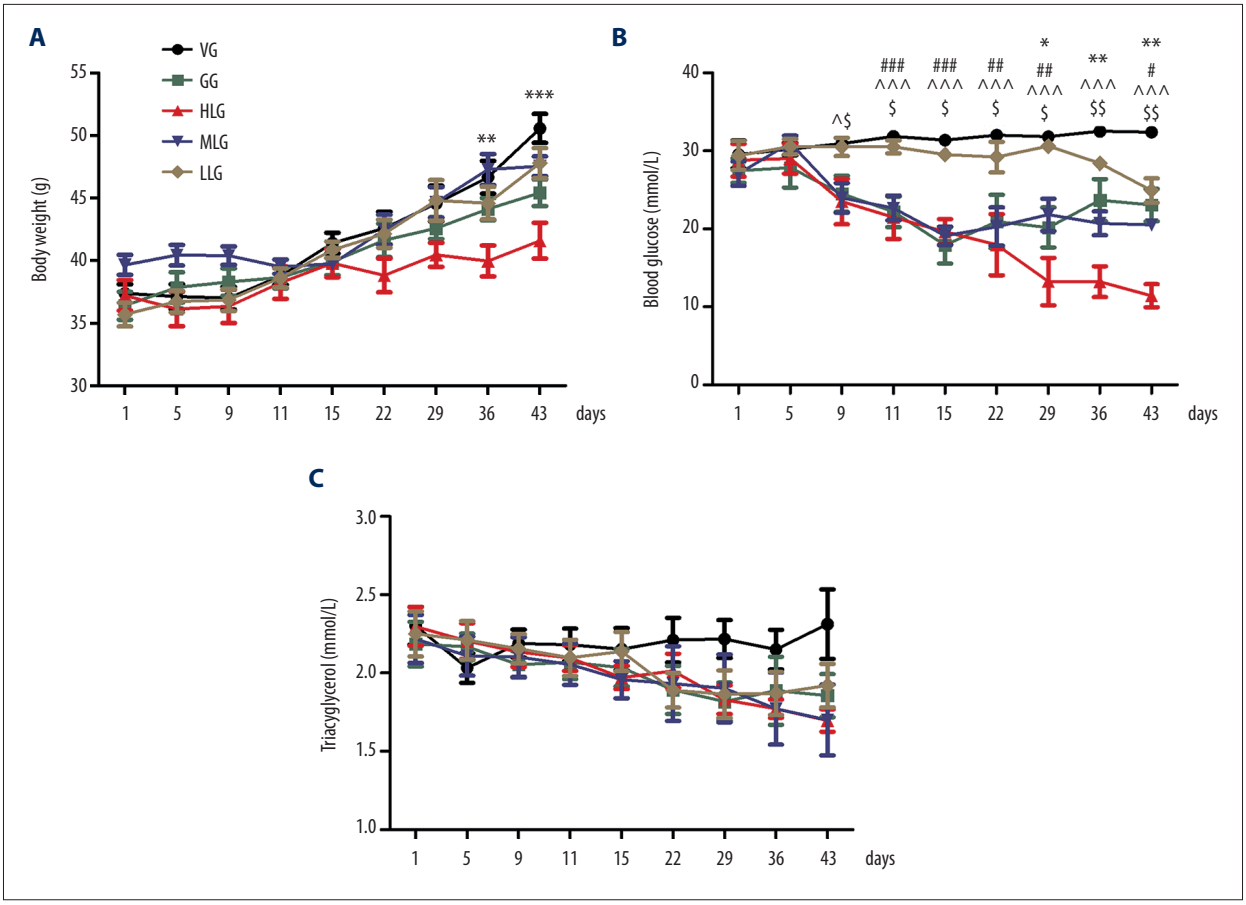

Figure 1. Effects of insulin glargine and liraglutide treatment on body weight, blood glucose, and serum triacylglycerol of db/db mice during six weeks of treatment. (**A**) Body weight. (**B**) Random blood glucose level. (**C**) Serum triacylglycerol level of db/db mice. Male db/db mice (n=40) were divided into five groups: the vehicle-treated group (VG) (n=8); the insulin glargine-treated group (GG) (dose, 450 μg/kg) (n=8), the low-dose liraglutide-treated group (LLG) (dose, 75 μg/kg) (n=8), the mid-dose liraglutide-treated group (MLG) (150 μg/kg) (n=8), and the high-dose liraglutide-treated group (HLG) (300 μg/kg) (n=8). The data represent the mean ±SEM. * P<0.05, ** P<0.01 HLG *vs.* GG. ^ P<0.05, ^^^ P<0.001 HLG *vs.* VG. # P<0.05, ## P<0.01, ### P<0.001 GG *vs.* VG. $ P<0.05, $$ P<0.01, $$$ P<0.001 MLG *vs.* VG.

the IPGTT, performed to evaluate pancreatic β-cell function after glucose stimulation, showed that the HLG had a significantly increased serum C-peptide compared with the GG, but the MLG and the LLG showed no difference when compared with the GG (P<0.05) (Figure 2C). Following the IPGTT, mice were sacrificed and the pancreas was weighed for each db/db mouse, and compared with the VG; the HLG showed a significant increase in the pancreas to body coefficient (P<0.05 and P<0.01, respectively), and this effect was not observed in the GG (Figure 2D). These findings may indicate that the high serum C-peptide and increase in pancreas weight might account for the improved glucose tolerance in the HLG.

High-dose liraglutide treatment upregulated pancreatic β-cell functional genes more than insulin glargine treatment in db/db mice

The expression levels of the insulin gene, *INS1*, in the pancreas of db/db mice measured by reverse transcription polymerase chain reaction (RT-PCR) was greatest in the HLG than MLG, the LLG, and the GG. Therefore, an improvement in insulin and C-peptide secretion may be a consequence of changes in insulin mRNA expression levels. Regulation of the expression of the insulin gene, *INS1*, was likely to have been due to the expression of a set of transcriptional factors that are typical of mature β-cells including pancreatic and duodenal homeobox 1 (Pdx1), paired box 4 (Pax4) and paired box 6 (Pax6). The expression of mRNA of these transcription factors was increased in a dose-dependent manner in all groups of mice treated with liraglutide, with a significant

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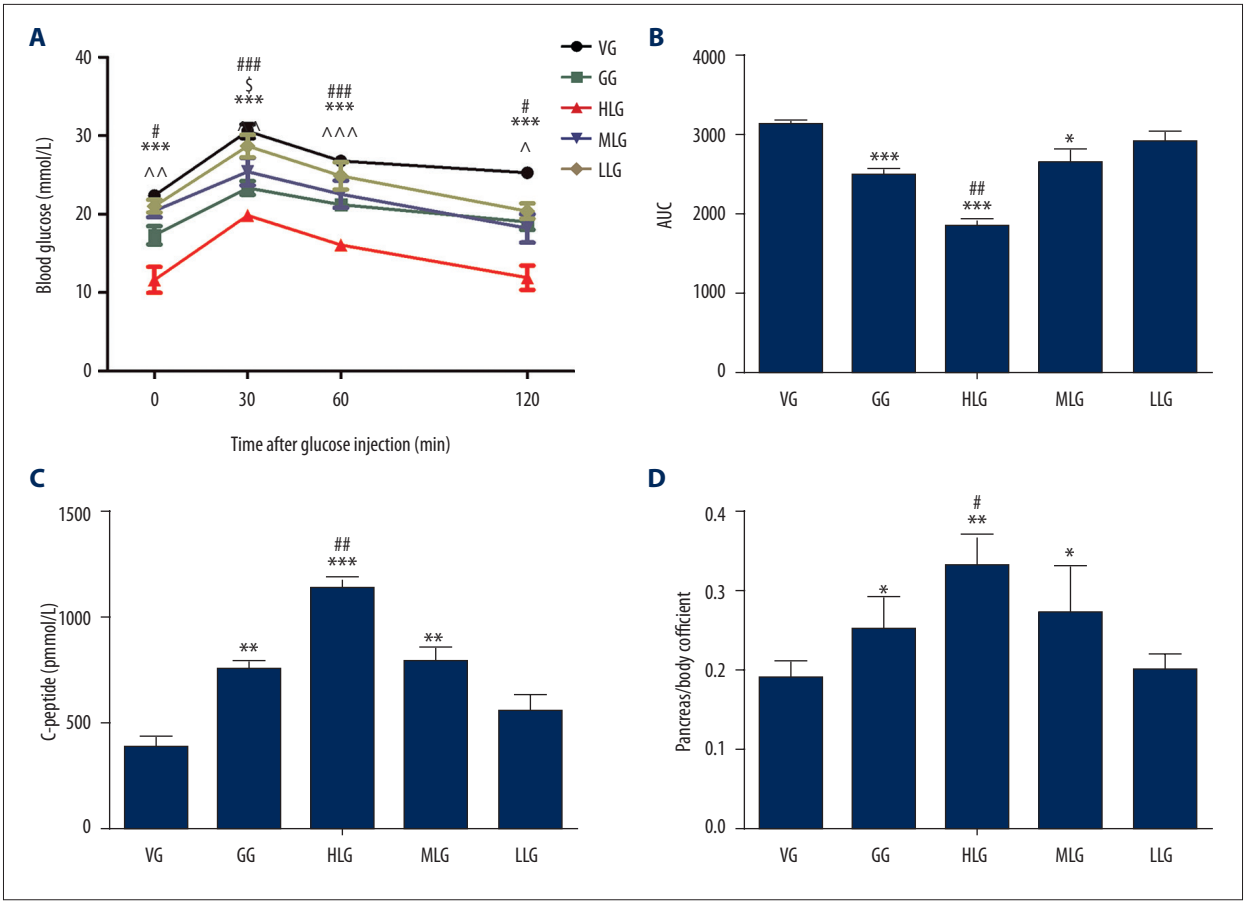

Figure 2. Glucose tolerance test (GTT) and serum C-peptide of db/db mice treated with insulin glargine and liraglutide. (**A**) # P<0.05, ## P<0.01, ### P<0.001 HLG *vs.* GG, *** P<0.001 HLG *vs.* VG, ^ P<0.05, ^^ P<0.01, ^^^ P<0.001 GG *vs.* VG. $ P<0.05 MLG *vs.* VG. (**B**) The area under the curve (AUC) of intraperitoneal glucose tolerance tests (GTT). (**C**) Serum C-peptide. (**D**) The pancreas to body weight coefficient. Male db/db mice (n=40) were divided into five groups: the vehicle-treated group (VG) (n=8); the insulin glargine-treated group (GG) (dose, 450 μg/kg) (n=8), the low-dose liraglutide-treated group (LLG) (dose, 75 μg/kg) (n=8), the mid-dose liraglutide-treated group (MLG) (150 μg/kg) (n=8), and the high-dose liraglutide-treated group (HLG) (300 μg/kg) (n=8). The data represent the mean ±SEM. * P<0.05, ** P<0.01, *** P<0.001 GG, HLG, MLG or LLG *vs.* VG. # P<0.05, ## P<0.01 HLG *vs.* GG.

increase in expression in the HLG compared with the GG (P<0.05) (Figure 3).

Discussion

Since 2005, the long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide, has been approved for the treatment of patients with type 2 diabetes mellitus (T2DM). Epidemiological studies and animal experiments have shown that GLP-1 receptor agonists have pleiotropic effects that may enhance their therapeutic effect in patients with T2DM, including the promotion of insulin secretion, the inhibition of gastric emptying, reduction in body weight, the increase in pancreatic β-cell mass, and the reduction in glucagon production [3,11]. Insulin glargine, a long-acting insulin analog, has been widely used in the treatment of T2DM [12,13]. Comparisons between the effects of GLP-1 receptor agonists with long-acting insulin analogs on the glucose control can assist in treatment decisions for patients with T2DM in clinical practice [14,15]. However, the effects on glucose control and protection of pancreatic β-cell functions by different GLP-1 receptor agonists and insulin glargine have not been well studied in diabetic db/db mice, which is widely used as an animal model for T2DM.

In the present study, the db/db mouse model was used in which the development of progressive diabetes is characterized by a reduced proliferation and increased apoptosis in pancreatic β-cells [16]. In this comparative study of treatment of the db/db mouse, the insulin glargine-treated group (GG) (dose, 450 μg/kg), was compared with the low-dose liraglutide-treated group (LLG) (dose, 75 μg/kg), the mid-dose liraglutide-treated group

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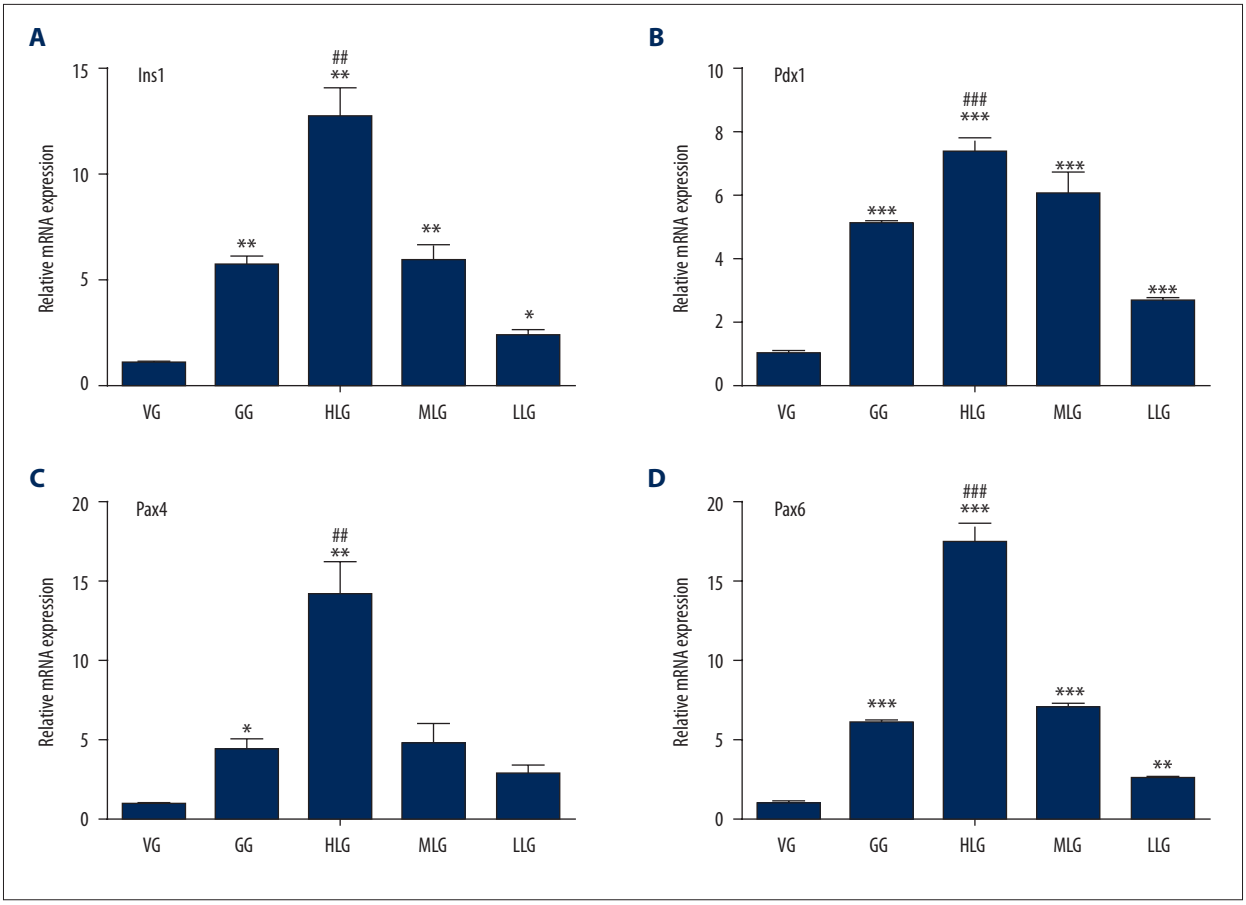

Figure 3. Expression levels of the *INS1* gene, pancreatic and duodenal homeobox 1 (Pdx1), paired box 4 (Pax4) and paired box 6 (Pax6) mRNA in db/db mice at the end of six weeks of treatment. The pancreatic mRNA expression levels of: (**A**) the *INSI* gene; (**B**) duodenal homeobox 1 (Pdx1); (**C**) paired box 4 (Pax4) Pax4, and (**D**) paired box 6 (Pax6). Male db/db mice (n=40) were divided into five groups: the vehicle-treated group (VG) (n=8); the insulin glargine-treated group (GG) (dose, 450 μg/kg) (n=8), the low-dose liraglutide-treated group (LLG) (dose, 75 μg/kg) (n=8), the mid-dose liraglutide-treated group (MLG) (150 μg/kg) (n=8), and the high-dose liraglutide-treated group (HLG) (300 μg/kg) (n=8). * P<0.05, ** P<0.01, *** P<0.001 GG, HLG, MLG or LLG *vs.* VG. ##P <0.01, ### P<0.001 HLG *vs.* GG.

(MLG) (150 μg/kg), and the high-dose liraglutide-treated group (HLG) (300 μg/kg) [17,18]. The findings were that at the end of the six-week treatment period of the study, liraglutide improved glycemic control in a dose-dependent manner in db/db mice, which was consistent with previously published studies [19,20]. Also, increased levels of serum C-peptide, a marker of insulin production by the pancreas, was associated with insulin glargine treatment (the GG) and was dose-dependent on liraglutide treatment (the HGL), compared with the vehicle treatment, with these changes reflected by the expression of the *INS1* gene. The findings of this study indicated that liraglutide and insulin glargine treatment could enhance pancreatic β-cell function, and the effects on the β-cell function of high-dose liraglutide were significantly greater than insulin glargine and were dose-dependent.

Previously published studies have shown that insulin therapy could significantly increase the body weight of db/db mice, possibly leading to insulin resistance [21]. In the present study, insulin glargine treatment reduced the body weight of db/db mice, possibly due to the short period of insulin glargine treatment. However, from the findings of this study, it was not possible to determine whether improving glycemic control by high-dose liraglutide and insulin glargine in db/db mice provided pancreatic β-cell rest resulting in the stimulation of insulin secretion. Therefore, future functional experiments are suggested to address these questions.

Pancreatic and duodenal homeobox 1 (Pdx1) and paired box 6 (Pax6) are crucial for pancreatic β-cell function through transcriptional control of key genes that are involved in insulin biosynthesis and secretion [22–24]. In previous studies, overexpression of pancreas-specific transcription factor, PDX1 (also

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known as insulin promoter factor 1), has been shown to induce the differentiation of non-endocrine pancreatic cells into β-cells [25]. Another key transcription factor, paired box 4 (Pax4) is essential in the generation of insulin-producing pancreatic β-cells, and overexpression of Pax4 in adult islets stimulates β-cell proliferation and increases their resistance to apoptosis [26,27]. In the present study, reverse transcription polymerase chain reaction (RT-PCR) was used to determine mRNA expression levels of key transcriptional factors and showed that Pax4 and also pancreatic and duodenal homeobox 1 (Pdx1) and paired box 6 (Pax6) were significantly upregulated in a dose-dependent manner in liraglutide-treated db/db mice. The expression levels of these three transcription factors were significantly increased in the HLG compared with the GG, indicating that high-dose liraglutide regulated glucose metabolism and protected β-cell function by increasing the mRNA expression levels of Pax4, Pax6, and Pdx1, inducing insulin secretion by promoting pancreatic β-cell proliferation or differentiation. These findings are supported by previous studies that have described a stimulatory effect on the pancreatic β-cell mass of liraglutide in diabetic db/db mice [28,29]. A limitation of the present study was the lack of the morphologic evaluation of the mouse pancreatic islets and the evaluation of pancreatic β-cell proliferation and differentiation in db/db mice. Future functional and morphological studies in this mouse model of diabetes are recommended to include morphological studies on the pancreatic β-cells.

Conclusions

The findings of this study were that liraglutide acted in a dose-dependent manner on glycemic control of db/db mice, and was more effective than insulin glargine when administered at a high dose. Compared with insulin glargine treatment, and low-dose liraglutide, high-dose liraglutide treatment improved glucose tolerance and β-cell function of db/db mice. The findings in this mouse model of type 2 diabetes mellitus (T2DM) supports the view that treatment with a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist may be a therapeutic approach to preserve pancreatic β-cell function in T2DM.

Conflicts of interest

None.

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