The Effects of Once-Weekly Dulaglutide and Insulin Glargine on Glucose Fluctuation in Poorly Oral-Antidiabetic Controlled Patients with Type 2 Diabetes Mellitus

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Aim. To compare the effects of once-weekly Dulaglutide with once-daily glargine in poorly oral-antidiabetic controlled patients with type 2 diabetes mellitus (T2DM).

Method. A total of 25 patients with T2DM admitted into Department of Endocrinology from December 2012 to August 2013 were randomly assigned into two groups: Dulaglutide group (n = 16) and glargine group (n = 9). All patients received either Dulaglutide or glargine treatments for 52 weeks. Continuous glucose monitoring systems (CGMS) were applied to them for two 72 h periods at before and after the treatment each. Patient general clinical data were collected and analyzed.

Result. Fast blood glucose (FBG) of the glargine group declined more significantly than the Dulaglutide group after treatment (p < 0.05). The mean blood glucose (MBG), standard deviation of blood glucose (SDBG), mean amplitude of glycemic excursion (MAGE) within a day, the largest amplitude of glycemic excursion (LAGE), MODD of glycemic excursion, the percentage of time (≤2.8 mmol/L, ≤3.9 mmol/L, ≥10.0 mmol/L, ≥13.9 mmol/L, 3.9–7.8 mmol/L, and 9–10.0 mmol/L), maximum glycemic value, and minimum glycemic value were similar between the two groups (p > 0.05). The incidence of hypoglycemia was also similar between the two groups (p > 0.05). Though serum levels of TNF-α, IL-6, and 8-PGF2α all decreased, significant reduction was found in TNF-α and 8-PGF2α. TNF-α was only significantly reduced in the Dulaglutide group, while 8-PGF2α was seen in both groups.

Conclusion. For T2DM patients with poorly controlled oral antidiabetic drugs, once-weekly Dulaglutide not only has the same effect on glucose fluctuation as once-daily glargine but also significantly reduced TNF-α and 8-PGF2α after a 52 week treatment protocol. This trial is registered with ClinicalTrials.gov: NCT01648582.

1. Introduction

According to the International Diabetes Federation (IDF), it is estimated that the number of adult diabetes mellitus in China had reached 109 million, while the number of adult diabetes mellitus in the whole world had reached 415 million [1]. Most of them suffered from type 2 diabetes mellitus (T2DM), which is characterized by insulin resistance, hyperglycemia, and inadequate insulin secretion which results from progressive pancreatic β-cell function decline [2]. Currently, there are various drugs used to treat diabetes mellitus, including insulin secretagogues, insulin sensitizer, α-glucosidase inhibitor, insulin, or insulin analogues, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1) analogues, and other oral antidiabetic drugs [3].

Recently, GLP-1 and its analogues have received more attention [4]. GLP-1 is a kind of incretin hormone secreted from L-cells of the intestine when blood glucose increases. Its receptor agonists, such as Exenatide, Liraglutide, Albiglutide, Lixisenatide, and Dulaglutide, activate corresponding signal transduction pathways by combining with GLP-1 receptors on the surface of cells [5]. Different from former GLP-1 receptor agonists which were usually injected 1-2 times a day, Dulaglutide is a new type of GLP-1 receptor agonist which can be injected subcutaneously once...
a week [6]. Dulaglutide activates GLP-1 receptors, improves glucose-dependent insulin secretion, lowers patient’s fasting blood glucose, suppresses the postprandial secretion of glucagon, reduces postprandial glucose, prolongs gastric emptying time, decreases appetite, and improves pancreatic β-cell functioning [7].

Recently, glucose fluctuation has been a new indicator in evaluating blood glucose [8]. By activating poly-metabolic pathways, glucose fluctuations can lead to microvascular and macrovascular complications [8]. Currently, few researches have been done on effects of GLP-1 receptor agonists 1~2 times per day on glucose fluctuations, and fewer have been done on effects of once-weekly drugs on glucose fluctuations.

Thus, the present study aims to determine the effect of Dulaglutide subcutaneous injection once a week with that of glargine injection once a day on glucose fluctuations of T2DM patients who were treated unsatisfactorily with metformin and/or sulfonylureas (SU) using the continuous glucose monitoring system (CGMS).

2. Methods

2.1. Subjects. This study was conducted at Department of Endocrinology; Nanjing Hospital affiliated to Nanjing Medical University, Nanjing. It was approved by the ethical committee of Nanjing Hospital. Written informed consent was obtained from all patients. Twenty-five patients with T2DM admitted into the Department of Endocrinology during the period between Dec. 2012 and Aug. 2013 were recruited as subjects of the present study. Patients were randomly assigned into two groups: the Dulaglutide group (n = 16) and the glargine group (n = 9), and treated for 52 weeks. 72 h CGMS was applied at 3 days before starting and 3 days after completing the Dulaglutide or glargine treatments. The inclusion criteria were: (1) Patients were >18 years old; (2) Patients with diagnosed T2DM for at least 6 months based on the World Health Organization’s (WHO) criteria [9]; (3) Patients had been taking metformin and/or sulfonylureas (SU) using the continuous glucose monitoring system (CGMS).

2.2. Study Protocol

2.2.1. Anti-Diabetic Drugs. Sixteen patients were randomized to receive once a week 0.75 mg (11 cases) and 1.5 mg (5 cases) Dulaglutide (Dulaglutide group). Patients and physicians were blinded to the dose of Dulaglutide. Nine patients received daily glargine (Lantus, Germany) (Glargine group). If patients’ FBG ≥ 7.8 mmol/L, the initial dose of glargine was 6 unit/day (U/D). Insulin dose was adjusted once or twice weekly. The glargine algorithm had a treat-to-target strategy [10], based on the average of the previous three FBG values.

2.2.2. Patient General Data. Gender, duration of diabetes mellitus, height, weight, BMI, blood pressure (BP), heart rate, corrected QT interval of electrocardiogram (ECG), and therapeutic schemes were collected by blinded physicians.

2.2.3. CGMS. Before and after 52 weeks of treatment, we applied CGMS (Medtronic MiniMed, blind CGMS) to the two groups for 72 hours to monitor their continuous glucose. CGMS sensor was inserted under the patients’ abdominal skin and connected to a glucose recorder to detect the glucose concentration of the interstitial fluid and have the data recorded. A mean value for each 5 minutes was stored and 288 measured values were recorded automatically every day with the glucose value, which can be effectively detected ranging from 2.2 to 22.2 mmol/L. The procedure was carried out for 72 hours. During the same period, capillary blood glucose levels of finger tips were measured at least 4 times a day to correct data from CGMS. The data were transmitted to a computer through an information collector and analyzed with the CGMS software 3.0.2. Patients were required to have the same time for diet and the same volumes of excise food intake during the period of CGMS study. The definition of hypoglycemia: blood glucose is lower than 3.9 mmol/L of blood glucose and lasts for 15 minutes. Patients would measure finger peripheral blood glucose at least 4 times/day; record the incidence of hypoglycemia. Patients would be suggested to take food if blood glucose < 3.9 mmol/L.

The following parameters were calculated:

(a) 24 hours Mean blood glucose (24 hours-MBG) and standard deviation of blood glucose (SDBG): the average level and SD of a total of 288 measured glucose values of 24 h with CGMS.

(b) Mean amplitude of glycemic excursion (MAGE), the largest amplitude of glycemic excursion (LAGE), M value and absolute means of daily difference (MODD).

(c) Percentage of hypoglycemia and hyperglycemia (≤ 2.8 mmol/L, ≤ 3.9 mmol/L, ≥ 10.0 mmol/L, ≥ 13.9 mmol/L, 3.9–7.8 mmol/L, 3.9–10.0 mmol/L).

(d) The maximum blood glucose (MAX-BG) and the minimum blood glucose (Min-BG).

2.2.4. Laboratory Examination. Fasting insulin (Ins 0) and fasting C-peptide (C-P0) were examined by chemiluminescence (Roche-E170, Roche, USA). HOMA-IR was calculated as Ins0 (μIU/mL) × Glu0 (mmol/L)/22.5. HbA1c was examined by High Performance Liquid Chromatography (HPLC:
3.2. Laboratory Test. There are no statistically significant differences in FBG, HbA1c, Ins-0, C-P0, HOMA-IR, amylase, lipase, pancreatic enzymes, liver and renal function, blood lipid, blood routine (white blood cell, platelet) between the two groups at baseline. However, statistically significant differences were only in hemoglobin, hematocrit and red blood cell counting. No statistical differences were found between the two groups for any measured parameters after 52 weeks.

3.3. CGMS Data. There are no statistically significant differences found in MBG, SDBG, LAGE, MAGE, MODD, and PT (≤2.8 mmol/L, ≤3.9 mmol/L, 3.9–7.8 mmol/L, 3.9–10.0 mmol/L, ≥10.0 mmol/L, ≥13.9 mmol/L). Max-BG or Min-BG either on baseline or after 52 weeks were similar (Table 5).
3.4. Oxidative Stress and Inflammatory Profile. To determine the effect of different drug treatments on oxidative stress and inflammation, we measured TNF-α, IL-6, and 8-PGF2α. Patients in all groups had higher inflammatory cytokine levels at baseline. After 52 week treatment, TNF-α levels significantly decreased in the Dulaglutide group ($p < 0.05$) (Table 4); however, this was not group and $-3.50 (-4.85, 0.55)$ for the glargine group, respectively, with no statistically significant differences. Variations from baseline levels of the two groups in MAGE were $-1.79 (-3.68, 2.74)$ for the Dulaglutide group and $0.32 (-2.88, 3.21)$ for the glargine group, but no statistically significant differences were found (Table 3).

### Table 2: Biochemical characteristics.

|                                | Dulaglutide group ($n = 16$) | Glargine group ($n = 9$) | $t$   | $P$    |
|--------------------------------|------------------------------|--------------------------|-------|-------|
| **Fasting blood glucose (mmol/L)** | Baseline 10.26 ± 2.84 | 10.72 ± 2.34 | −0.418 | 0.68  |
| **HbA1c (%)**                   | Baseline 8.65 ± 1.57 | 8.73 ± 0.64 | −0.186 | 0.854 |
| **Total amylase (U/L)**         | Baseline 69.44 ± 26.80 | 64.78 ± 17.35 | 0.467 | 0.645 |
| **Pancreatic enzymes (U/L)**    | Baseline 29.00 ± 9.16 | 28.22 ± 9.85 | 0.216 | 0.831 |
| **Lipase (U/L)**                | Baseline 43.94 ± 11.60 | 41.44 ± 14.15 | 0.477 | 0.638 |
| **Cholesterol (mmol/L)**        | Baseline 5.51 ± 1.34 | 5.55 ± 1.17 | −0.212 | 0.838 |
| **HDL-cholesterol (mmol/L)**    | Baseline 1.24 ± 0.28 | 1.31 ± 0.34 | −0.654 | 0.52  |
| **LDL-cholesterol (mmol/L)**    | Baseline 2.82 ± 0.81 | 2.54 ± 1.02 | 0.768 | 0.45  |
| **Triglyceride (mmol/L)**       | Baseline 1.64 ± 0.87 | 1.97 ± 1.63 | −0.655 | 0.519 |
| **Calcitonin (ng/L)**           | Baseline 2.24 ± 0.85 | 2.57 ± 0.73 | −0.954 | 0.35  |
| **White blood count (*10^9/L)** | Baseline 6.36 ± 1.42 | 5.84 ± 1.37 | 0.889 | 0.383 |
| **Haemoglobin (g/L)**           | Baseline 149.63 ± 11.77 | 139.89 ± 9.69 | 2.106 | 0.046*|
| **Haematocrit (g/L)**           | Baseline 0.45 ± 0.04 | 0.42 ± 0.03 | 1.706 | 0.102 |
| **Red blood count (*10^{12}/L)** | Baseline 4.91 ± 0.35 | 4.46 ± 0.50 | 2.65  | 0.014*|
| **Platelet count (*10^9/L)**     | Baseline 207.63 ± 68.46 | 180.11 ± 40.20 | 1.266 | 0.218 |
| **Blood urea nitrogen (mg/L)**  | Baseline 5.51 ± 1.34 | 5.55 ± 1.17 | −0.078 | 0.938 |
| **Creatinine (μmol/L)**         | Baseline 73.50 ± 15.48 | 65.56 ± 12.51 | 1.314 | 0.202 |
| **Alanine aminotransferase (U/L)** | Baseline 24.25 ± 13.93 | 22.00 (14.50, 35.50) | −0.142 | 0.901 |
| **Glutamate aminotransferase (U/L)** | Baseline 20.38 ± 5.84 | 16.78 ± 4.21 | 1.62  | 0.119 |
| **Microalbumin (mg/L)**         | Baseline 22.50 (16.00, 52.25) | 30.00 (11.00, 70.50) | −0.085 | 0.944 |
| **Microalbumin/creatinine (mg/g)** | Baseline 2.70 (1.13, 6.85) | 3.80 (1.15, 12.45) | −0.566 | 0.588 |
| **Fasting insulin (nmol/L)**    | Baseline 8.75 (5.30, 12.68) | 7.90 (6.00, 14.00) | −0.113 | 0.923 |
| **Fasting C-peptide (nmol/L)**  | Baseline 0.52 ± 0.31 | 0.41 ± 0.20 | 0.888 | 0.384 |
| **HOMA-IR (%)**                 | Baseline 0.93 ± 0.35 | 0.96 ± 0.38 | −0.185 | 0.855 |

HOMA-IR: homeostatic model assessment of insulin resistance.
seen in the glargine group. Though there were trends of IL-6 to reduce, no significant difference was found in both groups at 52 weeks compared with those at baseline. Serum 8-PGF2α levels significantly decreased in both the Dulaglutide and glargine groups after 52 week treatment as compared with baseline ($p < 0.05$) (Table 4). There were no significant differences found between groups at 52 weeks after treatment.

### 4. Discussion

The present study showed that that addition of once-weekly Dulaglutide has the same effect as once-daily glargine on

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**Table 3: CGMS results.**

| Variable   | Dulaglutide group ($n = 16$) | Glargine group ($n = 9$) | $t$  | $p$  |
|------------|-----------------------------|--------------------------|-----|-----|
| PT2.8      | 0 (0, 0)                    | 0 (0, 0)                 | 0   | 1   |
| 52w        | 0 (0, 0)                    | 0 (0, 0)                 | -1.925 | 0.054 |
| AUC2.8     | 0 (0, 0)                    | 0 (0, 0)                 | 0   | 1   |
| 52w        | 0 (0, 0)                    | 0 (0, 0)                 | -1.333 | 0.182 |
| PT3.9      | 0 (0, 0)                    | 0 (0, 0)                 | -0.15 | 0.88 |
| 52w        | 0 (0, 0)                    | 0 (0, 0)                 | -0.446 | 0.656 |
| AUC3.9     | 0 (0, 0)                    | 0 (0, 0.05)              | 1.925 | 0.054 |
| PT3.9–7.8  | 0 (0, 0)                    | 0 (0, 0)                 | -0.605 | 0.545 |
| 52w        | 51.50 (27.00, 62.75)        | 44.00 (22.50, 66.50)     | -0.482 | 0.63 |
| PT3.9–10   | 0 (0, 0)                    | 0 (0, 0)                 | -0.34  | 0.734 |
| 52w        | 50.50 (66.00, 91.75)        | 36.00 (15.50, 53.50)     | -1.359 | 0.174 |
| PT10       | 0 (0, 0)                    | 0 (0, 0)                 | -0.34  | 0.734 |
| 52w        | 19.50 (8.00, 34.00)         | 25.00 (11.50, 54.50)     | -1.048 | 0.295 |
| AUC10      | 0 (0, 0)                    | 0 (0, 0)                 | -0.425 | 0.671 |
| 52w        | 0.30 (0.10, 1.28)           | 0.40 (0.10, 2.45)        | -0.913 | 0.361 |
| PT13.9     | 0 (0, 0.11.50)              | 0 (0, 29.50)             | -0.427 | 0.669 |
| 52w        | 0.30 (0.03, 1.58)           | 0.30 (0.15, 0.45)        | -0.23  | 0.818 |
| MBG        | 0 (0, 0.18)                 | 0 (0, 0.65)              | 0.513  | 0.608 |
| 52w        | 11.93 ± 3.00                | 11.26 ± 2.08             | 0.598  | 0.556 |
| SDBG       | 8.63 ± 1.52                 | 8.83 ± 2.00              | -0.285 | 0.778 |
| 52w        | 2.75 ± 0.65                 | 2.67 ± 0.60              | 0.317  | 0.754 |
| MAX        | 2.24 ± 0.95                 | 2.91 ± 1.31              | -1.486 | 0.151 |
| 52w        | 17.70 ± 2.92                | 17.18 ± 2.31             | 0.46   | 0.65 |
| MIN        | 14.43 ± 3.47                | 15.14 ± 3.90             | -0.472 | 0.641 |
| 52w        | 7.19 ± 2.70                 | 6.43 ± 2.46              | 0.697  | 0.493 |
| Change     | -2.30 (−3.08, −0.15)        | -2.60 (−4.15, 1.25)      | -0.17  | 0.865 |
| Baseline   | 10.52 ± 1.85                | 10.74 ± 1.85             | -0.29  | 0.775 |
| LAGE       | 8.98 ± 3.76                 | 10.69 ± 3.86             | -1.078 | 0.292 |
| 52w        | 6.74 ± 1.99                 | 6.88 ± 2.20              | -0.157 | 0.877 |
| MAGE       | 5.86 ± 2.81                 | 7.09 ± 3.21              | -0.997 | 0.329 |
| 52w        | 26.76 (16.31, 58.85)        | 24.80 (16.04, 34.97)     | -0.481 | 0.63 |
| $M$-Value  | 5.19 (2.47, 14.96)          | 10.75 (4.42, 33.65)      | -1.585 | 0.113 |
| 52w        | 2.33 ± 1.33                 | 2.33 ± 0.83              | 0.002  | 0.999 |
| MODD       | 1.91 ± 0.90                 | 2.19 ± 0.62              | -0.82  | 0.424 |

PT: Percentage time of blood glucose; AUC: area under the curve; MBG: mean blood glucose; SDBG: standard deviation of blood glucose; MAX: the maximum blood glucose; MIN: the minimum blood glucose; LAGE: the largest amplitude of glycemic excursion; MAGE: mean amplitude of glycemic excursion; MODD: absolute means of daily difference.

### Table 4: Oxidative stress and inflammatory profile.

| Variable       | Dulaglutide group ($n = 16$) | Glargine group ($n = 9$) |
|----------------|-----------------------------|--------------------------|
| TNF-a (pg/ml)  | 7.23 (5.92, 8.74)           | 5.82 (4.89, 7.02)        |
| 52w            | 5.1 (4.24, 7.88)*           | 5.96 ± 1.35              |
| IL-6 (pg/ml)   | 0.87 ± 0.46                 | 0.95 (0.51, 1.72)        |
| 52w            | 0.64 ± 0.39                 | 0.61 (0.51, 1.08)        |
| PGF-2α (pg/ml) | 12.28 (10.71, 26.54)        | 11.05 (7.34, 17.97)      |
| 52w            | (3.62, 19.46)*              | (3.39, 9.09)*            |

* $p < 0.05$ vs baseline.
control of glucose fluctuations and oxidative stress and inflammation in patients with T2DM, who were poorly controlled by oral antihyperglycemic medications.

As a GLP-1 receptor agonist, Dulaglutide consists of GLP-1(7–37) covalently linked to an Fc fragment of human IgG4, thereby protecting the GLP-1 moiety from inactivation by dipeptidyl peptidase 4. The average biological half-life of Dulaglutide is 90 h, making it an ideal candidate for delivery once a week. Currently, few studies have been done on the effects of Dulaglutide on glucose fluctuation, among which the AWARD-4 trial studied Dulaglutide in 884 patients with T2DM [11]. The patients were randomly assigned to receive a 52-week combinational treatment of insulin lispro with once-weekly Dulaglutide or once-daily glargine with insulin lispro. It showed that Dulaglutide in combination with lispro resulted in a significantly greater improvement in glycemic control than glargine did. A substudy of this patient cohort (n = 144) received CGMS on weeks 0, 13, 26, and 52, respectively, to monitor blood glucose fluctuation [12]. It showed that the reduction of 24 h MBG was similar among the three groups at weeks 26 and 52. Though the percentage of time (PT) of normoglycemia (3.9–7.8 mmol/L) was similar, the percentage of near-normoglycemia of the Dulaglutide-1.5 mg group (3.9–10.0 mmol/L) was higher than the glargine group on week 26. However, the percentage time of hypoglycemia of the glargine group was similar between groups [11]. Similarly, AWARD-2 trial [18] found that on week 52, the total rate of hypoglycemia was similar between groups [11]. Similarly, AWARD-4 trial found that on weeks 26 and 52, the total rate of hypoglycemia was similar between groups [11]. Similarly, AWARD-2 trial [18] found that on week 52, the total rate and the total times of hypoglycemia and nocturnal hypoglycemia of the glargine group were all higher than those of Dulaglutide groups. Araki et al. [19] found that the total rate of hypoglycemia and nocturnal hypoglycemia of the glargine group were higher on week 26 in Japanese population. Thus, it seems that Dulaglutide has better control on hypoglycemia as compared with glargine.

Abdul–Ghani et al. [15], randomly assigned 231 poorly glycemic-controlled T2DM patients to receive once a week Exenatide/pioglitazone combinational treatment or basal/bolus insulin group for 18 months. They found the rate of hypoglycemia in patients received basal/bolus insulin injection was threefold of that of the patients in the combinational group. Diamant et al. [22] randomly assigned 586 T2DM patients to once-weekly albiglutide group or thrice-daily prandial insulin lispro group. Compared with that of the insulin group, the weekly combinational therapy group had less incidence of hypoglycemia [20]. The present study showed that the occurrence of hypoglycemia of the Dulaglutide group was similar to that of the glargine group, but was different from the Abdul–Ghani’s study [15]. It might be due to the different treatments applied in the present study, as higher risk of hypoglycemia may be associated with basal/bolus insulin injection as compared with oral anti-diabetic drugs. Different population races and diet habits may also contribute to the difference.

The present study found that FBG of the glargine group decreased significantly than that of the Dulaglutide group on week 52. AWARD-2 trial [18] compared the safety and efficacy of Dulaglutide (0.75 mg or 1.5 mg) with that of glargine in combination with metformin and Glimepiride. FBG of the glargine group declined more than the Dulaglutide 0.75 mg group on week 52 on AWARD-2. Similarly, AWARD-4 trial found that the FBG of the glargine group declined more on weeks 26 and 52. FBG in the current study was consistent with them, but was different from Araki study in which the FBG of

### Table 5: Microvascular complications and other treatments.

| Variable                  | Baseline | Week 52 |
|---------------------------|----------|---------|
|                           | Dulaglutide (n = 16) | Glargine (n = 9) | p | Dulaglutide (n = 16) | Glargine (n = 9) | p |
| Diabetic nephropathy, n (%)| 3        | 2       | 0.835 | 3 | 3                   | 0.412 |
| Other comorbidities, n (%) |          |         |       |              |         |       |
| Hyperlipidemia            | 5        | 4       | 0.509 | 6 | 4                   | 0.734 |
| Hypertension              | 11       | 5       | 0.509 | 11 | 5                   | 0.509 |
| Other treatments, n (%)    |          |         |       |              |         |       |
| CCB                       | 4        | 3       | 0.656 | 4 | 3                   | 0.656 |
| ACEI/ARB                  | 5        | 2       | 0.629 | 5 | 2                   | 0.629 |
| Beta-blockers             | 2        | 0       | 0.260 | 2 | 0                   | 0.260 |
| Statins                   | 3        | 2       | 0.835 | 4 | 2                   | 0.876 |

CCB: calcium channel blockers; ACEI/ARB: angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker.
the Dulaglutide group was similar to that of the glargine group on weeks 14 and 26 [19]. The differences may be due to the difference patient population selected in this study and different treatment protocol.

In the present study, HbA1c of the Dulaglutide group declined to a similar level to that of the glargine group on week 52. This is consistent with others [12, 13], Araki et al. [19] even found that the HbA1c of the Dulaglutide group declined more than that of the glargine group. This might be due to differences in patient population selection and treatment protocol. The present study found that the Dulaglutide group had a similar rate of HbA1c-control (percentage of HbA1c ≤ 6.5% and HbA1c ≤ 7%) to that of the glargine group on week 52. This is consistent with AWARD-4 study which found no statistical differences in rate of HbA1c-control of the three groups [11]. On the contrary, Abdul-Ghani et al. [15] found that higher rates of HbA1c-control were all seen in the weekly-Exenatide group. The difference might be due to differences in clinical protocol, race and sample size.

Decreased oxidation stress and inflammation markers decreased in both groups after 52 weeks’ treatment, notably in Dulaglutide group. This suggests that both treatments have anti-inflammatory and oxidative stress effects in T2DM and Dulaglutide has more effective therapeutic efficacy in reducing inflammation in T2DM.

Body weight reduction has been seen in both Dulaglutide and Exenatide treatments [7, 11, 18, 19, 22], Abdul-Ghani found that the body weight gain of the weekly-Exenatide group was only half of that of the control group, with the difference being of statistical significances in Qatar study [15]. Other studies found body weight loss of the Dulaglutide group [11, 18, 19]. Some studies [20, 22] found, when comparing glucose control of once-weekly-albiglutide with that of glargine and comparing twice-daily Exenatide with that of glargine, and found that patients received Exenatide had significant lower body weight. In the present study; however, no significant differences in body weight reduction was found between the two groups at week 52. This might be due to the small sample-size of the present study.

Studies showed increase in amylase, lipase, and pancreatic enzymes in AWARDs studies and Araki’s studies [11, 16–19, 23]. The present study also found that the amylase and lipase of the Dulaglutide group increased significantly as compared with those of the glargine group. However, we did not find statistically significant differences in pancreatic enzymes of the two groups. These were consistent with Araki’s studies [19].

No adverse events such as acute pancreatitis, pancreatic carcinoma etc., were found during study course [24]. The mechanism of pancreatic enzymes might be due to the increased replication of pancreatic duct cell with obesity and T2DM [25].

The study has several limitations. Firstly, the sample size is small. Secondly, the mechanism of Dulaglutide on reduction of inflammatory biomarkers is unknown. Future study is needed to explore the underlined mechanism.

In conclusion, for T2DM patients with poorly controlled oral antidiabetic drugs, once-weekly Dulaglutide not only has the same effect on glucose fluctuation as once-daily glargine, but also significantly reduced TNF-α and 8-PGF2α after a 52-week treatment protocol.

**Data Availability**

The data are restricted to researchers approved by ethical committee of Nanjing Hospital affiliated to Nanjing Medical University, Nanjing. Other researcher may access the data upon request and approval of ethical committee of Nanjing Hospital affiliated to Nanjing Medical University, Nanjing.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors’ Contributions**

Jie Wang and Hui-qin Li are equally contributed.

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