Effect of liraglutide on atherosclerosis in patients with impaired glucose tolerance: A double-blind, randomized controlled clinical trial

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Abstract. Glucagon-like peptide-1 receptor agonist liraglutide may have beneficial effects on atherosclerosis development in impaired glucose tolerance (IGT). To the best of our knowledge, however, little conclusive evidence from clinical trials has been presented. The present study aimed to investigate the effect of liraglutide on atherosclerosis progression in patients with IGT. The present study was a double-blind, randomized controlled clinical trial. A total of 39 of patients aged 20-75 years who were overweight or obese (BMI, 27-40 kg/m^2) and presented IGT were randomized to receive liraglutide (n=17) or lifestyle interventions (n=22) for 6 months. Serum glucose and insulin (INS) levels, lipid profile, inflammatory biomarkers and carotid intima-media thickness (CIMT) were assessed at the start and end of each treatment. Side effects were also recorded. Liraglutide treatment was found to significantly improve glycaemia, including glycosylated hemoglobin, fasting and postprandial glucose as well as INS levels (all P<0.001). Liraglutide also significantly decreased serum total cholesterol and low-density lipoprotein levels (all P<0.001). Furthermore, serum levels of inflammatory biomarkers, as well as CIMT, were decreased following liraglutide treatment compared with those in the lifestyle intervention group (all P<0.001). Kaplan-Meier analysis showed that the risk of vasculopathy in the liraglutide group was lower than that in the lifestyle intervention group (log-rank test; P=0.041). The monitoring of drug-associated side effects indicated that the dose of liraglutide (0.6 to 1.2 mg/QD via subcutaneous injection) was safe and well-tolerated. The present study suggested that liraglutide may slow atherosclerosis development and improve inflammatory status as well as intimal function in patients with IGT with few side effects. The trial was registered through the Chinese Clinical Trial Registry (ChiCTR; trial registration no. ChiCTR2200063693; retrospectively registered) on Sep 14, 2022.

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Introduction

The prevalence of type 2 diabetes imposes notable social and economic burdens globally (1). Before onset of type 2 diabetes, individuals can live in a high-risk state of prediabetes, defined as impaired fasting glucose or impaired glucose tolerance (IGT) (2). IGT is an intermediate category between normal glucose tolerance and overt diabetes (3), which can be identified using an oral glucose tolerance test. The number of individuals with IGT has been increasing for decades with an estimated 374 million individuals in 2017, equal to 7.7% of the worldwide population aged 18-99 years (1). Individuals with IGT are at high risk of progression to type 2 diabetes (4), cardiovascular disease (5) and mortality (6).

Previous clinical trials have suggested that lifestyle interventions, including diet and exercise, can effectively slow the progression from IGT to type 2 diabetes (7-9). However, not all individuals with prediabetes achieve the recommended lifestyle modifications and may instead need pharmacotherapy. Antidiabetic drugs, such as metformin, acarbose, rosiglitazone, pioglitazone and liraglutide, have proven beneficial for the prevention of diabetes and underlying prediabetes (8,10-13). Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that stimulates insulin (INS) secretion, inhibits glucagon secretion and lowers plasma glucose levels after binding to the GLP-1 receptor (14). Liraglutide not only protects and restores pancreatic β-cell activity but is also involved in atherosclerosis prevention in patients with diabetes (15-17). For individuals with IGT, preclinical studies have demonstrated that liraglutide may have beneficial effects on atherosclerosis and potentially reduce the risk for cardiovascular disease (18,19). However, to the best of our knowledge, little conclusive evidence from clinical trials has been shown. The present study was therefore performed to evaluate the efficacy and safety of liraglutide for prevention of atherosclerosis progression in patients with IGT.

Materials and methods

Participants. The study protocol was approved by the Institutional Review Board of the Chengyang People's Hospital in Qingdao (China; approval no. CYQRMYY2019-09-11) and performed following the 1964 Declaration of Helsinki and its later amendments. All study participants provided written informed consent. A total of 39 patients (26 female and 13 male) aged 20-75 years who were overweight or obese (BMI, 27-40 kg/m^2) and diagnosed with IGT from October 2019 to September 2021 in Chengyang People's Hospital were included in the present study. Glucose tolerance status was defined using an oral glucose tolerance test (OGTT) according to the World Health Organization criteria (20). The exclusion criteria were as follows: i) Type 1 or 2 diabetes; ii) lower limb ischemia; iii) treatment with hypoglycemic drugs or angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist during the trial; iv) chronic disease or health conditions; v) acute illness (such as infection) and vi) pregnancy or lactation.

The patient baseline clinical characteristics, including age, sex, height, weight, BMI, waist circumference (WC), hip circumference (HC), systolic blood pressure (SBP) and diastolic blood pressure (DBP), were recorded.

Study design. The study period was October 2009 to September 2021. Participants were randomized to receive either liraglutide (n=17) or lifestyle interventions (n=22) for 6 months. Liraglutide was injected subcutaneously daily before breakfast. The dose was escalated weekly from 0.6 to 1.2 mg (increments, 0.1 mg per week). Lifestyle interventions included dietary intervention and physical activity. The dietary intervention involved advice and counseling to develop an individual plan for behavioral change aiming to achieve the following: Total dietary energy intake >50% from carbohydrates; decreased total and saturated fat intake with <30% total dietary energy from fat intake; increased fiber intake and weight loss to achieve BMI <25 kg/m^2 (21,22). The physical activity intervention was designed to encourage participation in increased physical activity equivalent to 30 min of moderate aerobic physical activity/day. Both participants and study administrators (physicians, nurses, dietitians and coordinators) were blinded to the treatment assignment.

OGTT. Following 14 h of overnight fasting, all subjects were admitted to the Chengyang People's Hospital in Qingdao (China) between 8:00 and 9:00 a.m. After resting for 30 min, venous blood (2 ml) was drawn to measure fasting glucose and INS levels. A 75-g oral glucose load was administered over a 1 min period. Blood draws for glucose and analysis of INS levels were performed 60 and 120 min after administration of the glucose load. Serum INS was measured using the Mercodia Insulin ELISA kit (cat. no. 10-1113-01; Mercodia AB) (23).

Biochemical analysis. Blood samples were collected after 14 h overnight fasting at baseline and after 4 months of each treatment. Serum levels of triglyceride (TG) and total cholesterol (TC) were measured using an enzymatic method (Roche Diagnostics). The phosphotungstic acid-Mg^{2+} method was used to determine high-density lipoprotein (HDL) concentrations. Low-density lipoprotein (LDL) was estimated in samples with a triglyceride level <400 mg/dl, using the modified Friedewald formula (24).

The glycosylated hemoglobin (HbA1c) levels were measured through boronate-affinity high-performance liquid chromatography (Premier Hb9210™; Trinity Biotech, Inc.). The analytical column contains aminophenylboronic acid bonded to a porous polymer support (gel) and pumps transfer reagents and patient samples through the analytical column. Modules of the instruments are as follows: SPD 20A UV detector, DGU-20A5 degasser, SIL-20A HT autosampler, LC-20AT pump (liquid chromatograph) and CTO-IOAS column oven. Briefly, to a 5 μl sample, a 1,250 μl hemolysis reagent was added and the mixture was left for 30 min at 37˚C. The precipitated protein was removed by centrifugation at 10,000 x g at 4˚C for 2 min. A total of 20 μl of the supernatant was injected into the chromatographic system. Separation of HbA1c was achieved with a 35x4.6 mm cation exchanger column (ImmuChrom GmbH) with a particle size of 3 μm at a flow rate of 1.5 ml/min. The areas of peaks detected by UV detector (415 nm) were used for quantification. HbA1c levels were expressed as %. To minimize inter-batch analytical variation, all samples from any given volunteer were assayed in a single batch. Each sample from one subject was assayed in duplicate, using the analytical system in accordance with the manufacturer's instructions. The same lots of calibrators, reagent lot and quality-control materials were used throughout, and analyses were performed by a single analyst.

C-reactive protein (CRP) levels were measured using the immunoturbidimetric method (CRPL3 assay; Roche Diagnostics) on a Cobas 702 module (Roche Diagnostics). TNF-α (cat. no. YSRIBIO-3736), IL-1β (cat. no. YSRIBIO-3292), IL-2α (cat. no. YSRIBIO-4666) and IL-6 (cat. no. YSRIBIO-4610) levels were measured using ELISA kits obtained from Shanghai Yansheng Biochemical Reagents Co., Ltd. The ELISA procedure was performed according to the manufacturer' instructions. White blood cell (WBC) count analysis was performed using using the Sysmex XE 2100 automated hematology system (Sysmex Corporation) (25).

Ultrasonography of carotid intima-media thickness (CIMT). B-mode real-time ultrasound was performed at baseline and after 4 months of treatment to evaluate arterial wall thickness in the carotid arteries as a surrogate marker of subclinical atherosclerosis (26). All examinations were performed by a single examiner in a blinded manner using the same ultrasound machine (Acuson Antares™ ultrasound system, premium edition; Siemens Healthineers), without access to previous scans when follow-up studies were performed. The ultrasound examination was performed in a standardized manner and specific sonographic images were obtained for comparison.

Patients were examined in the supine position and each carotid wall or segment was evaluated to identify IMT, as previously reported (27). Each scan of the common carotid artery began just above the clavicle and the transducer was moved to the carotid bifurcation and along the internal carotid artery. In total, three segments were identified and measured in anterior and posterior planes on each side: i) Distal 1.0 cm of the common carotid artery proximal to

the bifurcation; ii) the bifurcation and iii) proximal 1.0 cm of the internal carotid artery. At each of these sites, IMT was determined, defined as the distance between the echogenic line representing the intimal blood interface and the outer echogenic line representing the adventitial junction. IMT <0.9 mm was defined as normal; 0.9 mm≤ IMT <1.3 mm was defined as intimal medial thickness; and IMT ≥1.3 mm was defined as plaque. In addition, electrocardiogram revealed the general condition of the coronary arteries. ST segment or T wave change on electrocardiogram was considered as myocardial ischemia.

Follow-up. The primary endpoint was occurrence of atherosclerosis in macrovasculature, as well as in peripheral and visceral vessels. Patients were followed up once every 3 months, with a total follow-up duration of 6 months. The patient clinical profile and laboratory measurements were recorded at each visit. The side effects during the intervention were monitored to assess the tolerance and safety of each treatment.

Statistical analysis. Statistical analysis was performed using SPSS version 22.0 (IBM Corp.). The normality of distribution of the variables data was assessed using Shapiro-Wilk test. Data normally distributed are presented as mean ± standard deviation and tested using Student's t test. If the data were skewed, the Wilcoxon rank sum test was used to assess differences in changes before and after treatment between the two groups. Categorical data was compared using χ^2 test or Fisher's exact probability method. Kaplan-Meier survival analysis and a log-rank test were used to compare the risk of vascular disease following treatment between the two groups. A two-tailed P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics of enrolled patients. Individuals randomized to receive liraglutide or lifestyle intervention had similar baseline characteristics including sex (P=0.819), age (P=0.322), BMI (P=0.596), WC (P=0.734), HC (P=0.292), DBP (P=0.795) and SBP (P=0.547) (Table I). BMI, WC and HC after liraglutide treatment were lower than those after lifestyle intervention (all P<0.001). DBP and SBP levels did not show any statistically significant difference between the treatment arms (all P>0.05).

Side effects in liraglutide treatment group and lifestyle intervention group. Treatment-associated side effects are shown in Table SI. The most common side effect of liraglutide was nausea (n=4; 23.5%). There was no significant difference in side effects between liraglutide treatment and lifestyle intervention.

Effect of liraglutide treatment on serum glucose and INS levels. Liraglutide treatment could induce a greater reduction in HbA1c compared with lifestyle intervention (P<0.001; Table II). Similar trends were also observed for fasting blood glucose, fasting INS, 2 h postprandial blood glucose and 2 h postprandial INS between liraglutide treatment and lifestyle intervention (all P<0.001; Table II).

Effect of liraglutide treatment on lipid profile. Liraglutide treatment significantly decreased TC and LDL levels compared with lifestyle intervention (all P<0.001; Table III). However, no changes in TG and HDL were observed.

Effect of liraglutide treatment on inflammatory markers. Liraglutide treatment significantly decreased levels of WBC, CRP, TNF-α, IL-1β, IL-2α and IL-6 compared with lifestyle intervention (all P<0.001; Table IV).

Effect of liraglutide treatment on the development of atherosclerosis. The levels of CIMT decreased significantly in patients treated with liraglutide compared with lifestyle intervention (P<0.001; Table V). Although the lifestyle intervention group exhibited a higher incidence of atherosclerosis in coronary and peripheral arteries compared with that in the liraglutide treatment group, no significant difference was observed (all P>0.05; Table SII). Based on the Kaplan-Meier analysis, the incidence of vascular disease in the liraglutide group was significantly lower than that in the lifestyle intervention group (log-rank test P=0.041; Fig. 1).

Discussion

In the present study, the efficacy and safety of liraglutide were evaluated for prevention of atherosclerotic development in patients with IGT. A greater decrease in CIMT was observed in patients treated with liraglutide compared with those who received lifestyle interventions. Furthermore, hematological and biochemical examination indicated that liraglutide treatment ameliorated the lipid profile and inflammation in patients with IGT.

Cardiovascular disease causes disability and death in patients with diabetes. La Sala *et al* (28) highlighted in a review that the appearance of atherosclerosis may start as early as the onset of diabetes. Moreover, a systematic review and meta-analysis highlighted a series of large-scale epidemiological studies that showed that early manifestation of diabetes, especially IGT, aggravates atherosclerosis and increase the risk of developing cardiovascular diseases (5,29-31). IGT represents an intermediate metabolic state between normal glucose homeostasis and hyperglycemia, which has been suggested as a strong predictor of type 2 diabetes and macrovascular disease (4,5). Therefore, interventions should be performed during the early stage of diabetes to decrease the occurrence of cardiac complications.

IGT has an insidious onset and its non-specific clinical findings may not be instantly discernible. With the effect of behavior and lifestyle on blood glucose levels, 30% of patients with IGT eventually develop diabetes (4). The Da Qing Diabetes Prevention Outcome Study was the first global study to report that lifestyle changes could reduce the risk of cardiovascular events in patients with IGT (32). However, changing lifestyle required long-term adherence and patients often exhibit poor compliance (33). Therefore, for those who cannot adhere to a healthy lifestyle for a long period or have a poor response to lifestyle interventions, therapeutic interventions should be considered. At present, disputes remain regarding the optimum regimens for pre-diabetes. The DPP (metformin) (8), DREAM (INS sensitizer) (11) and STOP-NIDDM (acarbose) (34)

Table I. Clinical characteristics of participants before and after treatment.

	Lifestyle intervention (n=22)			Liraglutide (n=17)				
Characteristic	Pre-treatment	Post-treatment	Δ change	Pre-treatment	Post-treatment	Δ change	P-value[a]	P-value[b]
Sex, female, n (%)	15 (68.18)	15 (68.18)	NA	11 (64.71)	11 (64.71)	NA	0.819	NA
Mean age, years	48.91±10.12	49.27±10.01	0.41±0.50	44.92±14.69	45.35±14.75	0.41±0.51	0.322	1.000
BMI, kg/m^2	26.21±4.33	26.15±3.21	-0.06±0.08	26.84±2.47	23.38±3.71	-3.46±0.67	0.596	<0.001
Waist circumference, cm	87.12±5.74	86.47±5.36	-0.65±0.28	86.52±4.98	82.31±5.48	-4.21±0.75	0.734	<0.001
Hip circumference, cm	102.86±5.88	99.98±5.49	-2.88±0.41	101.02±4.51	90.03±4.07	-10.99±1.42	0.292	<0.001
Diastolic blood pressure, mmHg	120.52±18.39	119.01±17.16	-1.51±0.74	118.86±21.13	117.26±20.19	-1.60±0.55	0.795	0.677
Systolic blood pressure, mmHg	69.47±11.13	69.22±11.64	-0.25±0.22	67.33±10.57	67.02±11.16	-0.31±0.34	0.547	0.508

NA, not applicable. [a]Comparing pre-treatment values between the two groups. [b]Comparing Δ change between the two groups.

Table II. Dynamic changes of serum HbA1c, glucose and insulin before and after treatment.

	Lifestyle intervention (n=22)			Liraglutide (n=17)			
Parameter	Pre-treatment	Post-treatment	Δ change	Pre-treatment	Post-treatment	Δ change	P-value[a]
HbA1c, %	5.91±0.33	5.89±0.29	-0.02±0.02	5.98±0.42	5.16±0.39	-0.82±0.07	<0.001
Fasting blood glucose, mmol/l	6.02±1.48	6.04±1.85	0.01±0.02	5.97±1.28	5.75±1.21	-0.22±0.06	<0.001
Fasting insulin, mu/l	15. 42±3.57	14. 94±4.39	-0.48±0.06	15.77±2.94	8.86±3.36	-6.91±0.42	<0.001
2 h postprandial blood glucose, mmol/l	9.26±1.19	8.72±1.60	-0.54±0.04	9.33±1.46	6.84±1.19	-2.49±0.27	<0.001
2 h insulin, mU/l	92.48±21.02	90.7±26.89	-1.78±0.83	91.38±14.68	47.94±19.98	-43.44±5.36	<0.001

[a]Comparing Δ change between the two groups. HbA1c, glycosylated hemoglobin.

Table III. Dynamic changes of lipid profile before and after treatment.

	Lifestyle intervention (n=22)			Liraglutide (n=17)			
Parameter	Pre-treatment	Post-treatment	Δ change	Pre-treatment	Post-treatment	Δ change	P-value[a]
Triglyceride, mmol/l	1.29±0.88	1.24±0.45	-0.05±0.04	1.27±0.53	1.21±0.36	-0.06±0.06	0.537
Total cholesterol, mmol/l	5.59±1.04	5.51±1.14	-0.07±0.08	5.53±0.98	4.42±0.95	-1.11±0.19	<0.001
High-density lipoprotein, mmol/l	1.50±0.18	1.48±0.28	-0.02±0.03	1.48±0.26	1.45±0.34	-0.03±0.05	0.443
Low-density lipoprotein, mmol/l	2.76±1.19	2.68±1.58	-0.08±0.24	9.32±1.46	6.84±1.19	-2.49±0.51	<0.001

[a]P-value was calculated by comparing Δ change.

Table IV. Dynamic changes of inflammatory markers before and after treatment.

	Lifestyle intervention (n=22)			Liraglutide (n=17)			
Parameter	Pre-treatment	Post-treatment	Δ change	Pre-treatment	Post-treatment	Δ change	P-value[a]
White blood cell, x10^9/l	6.94±0.54	6.95±0.38	0.01±0.01	6.94±0.55	5.17±0.39	-1.77±0.21	<0.001
C-reactive protein, mg/l	5.39±1.05	5.43±0.81	0.04±0.03	5.38±0.97	2.41±0.51	-2.97±0.35	<0.001
TNF-α, ng/l	25.65±3.86	24.18±5.25	-1.47±0.42	26.53±3.57	14.01±3.97	-12.53±0.73	<0.001
IL-1β, ng/l	54.56±7.78	51.97±12.03	-2.59±4.68	54.14±6.29	30.84±7.41	-23.29±8.71	<0.001
IL-2α, ng/l	2.89±0.30	2.78±0.54	-0.11±0.07	2.82±0.36	0.87±0.24	-1.96±0.42	<0.001
IL-6, ng/l	15.37±2.49	15.13±2.91	-0.24±0.22	15.69±2.24	6.65±1.51	-9.04±0.72	<0.001

[a]Comparing Δ change between the two groups.

Table V. Dynamic changes of CIMT before and after treatment.

Parameter	Lifestyle intervention (n=22)			Liraglutide (n=17)			P-value[a]
	Pre-treatment	Post-treatment	Δ change	Pre-treatment	Post-treatment	Δ change	
CIMT, mm	0.91±0.23	0.92±0.18	0.01±0.01	0.91±0.25	0.70±0.16	-0.21±0.07	<0.001

[a]P-value was calculated by comparing Δ change between the two groups. CIMT, carotid intima-media thickness.

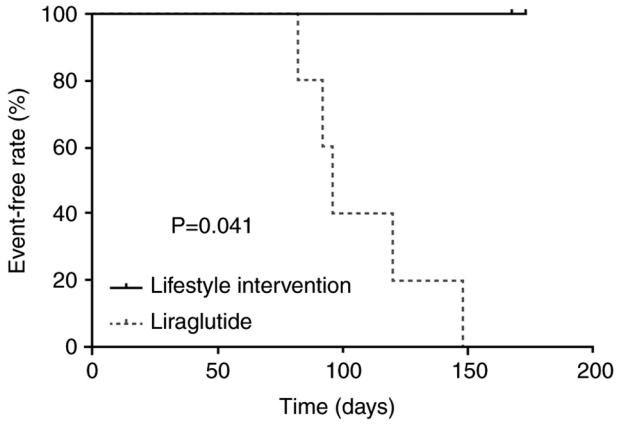

Figure 1. Kaplan-Meier curve of incidence of vascular disease for liraglutide treatment and lifestyle intervention groups. The log-rank P-value is reported.

studies have shown that medications notably decrease the risk of diabetes and cardiovascular disease.

An ideal option for IGT treatment may be a drug that can lower the postprandial blood glucose levels and restore the first phase of INS secretion with no serious side effects (such as gastrointestinal reaction, weight gain and hypoglycemia). With the gradual application of novel hypoglycemic drugs (such as GLP-1 receptor agonists) in clinical practice, liraglutide has also attracted attention (35-37). Liraglutide has 97% amino acid sequence homologous to native human GLP-1, which preserves the biological activity of native GLP-1 and is resistant to degradation (37). Furthermore, liraglutide activates the GLP-1 receptor on the surface of pancreatic cells, increases cyclic adenosine monophosphate in the cells, promotes INS release, inhibits glucagon secretion and improves the sensitivity of peripheral tissue to INS (38,39).

By binding to the GLP-1 receptor in the gastrointestinal tract, liraglutide could directly inhibit gastric emptying, slowing gastrointestinal peristalsis and gastric juice secretion (37). It may also interfere with absorption of nutrients and enable weight loss (40). *In vivo* studies have showed that the GLP-1 receptor agonist liraglutide could improve the cell ultrastructure in IGT rats, inhibit excessive proliferation of α islet cells, decrease the excessive synthesis of glucagon, improve the structure of pancreatic islets, alleviate INS resistance and delay the development of glucose metabolism disorder (18,41). In the present study, metabolic markers such as TC and LDL for patients with IGT were significantly improved following treatment with liraglutide, suggesting that liraglutide may serve as a therapeutic strategy for IGT management.

Previous studies have found that the levels of CIMT are significantly increased in the early stages of IGT (42,43). IGT is a risk factor for carotid atherosclerosis (44,45). The European Society of Cardiology and the European Society of Hypertension guidelines recommend CIMT >0.9 mm as a marker of target organ injury in atherosclerosis (46). Preclinical studies have shown that the gradual emergence of atherosclerotic plaques is associated with oxidative stress injury, macrophage-mediated phagocytosis and formation of foam cells (47,48). Furthermore, exacerbated INS resistance and production of proinflammatory cytokines also promote

development of atherosclerosis. Existing evidence suggests that liraglutide may inhibit activation of NF-κB, which serves as an essential inflammatory biomarker for regulating the balance of the proinflammatory-anti-inflammatory system (49,50). Zhang *et al* (51) demonstrated that liraglutide protects cardiomyocytes from IL-1β-induced metabolic disturbance and mitochondrial dysfunction. The present study showed that inflammatory indicators and CIMT were significantly decreased following treatment with liraglutide, suggesting that GLP-1 receptor agonist improved the inflammatory response in patients with IGT and slowed the occurrence of atherosclerosis.

The present study has certain limitations. First, the sample size was relatively small. Therefore, a larger prospective study is required to verify the results. Secondly, the diet type and schedule were not controlled for lifestyle interventions, which may have led to differences in outcomes between patients. Thirdly, the follow-up duration was short. Since vascular disease has a slow and insidious onset, statistical significance may have been achieved for several outcomes with a longer follow-up period and more events. In addition, only blood tests and CIMT were performed to evaluate atherosclerotic development. Although several indices (such as aortic plaque burden) have also been considered as key indicators of atherosclerosis in preclinical research (52), their diagnostic value remains to be validated in clinical studies. Other indices, such as ankle-brachial index (53) and arterial pulse wave velocity (54), are also key indicators of atherosclerotic progression. However, these indices were not employed in the present study due to low patient compliance. These indices should be included in a future prospective study.

In conclusion, GLP-1 receptor agonist liraglutide may slow atherosclerosis development and improve the inflammatory status and intimal function in patients with IGT with few side effects.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XR conceived and designed the study and revised the manuscript. LS contributed to data collection and analysis and drafted the manuscript. YY and YL performed data analysis and manuscript revision. XR and LS confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were performed following the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All procedures were approved by the Institutional Review Board of the Chengyang People's Hospital in Qingdao (approval no. CYQRMYY2019-09-11). Written informed consent was obtained from all participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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