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ORIGINAL RESEARCH

Pancreatic Safety of Once-Weekly Dulaglutide in Chinese Patients with Type 2 Diabetes Mellitus: Subgroup Analysis by Potential Influencing Factors

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ABSTRACT

Introduction: In the randomized, open-label, parallel-arm, active-controlled phase III AWARD-CHN2 trial, once-weekly dulaglutide plus concomitant oral antihyperglycemic medications (OAMs) improved HbA1c over 26 weeks compared with once-daily insulin glargine in patients with type 2 diabetes mellitus (T2DM). This *post-hoc* subgroup analysis of AWARD-CHN2 investigated the pancreatic safety of dulaglutide in Chinese patients with T2DM, stratified by potential influencing factors.

Methods: Changes in pancreatic enzyme (pancreatic amylase, total amylase, and lipase) levels over 26 weeks were assessed and stratified by patient age (< 60, ≥ 60 years), sex (female, male), duration of diabetes (< 10, ≥ 10 years), baseline weight (< 70, ≥ 70 kg), BMI (< 25, ≥ 25 kg/m^2), HbA1c (< 8.5, ≥ 8.5%), triglycerides (< 2.3, ≥ 2.3 mmol/L), and concomitant OAMs (metformin, sulfonylurea, metformin plus sulfonylurea).

Results: A total of 203 Chinese patients with T2DM were included in this *post-hoc* analysis. Pancreatic enzyme levels increased within the normal range from baseline to Week 26, and no pancreatitis events were confirmed by independent adjudication. Least-squares mean increase in pancreatic amylase (U/L) from baseline to Week 26 was comparable across all subgroups with no statistically (all P-values > 0.05) or clinically significant between-group differences for age (< 60 years: 5.34; ≥ 60 years: 6.71), sex (female: 5.85; male: 5.66), duration of diabetes (< 10 years: 6.15; ≥ 10 years: 4.85), weight (< 70 kg: 6.19; ≥ 70 kg: 5.39), BMI (< 25 kg/m^2: 5.92; ≥ 25 kg/m^2: 5.61), HbA1c (< 8.5%: 6.82; ≥ 8.5%: 4.08), triglycerides (< 2.3 mmol/L: 4.94; ≥ 2.3 mmol/L: 8.04), and concomitant OAMs (metformin: 5.68; sulfonylurea: 5.44; metformin plus sulfonylurea: 5.87). Similar results were observed for total amylase and lipase.

Conclusion: In Chinese patients with T2DM receiving dulaglutide 1.5 mg in AWARD-CHN2, elevations of pancreatic enzymes over 26 weeks

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were within the normal range and were neither associated with pancreatitis nor baseline factors, which suggests the clinical use of dulaglutide in Chinese patients with T2DM is not associated with pancreatic safety issues.
Clinical Trial registration: NCT01648582.

Keywords: Chinese patient; Dulaglutide; Pancreatic safety; Subgroup analysis; Type 2 diabetes

Key Summary Points
Why carry out this study?
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are effective and safe for the treatment of type 2 diabetes (T2DM) but have been controversially linked to a possible increased risk of acute pancreatitis
This study evaluated the pancreatic safety of dulaglutide 1.5 mg, a GLP-1 RA, stratified by potential influencing factors, in Chinese patients with T2DM included in the phase III AWARD-CHN2 study
What was learned from the study?
In Chinese patients with type 2 diabetes receiving dulaglutide 1.5 mg, elevations of pancreatic enzymes (pancreatic amylase, total amylase, and lipase) over 26 weeks were within the normal range and were associated with neither pancreatitis nor baseline factors (patient age, sex, duration of diabetes, bodyweight, BMI, HbA1c, triglyceride level, or use of concomitant oral antihyperglycemic medications)
The clinical use of dulaglutide in Chinese patients with type 2 diabetes is not associated with pancreatic safety issues

INTRODUCTION

Type 2 diabetes (T2DM) is a progressive condition characterized by insulin resistance and progressive loss of β-cell function, which results in chronic hyperglycemia [1]. The prevalence of diabetes in China is increasing year by year and is estimated to be 12.8% based on the latest epidemiological survey conducted in China [2].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) provide an effective treatment option for patients with T2DM with a relatively low risk of hypoglycemia and can also reduce bodyweight [3] However, there has been some controversy around a possible association between GLP-1 RAs and acute pancreatitis since cases of pancreatitis were observed in patients treated with exenatide in 2006 [4] Two subsequent studies conducted in the USA, a cross-sectional database study [5] and a population based case–control study [6], reported an increased risk of pancreatitis and hospitalization for acute pancreatitis, respectively, in adults with T2DM receiving the GLP-1 RAs sitagliptin and exenatide. In contrast, several more-recent reviews of clinical trial evidence have found no increased risk of pancreatitis associated with GLP-1 RAs; a 2017 review of GLP-1 RA clinical trials [7] and a 2019 meta-analysis of seven GLP-1 RA cardiovascular outcome trials both found no increased risk of pancreatitis for patients receiving GLP-1 RAs versus placebo [8]. Following a comprehensive review of data for incretin-based therapies, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) concluded that the available evidence does not support concerns about pancreatic safety for this class of drugs [9].

Dulaglutide is a GLP-1 RA approved in the EU, USA and China as a treatment for patients with T2DM [10]. The approval of dulaglutide in T2DM was supported by a series of Phase III trials under the AWARD (Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes) programme [10]. Collectively, these trials showed that dulaglutide, either as monotherapy or combined with other oral antihyperglycemic medication(s) (OAM), as well as

insulin, was effective and generally well tolerated [10]. The randomized, Phase III AWARD-CHN2 trial compared the efficacy and safety of once-weekly dulaglutide versus daily insulin glargine in a predominantly Asian population of patients with T2DM inadequately controlled with metformin and/or a sulphonylurea [11]. The primary results showed that once-weekly dulaglutide, 1.5 or 0.75 mg, provided significantly greater improvements in HbA1c over 26 weeks of treatment, with weight loss versus weight gain and less hypoglycemia, compared with once-daily insulin glargine [11]. Safety data from AWARD-CHN2 revealed small elevations in pancreatic enzyme levels within the normal range over time, with no confirmed cases of pancreatitis [11].

The etiology of acute pancreatitis is multifactorial and the most common risk factors include gallstones, alcohol use, hypertriglyceridemia and obesity [12–17]. Older individuals typically experience a higher incidence of gallstone-related acute pancreatitis due to abated functional reserves in organ systems [18, 19]. In addition, T2DM is associated with an increased risk of acute pancreatitis [20, 21]. However, the use of OAMs has been found to reduce pancreatitis risk, with a positive association reported between risk reduction and both the number of OAMs used and duration of OAM treatment [21] Therefore, patient age, bodyweight, body mass index (BMI), triglyceride levels, and use of concomitant OAMs are considered potential influencing factors for pancreatic safety in patients with T2DM. Given the high prevalence of T2DM among elderly Chinese people [22] and the preferential use of GLP-1 RAs in overweight and obese patients, due to their promotion of weight loss [23], it is particularly important to thoroughly investigate pancreatic safety in these patient subgroups.

Biomarkers of pancreatic inflammation including levels of pancreatic amylase, total amylase and lipase are routinely measured as part of a diagnosis of pancreatitis in clinical practice [13]. These biomarkers were also measured in several China registration trials of GLP-1 RAs including dulaglutide [24, 25] and lixisenatide [26]. However, to date there has been no investigation of the pancreatic safety of GLP-1 RAs in a Chinese patient population stratified by the aforementioned potential influencing factors. This *post-hoc* subgroup analysis aimed to evaluate the pancreatic safety of dulaglutide 1.5 mg in Chinese patients included in the AWARD-CHN2 study stratified by potential influencing factors. This represents the first such analysis of pancreatic safety stratified by potential influencing factors in Chinese patients with T2DM treated with GLP-1 RAs.

METHODS

Study Design

This was a *post-hoc* subgroup analysis of the AWARD-CHN2 study. The study design and patient eligibility criteria of AWARD-CHN2 (NCT01648582) have been published previously [11]. In brief, AWARD-CHN2 was an open-label (blinded to dulaglutide dose), randomized, non-inferiority study that compared the efficacy and safety of once-weekly dulaglutide 1.5 mg or 0.75 mg versus once-daily insulin glargine in patients with T2DM [11]. The study was conducted at 45 sites in China, Russia, Mexico and South Korea between August 2012 and December 2014 [27]. Patients randomly assigned to dulaglutide 1.5 mg received a fixed, double-blind dose by subcutaneous injection once weekly and continued with their usual dose and regimen of OAM (metformin and/or a sulphonylurea). The primary efficacy endpoint was change in HbA1c from baseline to Week 26. The study protocol received approval from the ethics review board at each study center including the master ethics review board at Ruijin Hospital Affiliated to Shanghai Jiao Tong University. The study was conducted in-line with the ethical principles outlined in the Declaration of Helsinki and local regulations, and all patients provided written informed consent before randomization.

Study Population

AWARD-CHN2 included 774 adult patients (≥ 18 years, 607 Chinese patients) diagnosed

with T2DM for ≥ 6 months based on the World Health Organization's diagnostic and classification criteria, with a BMI ≥ 19.0 and ≤ 35.0 kg/m^2, and HbA1c ≥ 53.0 and ≤ 96.7 mmol/mol (≥ 7.0 to ≤ 11.0%) [11]. Eligible patients were also required to have been receiving metformin and/or a sulphonylurea for at least 3 months and been on a stable therapeutic dose for at least 8 weeks before screening. Key exclusion criteria included patients with type 1 diabetes, a clinically significant gastric emptying abnormality, clinical signs or symptoms of pancreatitis, a history of chronic pancreatitis or acute pancreatitis at visit 1, serum amylase concentration ≥ 3 times the upper limit of normal (ULN) and/or a serum lipase concentration ≥ 2 times the ULN at visit 1, serum calcitonin concentration ≥ 20 ng/L (5.83 pmol/L), and receipt of insulin or a GLP-1 RA within 3 months before screening. The present *post-hoc* analysis included all Chinese patients in the safety population of the AWARD-CHN2 study who received at least one dose of dulaglutide 1.5 mg.

Measurements

This *post-hoc* subgroup analysis evaluated pancreatic safety in patients receiving dulaglutide 1.5 mg by assessing least-squares (LS) mean change in pancreatic enzyme levels (pancreatic amylase, total amylase, and lipase) from baseline to Week 26, stratified by potential influencing factors. The potential influencing factors included in the analysis were: patient age (< 60 or ≥ 60 years), sex (male or female), duration of diabetes (< 10 or ≥ 10 years), baseline weight (< 70 or ≥ 70 kg), baseline BMI (< 25 or ≥ 25 kg/m^2), baseline HbA1c (< 8.5 or ≥ 8.5%), baseline triglycerides (< 2.3 or ≥ 2.3 mmol/L; selected based on the National Cholesterol Education Program [NCEP] Adult Treatment Panel III [ATP III] criteria [28]), and concomitant OAMs (metformin only, sulfonylurea only, or metformin plus sulfonylurea).

Potential instances of pancreatitis were adjudicated by the Duke Clinical Research Institute Clinical Event Classification Group, which is an independent committee external to Eli Lilly and Company consisting of expert physicians. Two of the following three criteria were required for an event to be adjudicated as confirmed acute pancreatitis: (1) abdominal pain, characteristic of acute pancreatitis; (2) serum amylase and/or lipase level ≥ 3 times the ULN; (3) characteristic findings of acute pancreatitis on computed tomography (CT) or magnetic resonance imaging (MRI) [12]. All laboratory analyses were performed at a central laboratory (Quintiles). Normal laboratory ranges used as reference limits when evaluating pancreatic enzymes were 13–53 U/L for pancreatic amylase, 20–112 U/L for total amylase and 0–60 U/L for lipase.

Statistics

This analysis was conducted on a safety population set (defined as all patients who received ≥ 1 dose of dulaglutide 1.5 mg). The LS mean changes in pancreatic enzyme levels and accompanying 95% CIs were calculated using a mixed model with repeated measures, where baseline enzyme level, subgroup factor, visit number and the interaction term between the subgroup factor and the visit number were treated as covariates and the patient was treated as a random effect. Categorical variables were summarized as counts and percentages and continuous variables were summarized using, mean (standard deviation [SD]). All analyses were performed using SAS Version 9.4.

RESULTS

Patients

A total of 203 Chinese patients who received dulaglutide 1.5 mg for 26 weeks were included in this analysis. Patients had a mean age of 54.6 ± 10.0 years, 59.1% were male, the mean BMI was 25.9 ± 3.2 kg/m^2, the mean body weight was 72.1 ± 12.2 kg, and the mean baseline triglyceride level was 2.2 ± 1.8 mmol/L (Table 1). The mean duration of diabetes was 7.7 ± 4.6 years and at baseline the mean HbA1c was 8.4 ± 1.2%. Furthermore, the majority of patients were receiving metformin

Table 1 Patient demographics and baseline characteristics

Variable[a]	Dulaglutide 1.5 mg (*n* = 203)
Age, years	54.6 (10.0)
Males, *n* (%)	120 (59.1)
Weight, kg	72.1 (12.2)
Body mass index, kg/m^2	25.9 (3.2)
Duration of diabetes, years	7.7 (4.6)
Baseline HbA1c, %	8.4 (1.2)
Triglycerides, mmol/L	2.2 (1.8)
Pancreatic amylase, U/L	25.3 (10.8)
Total amylase, U/L	57.0 (18.9)
Lipase, U/L	39.9 (21.1)
Gall stones, *n* (%)	0 (0)
Concomitant OAMs, *n* (%)	
Metformin only	87 (42.9)
Metformin + sulfonylurea	86 (42.4)
Sulfonylurea only	30 (14.8)

OAMs oral antihyperglycemic medications
[a] Values are mean (SD) unless specified

monotherapy (42.9%) or metformin plus sulfonylurea (42.4%). At baseline, the mean levels of pancreatic amylase, total amylase and total lipase were 25.3 ± 10.8 U/L, 57.0 ± 18.9 U/L, and 39.9 ± 21.1 U/L, respectively (Table 1).

Pancreatic Safety

Overall, a moderate and comparable increase in pancreatic amylase, total amylase and lipase levels within the normal range was observed between baseline and Week 26 in all patient subgroups (Table 2). No confirmed incidences of pancreatitis were reported by independent adjudication.

The LS mean increase in pancreatic amylase (U/L) from baseline to Week 26 was comparable across patients stratified by age (< 60 years: 5.34 [95% confidence interval [CI]: 3.35, 7.32]); ≥ 60 years: 6.71 [3.59, 9.83]), sex (female: 5.85 [3.28, 8.42]; male: 5.66 [3.44, 7.87]), duration of diabetes (< 10 years: 6.15 [4.13, 8.17]; ≥ 10 years: 4.85 [1.81, 7.89]), baseline weight (< 70 kg: 6.19 [3.67, 8.70]; ≥ 70 kg: 5.39 [3.14, 7.64]), baseline BMI (< 25 kg/m^2: 5.92 [3.36, 8.49]; ≥ 25 kg/m^2: 5.61 [3.40, 7.82]), baseline HbA1c (< 8.5%: 6.82 [4.67, 8.97]; ≥ 8.5%: 4.08 [1.40, 6.75]), baseline triglycerides (< 2.3 mmol/L: 4.94 [2.99, 6.89]; ≥ 2.3 mmol/L: 8.04 [4.74, 11.33]), and concomitant OAMs (metformin only: 5.68 [3.10, 8.26]; sulfonylurea only: 5.44 [0.83, 10.06]; metformin plus sulfonylurea: 5.87 [3.37, 8.37]) (Fig. 1). P-values were > 0.05 for all intra-subgroup differences.

Similar results were observed for the changes in total amylase (Fig. 2) and lipase (Fig. 3) between baseline and Week 26.

DISCUSSION

To our knowledge, this *post-hoc* subgroup analysis of AWARD-CHN2 is the first analysis conducted in Chinese patients with T2DM to investigate the pancreatic safety of dulaglutide, or any GLP-1RA, stratified by influencing factors. The results demonstrated that once-weekly dulaglutide 1.5 mg was associated with moderate increases in pancreatic enzyme levels within the normal range, with no events confirmed as pancreatitis by independent adjudication. Furthermore, comparable increases in pancreatic enzyme levels were observed between subgroups of patients stratified by key demographic characteristics and factors that may be associated with pancreatic safety including age, sex, duration of diabetes, weight, BMI, baseline HbA1c, baseline triglycerides, and concomitant OAM use. Together, these findings suggest that the clinical use of dulaglutide 1.5 mg in Chinese patients is not associated with pancreatic safety issues.

The findings of our analysis are further supported by other recent evidence for the pancreatic safety of dulaglutide. Data from a pooled assessment of pancreatic safety from four Phase II and five Phase III trials reported a comparable exposure-adjusted incidence rate of acute

Table 2 Mean pancreatic enzyme levels at baseline and Week 26 in Chinese patients with T2DM receiving dulaglutide 1.5 mg, stratified by potential influencing factors

Subgroup	*n*	Pancreatic amylase, U/L		Total amylase, U/L		Lipase, U/L	
		BL	W26	BL	W26	BL	W26
Age							
< 60 years	143	24.06	30.18	54.78	62.46	38.31	51.42
≥ 60 years	60	28.23	34.23	62.18	69.40	43.63	52.77
Sex							
Male	120	25.63	31.77	57.35	64.66	40.18	52.42
Female	83	24.81	30.78	56.42	64.19	39.46	51.00
Duration of diabetes							
< 10 years	145	23.99	30.82	55.01	63.51	37.71	51.72
≥ 10 years	58	28.55	32.53	61.86	66.56	45.31	52.00
Baseline weight							
< 70 kg	89	24.74	31.22	58.42	65.85	39.67	52.20
≥ 70 kg	114	25.73	31.45	55.84	63.33	40.04	51.50
Body mass index							
< 25 kg/m^2	88	24.93	31.17	57.11	65.60	39.57	49.74
≥ 25 kg/m^2	115	25.57	31.48	56.86	63.61	40.12	53.33
Baseline HbA1c							
< 8.5%	123	26.21	32.83	58.02	66.63	40.27	54.86
≥ 8.5%	80	23.89	29.04	55.36	61.07	39.29	47.07
Baseline triglycerides							
< 2.3 mmol/L	149	26.38	31.40	57.54	64.18	41.01	51.04
≥ 2.3 mmol/L	54	22.31	31.19	55.41	65.25	36.78	53.98
Concomitant OAMs							
Metformin only	87	24.70	31.10	54.91	63.05	39.59	51.23
SU only	30	25.10	30.71	56.47	63.92	39.83	49.29
Metformin + SU	86	25.97	31.76	59.23	65.92	40.20	53.07

BL baseline, *HbA1c* glycated hemoglobin, *OAM* oral antihyperglycemic medication, *SU* sulfonylurea, *W26* Week 26

pancreatitis for patients receiving dulaglutide versus placebo [30]. Our results are also supported by prior investigations of dulaglutide safety in Asian patients. In the Phase III AWARD-CHN1 trial, among a cohort of East-Asian patients with T2DM who received dulaglutide or glimepiride, no adjudicated cases of acute or chronic pancreatitis occurred and no patients experienced increases in pancreatic amylase or total amylase levels > 3 times the ULN after 26 weeks [24]. Similarly, a pooled analysis of three Phase III studies of dulaglutide

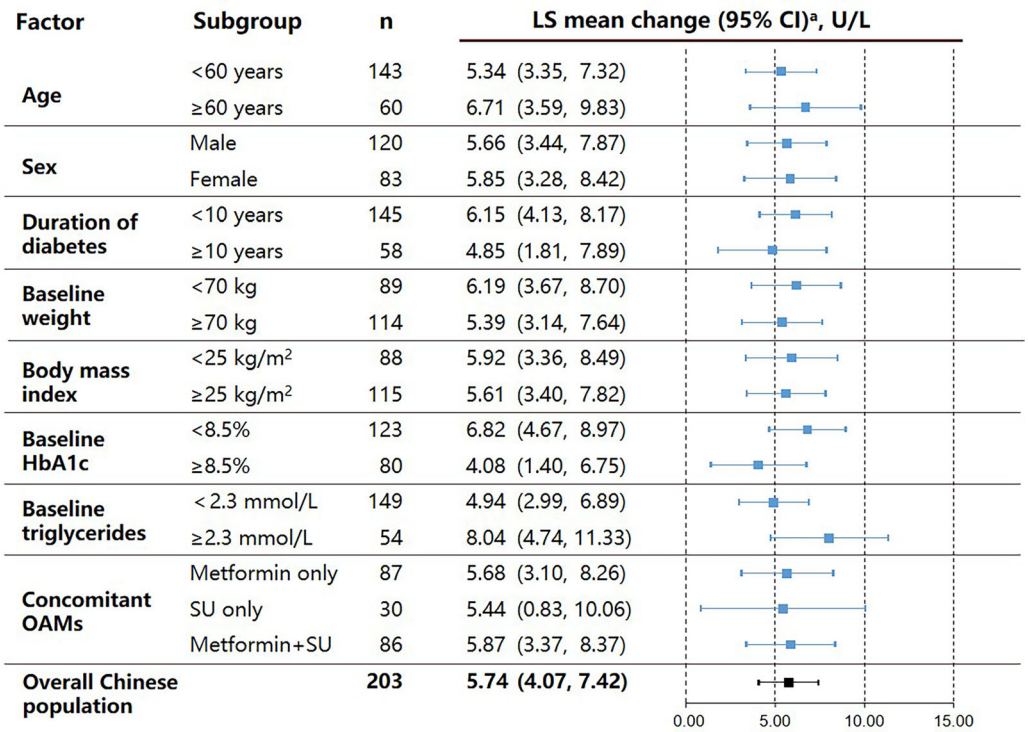

Fig. 1 Least squares mean change in pancreatic amylase level in Chinese patients with T2DM receiving dulaglutide 1.5 mg from baseline to 26 weeks of treatment, stratified by potential influencing factors. [a]LS means and 95% CIs within each patient subgroup were calculated using a MMRM model. All p values were > 0.05 for each subgroup comparison. *CI* confidence interval, *HbA1c* glycated hemoglobin, *LS* least squares, *MMRM* mixed-model repeated measures, *OAM* oral antihyperglycemic medication, *SU* sulfonylurea

conducted in Japanese patients with T2DM reported increases from baseline amylase and lipase levels but a very low incidence of acute pancreatitis (2/917 patients, confirmed by independent adjudication) [31]. Finally, although our study does not report long-term safety data, evidence for the long-term safety of dulaglutide was provided by the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) study which demonstrated no significant difference in the incidence of adjudicated pancreatic adverse events between dulaglutide and placebo over a median follow-up of 5.4 years [32]. Although the above-mentioned studies and analyses have previously shown no association between dulaglutide use and pancreatic safety, most were conducted in predominantly Caucasian patients and there are known differences in the etiology, risk factors for, and incidence of pancreatitis between patients of different racial and social backgrounds [29]. Furthermore, the present study builds on this previous research by conducting a deeper investigation of pancreatic safety grouped by known risk factors for pancreatitis. Given that China has an ageing population and that patients with T2DM have a high prevalence of obesity and hypertriglyceridemia, the present analysis would provide new and important information to inform clinical practice.

An aging population has contributed to the increased prevalence of total diabetes in China, with a current estimated prevalence of 20.2% in people aged > 60 years [22]. Aging is also associated with many T2DM comorbidities including renal impairment and a high risk for adverse events such as recurring hypoglycemia. In addition, an appreciable increase in the incidence of, and risk of mortality from, acute pancreatitis has been observed among elderly

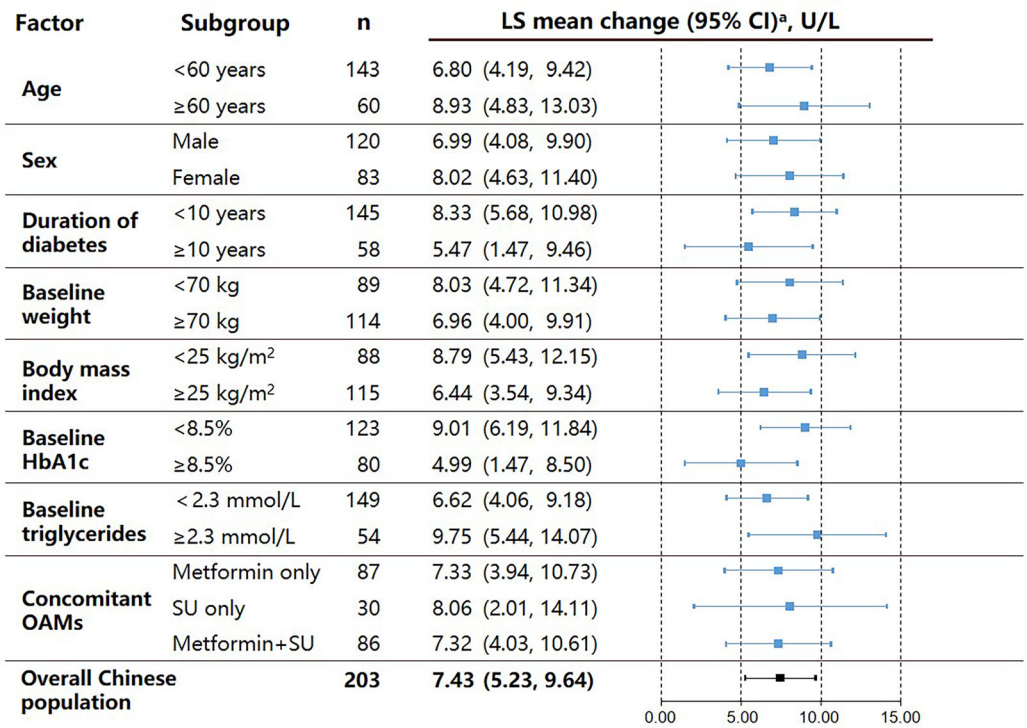

Fig. 2 Least squares mean change in total amylase level in Chinese patients with T2DM receiving dulaglutide 1.5 mg from baseline to 26 weeks of treatment, stratified by potential influencing factors. [a]LS means and 95% CIs within each patient subgroup were calculated using a MMRM model. All p values were > 0.05 for each subgroup comparison. *CI* confidence interval, *HbA1c* glycated hemoglobin, *LS* least squares, *MMRM* mixed-model repeated measures, *OAM* oral antihyperglycemic medication, *SU* sulfonylurea

patients (> 60 years) [33]. Previous studies have shown that the efficacy and safety of dulaglutide is similar across patient age groups [34, 35]. Furthermore, liraglutide and exenatide have been shown to be well tolerated regardless of patient age [36, 37]. However, the safety outcomes reported by these prior studies mainly included hypoglycemia and gastrointestinal adverse events, and there are limited data on the pancreatic safety of GLP-1 RAs in elderly patients. The present study addresses this knowledge gap and provides evidence that the pancreatic safety profile of dulaglutide is similar in Chinese patients with T2DM aged < 60 and ≥ 60 years and, together with previous reports, suggests dulaglutide is a safe and effective treatment option for elderly patients with T2DM [34, 35]. The results of this analysis also showed no association between patient sex and pancreatic safety of dulaglutide.

GLP-1 RAs improve glycemic control and promote weight loss [23], thus they are frequently prescribed to patients with T2DM who are overweight or obese [38, 39]. However, obesity is known to increase the incidence and severity of acute pancreatitis [14], which makes it particularly important to investigate the pancreatic safety of GLP-1 RAs in overweight/obese T2DM patients. The present study showed moderate elevations of amylase and lipase within a normal range in overweight and obese patients, which is in accordance with a previous study of liraglutide that reported asymptomatic elevations of amylase and lipase in overweight/obese participants that did not predict subsequent development of acute pancreatitis [40]. The present study further demonstrated no association between bodyweight and pancreatic enzyme levels. Our data show no pancreatic safety concerns with dulaglutide treatment in

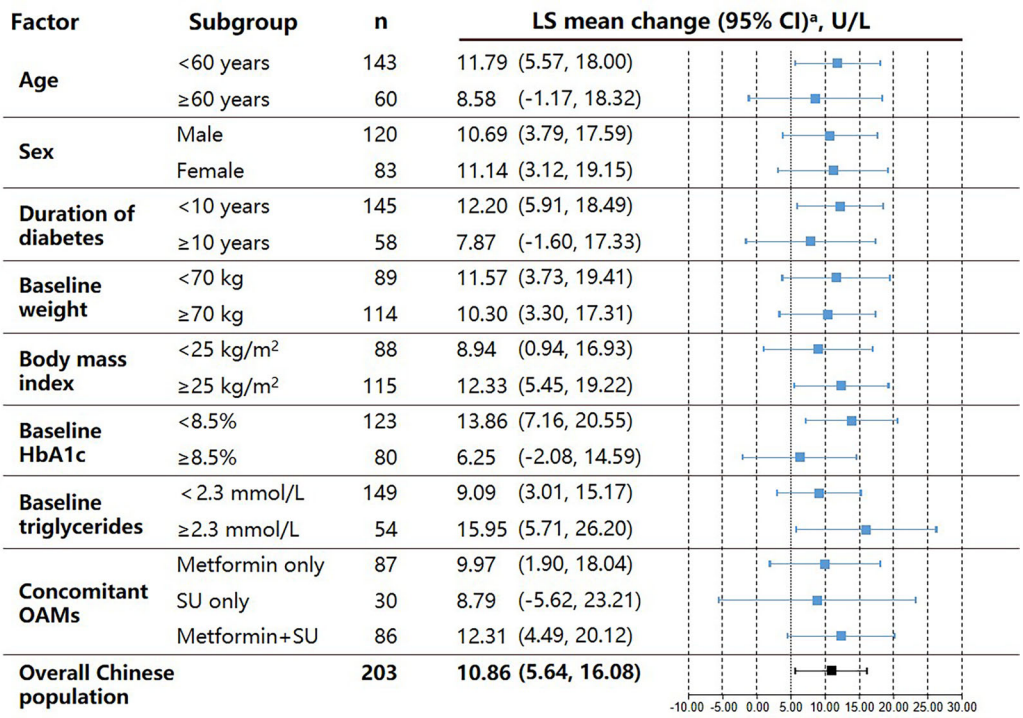

Fig. 3 Least squares mean change in lipase level in Chinese patients with T2DM receiving dulaglutide 1.5 mg from baseline to 26 weeks of treatment, stratified by potential influencing factors. [a]LS means and 95% CIs within each patient subgroup were calculated using a MMRM model. All p values were > 0.05 for each subgroup comparison. *CI* confidence interval, *HbA1c* glycated hemoglobin, *LS* least squares, *MMRM* mixed-model repeated measures, *OAM* oral antihyperglycemic medication, *SU* sulfonylurea

Chinese patients with T2DM regardless of their baseline bodyweight or BMI.

Hypertriglyceridemia is another well-documented cause of acute pancreatitis [15–17], accounting for up to 9% of cases [41–44]. Both risk and severity of acute pancreatitis increase with increasing triglyceride levels [45]. Acute pancreatitis secondary to hyperlipidemia is characterized by several presentations, among which the most common is a patient with poorly controlled T2DM with a history of hypertriglyceridemia [46]. Therefore, evidence for the pancreatic safety of GLP-1 RAs in T2DM patients with hypertriglyceridemia is vital to support clinical decision making. A serum triglyceride level of 2.3–5.6 mmol/L is classified as "high triglycerides" and ≥ 5.6 mmol/L as "very high triglycerides" according to the NCEP ATP III criteria [28]. Based on these criteria, a triglyceride level of 2.3 mmol/L was selected as the cut-off for this analysis and dulaglutide demonstrated similar pancreatic safety irrespective of triglyceride level. Due to a limited number of patients with a serum triglyceride level ≥ 5.6 mmol/L (data not shown), we did not further stratify patients using this higher cut-off. Our results show that dulaglutide can be considered a safe treatment option for patients with T2DM and high triglycerides; however, the results should be cautiously interpreted for patients with serum triglyceride levels ≥ 5.6 mmol/L.

In the clinical setting, dulaglutide is most frequently used in combination with concomitant OAMs, most commonly metformin and/or a sulphonylurea [47–49]. The evidence on the influence of OAM use on pancreatic safety is equivocal. Antonio et al. reported that long-term use of metformin was associated with a decreased risk of pancreatitis, while

sulfonylureas seemed to increase the risk [50]. Blomgren et al. found that the sulfonylurea glyburide increased the risk of acute pancreatitis, but metformin did not reduce the risk [51]. Interestingly, Lai et al. reported that use of OAMs reduced the risk of acute pancreatitis among T2DM patients, particularly those taking metformin, sulfonylureas, thiazolidinediones, or α-glucosidase inhibitors, and the risk was reduced as the number of drugs used increased [21]. Despite the confounding factors of concomitant OAMs, the results of the present study show similar changes in pancreatic enzyme levels for patients receiving concomitant sulphonylurea, metformin or both in combination. These findings show that dulaglutide is not associated with pancreatic safety concerns in patients receiving metformin and/or sulphonylurea.

While data suggest that T2DM is associated with an increased risk of acute pancreatitis and pancreatic cancer [20, 50], the increased incidence can be largely attributed to the higher prevalence of obesity and other T2DM-associated conditions such as cholelithiasis in this patient population [52]. Despite this, T2DM-specific characteristics have been investigated as risk factors for both acute pancreatitis and pancreatic cancer. For example, longer duration of T2DM has been associated with an increased risk of developing pancreatic cancer [53]. However, a study comparing 1426 patients with diabetes (90.9% with T2DM) against matched individuals without diabetes from the same community found no association between duration of diabetes or HbA1c level and incidence of pancreatitis [52]. Similarly, the results of the present study found no association between increase in pancreatic enzyme levels and duration of T2DM or baseline HbA1c level among patients with T2DM receiving dulaglutide.

Limitations of this analysis include that it is a post hoc subgroup analysis of a larger study, with a population of over 203 Chinese patients, representing approximately 25% of the population of the original AWARD-CHN2 trial, and this may have limited the power of statistical testing [11]. However, despite the relatively small patient number, the present analysis represents one of the largest data sets collected on dulaglutide use in Chinese patients to date. Furthermore, no incidence of pancreatitis was observed among patients with T2DM receiving dulaglutide in the AWARD-CHN1 (n = 492) [24] or AWARD-CHN2 studies (n = 515) [11], giving data from a combined total of 1007 patients that support our findings. Another potential limitation is that patients with a history of pancreatitis were excluded from the AWARD-CHN2 study which may have led to selection bias. In addition, pancreatic safety was not evaluated in patients with 'very high' triglyceride levels (≥ 5.6 mmol/L), which may limit the generalizability of the results to patients with extremely elevated triglyceride levels. Although our analysis did not include comparative pancreatic safety data from Chinese patients included in AWARD-CHN2 who received insulin glargine, there have been no previous reports of pancreatic safety events with insulin glargine and the pancreatic safety of insulin glargine was already described in the primary AWARD-CHN2 publication [11]. Finally, this analysis presents results through 26 weeks of treatment, which does not allow assessment of longer-term effects of dulaglutide on the pancreas.

CONCLUSIONS

In Chinese patients with T2DM treated with dulaglutide 1.5 mg in the AWARD-CHN2 study, modest elevations in pancreatic enzymes within the normal range were observed between baseline and Week 26 and were not associated with clinically relevant pancreatitis events. Changes in pancreatic enzyme levels did not show any association with patient age, sex, duration of diabetes, baseline bodyweight, BMI, HbA1c, triglyceride level or use of concomitant OAMs. The results suggest that the clinical use of dulaglutide in Chinese patients is not associated with pancreatic safety issues. However, for safety reasons, GLP-1 RA treatment is not recommended for patients with suspected or diagnosed pancreatitis.

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Compliance with Ethics Guidelines. The study protocol received approval from the ethics review board at each study center including the master ethics review board at Ruijin Hospital Affiliated to Shanghai Jiao Tong University. The study was conducted in-line with the ethical principles outlined in the Declaration of Helsinki and local regulations, and all patients provided written informed consent before randomization. A full list of the Institutional Review Boards that approved this study can be found in the Supplementary Material.

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

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