Comparison of Exenatide and Metformin Monotherapy in Overweight/Obese Patients with Newly Diagnosed Type 2 Diabetes

Jia Liu, Yanjin Hu, Yuan Xu, Yumei Jia, Li Miao, and Guang Wang

Department of Endocrinology, Beijing Chao-Yang Hospital, Capital Medical University, No. 8, Gongti South Road, Chaoyang District, Beijing 100020, China

Correspondence should be addressed to Guang Wang; drwg6688@126.com

Received 7 May 2017; Revised 19 August 2017; Accepted 7 September 2017; Published 20 November 2017

Academic Editor: Mario Maggi

Copyright © 2017 Jia Liu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Aims. The present study assessed the therapeutic effect of exenatide and metformin as the initial therapy on overweight/obese patients with newly diagnosed type 2 diabetes (T2D). Methods. The prospective, nonrandomized, intervention study enrolled a total of 230 overweight or obese patients with newly diagnosed T2D who were administrated exenatide or metformin hydrochloride for 12 weeks. Results. 224/230 patients, including 106 in the exenatide group and 118 in the metformin group, completed the 12-week treatment. Both exenatide and metformin significantly decreased the HbA1c levels in overweight/obese patients with newly diagnosed T2D (all $P < 0.05$). The reduction in HbA1c and the proportion of patients with HbA1c $< 7.0\%$ (53 mmol/mol) were higher in the exenatide group than in the metformin group (all $P < 0.05$). The exenatide treatment caused a greater decline in the body weight and BMI as compared to the metformin treatment (all $P < 0.01$). The exenatide treatment ($\beta = 0.41$, $P < 0.01$) and baseline HbA1c level ($\beta = -0.84$, $P < 0.01$) were independent influencing factors for the decrease in HbA1c level. Conclusions. For an initial therapy in overweight/obese patients with newly diagnosed T2D, exenatide causes a better glycemic control than metformin. This trial is registered with NCT03297879.

1. Introduction

Type 2 diabetes (T2D) is a common metabolic disease with high morbidity and mortality due to T2D-related complications [1]. Obesity is a major risk factor for T2D as it induces chronic inflammation, endoplasmic reticulum stress, mitochondrial dysfunction, and insulin resistance [2]. The impact on body weight is also considered a critical aspect of the clinical evaluation of hypoglycemic drugs. Several studies have confirmed that some hypoglycemic drugs like sulfonylureas, thiazolidinediones, or insulin tend to cause gain weight, while metformin leads to no change or mild decline in body weight [3]. Thus, metformin is frequently used as a first-choice therapy in overweight/obese T2D patients [3]. Glucagon-like peptide-1 (GLP-1) receptor agonist is a novel agent approved for treating T2D and has been demonstrated to induce significant weight loss in overweight/obese T2D patients [3–6]. However, it is yet unclear whether as initial treatment, GLP-1 receptor agonist contributes to an improved therapeutic efficacy than metformin in overweight/obese patients with newly diagnosed T2D. Exenatide is a classical drug of a GLP-1 receptor agonist. In the present study, we assessed the therapeutic effect of exenatide and metformin as the initial therapy on overweight/obese patients with newly diagnosed T2D.

2. Materials and Methods

2.1. Subjects. The present study was a prospective, nonrandomized, intervention study, performed between September 2013 and October 2015 at the Department of Endocrinology in Beijing Chao-Yang Hospital affiliated to Capital Medical University. We consecutively enrolled 230 drug-naïve, overweight, or obese patients with newly diagnosed T2D, who fulfilled the following inclusion criteria: (1) age 20 to
expressed as mean ± standard deviation (SD). In the event of failure to follow a normal distribution, the values of TG, FINS, HOMA-IR, and HOMA-β were presented as medians (the upper and lower quartiles). Variables that were nonnormally distributed were log-transformed before analysis. Comparisons between the groups were assessed by the independent sample t-test and ANOVA test. The differences of proportions were analyzed by the chi-square test. The changes in parameters from baseline within groups were evaluated using the two-tailed paired t-test. Multivariate regression analysis was applied to assess the correlations between the change in HbA1c level and relevant variables. Statistical significance was inferred when \( P < 0.05 \).

3. Results

3.1. Baseline Characteristics in the Exenatide and Metformin Groups. Table 1 presents the baseline characteristics of the exenatide and metformin groups. Age, gender, the proportion of obese patients, body weight, BMI, TC, LDL-C, HDL-C, TG, FBG, FINS, HbA1c, HOMA-IR, and HOMA-β were comparable in the two groups (all \( P > 0.05 \)).

3.2. Changes in Anthropometric Measurements after Exenatide or Metformin Treatment. During therapy, 4 patients (3.6%) in the exenatide group dropped out of the study because of moderate-to-severe nausea and vomiting, whereas 2 patients (1.7%) in the metformin group dropped out because of moderate-to-severe vomiting and diarrhea.

After the 12-week treatment, significant reductions in body weight and BMI were observed in the exenatide and metformin groups (all \( P < 0.05 \)) (Table 2). However, the exenatide treatment demonstrated a greater decline in the body weight and BMI as compared to the metformin treatment (all \( P < 0.01 \)) (Table 2).

3.3. Alterations in Glucose Metabolic Parameters after Exenatide or Metformin Treatment. Both exenatide and metformin treatments significantly decreased the FBG and HbA1c levels at 12 weeks (all \( P < 0.05 \)) (Table 2); however, no difference was observed in the reductions in FBG between exenatide and metformin treatments. Nevertheless, the HbA1c levels in the exenatide group were reduced more than those in the metformin group (one-way ANOVA, \( P < 0.01 \)) (Table 2). The proportion of patients with HbA1c < 7.0% (53 mmol/mol) in the exenatide group was 79.5%, which was higher than the 64.0% in the metformin group (all \( P > 0.05 \)) (Table 2).

We also observed a significant increase in HOMA-β in the two groups after exenatide or metformin treatment (all \( P < 0.05 \)) (Table 2). The increase in the HOMA-β value of the exenatide group was higher than that of the metformin group \([33.01 (20.19–45.82) versus 14.03 (6.34–21.72), P < 0.01] \). However, the decrease in the HOMA-IR value was similar after 12 weeks of exenatide or metformin treatment (all \( P > 0.05 \)) (Table 2).

Interestingly, exenatide did not cause a greater decrease in the HbA1c level than metformin after adjustment for the reduced body weight following the 12-week treatment.
(P > 0.05). However, the greater increase in the HOMA-β value was still observed in the exenatide group than in the metformin group postadjustment for the decrease in FBG (P < 0.05).

### 3.4. Changes in Lipid Profile after Exenatide or Metformin Treatment

Both exenatide and metformin significantly reduced the TC levels after 12 weeks of treatment (P < 0.05) (Table 2). Moreover, a significant decrease in the plasma TG levels of the exenatide group and LDL-C levels of the metformin group was also observed posttreatment (all P < 0.05) (Table 2). In the exenatide group, the TG levels showed a greater decline as compared to those in the metformin treatment group (P < 0.01) (Table 2).

### 3.5. Multivariate Regression Analysis to Find the Correlation between the Decrease in HbA1c Level and Relevant Variables

Multivariate regression analysis was used to further assess the relationships between the decrease in the HbA1c level and related variables. The influence of six variables such as age, gender, body mass index, baseline HbA1c, baseline FBG, and drug treatment was assessed. The analysis indicated that the exenatide treatment (β = 0.41, P < 0.01) and baseline HbA1c level (β = −0.84, P < 0.01) were independent influencing factors for the decrease in HbA1c level.

### 3.6. Adverse Events

During the 12-week treatment with exenatide or metformin, no major hypoglycemia was observed in any patient (Table 3). Incidences of minor hypoglycemia

---

**Table 1: Baseline characteristics of the exenatide and metformin groups.**

| Parameters               | Exenatide (n = 110) | Metformin (n = 120) | P  |
|--------------------------|---------------------|---------------------|----|
| Age, y                   | 45.77 ± 10.60       | 48.05 ± 8.04        | 0.097 |
| Gender, males/females, n | 64/46               | 71/49               | 0.880 |
| Overweight/obesity, n    | 57/53               | 63/57               | 0.918 |
| Body weight, kg          | 78.76 ± 10.01       | 77.98 ± 11.88       | 0.907 |
| BMI, kg/m²               | 27.83 ± 2.38        | 27.57 ± 3.56        | 0.815 |
| TC, mmol/L               | 5.21 ± 1.25         | 5.29 ± 1.22         | 0.664 |
| LDL-C, mmol/L            | 3.07 ± 0.89         | 3.05 ± 0.90         | 0.864 |
| HDL-C, mmol/L            | 1.12 ± 0.43         | 1.24 ± 0.29         | 0.087 |
| TG, mmol/L               | 2.07 (1.27–3.99)    | 1.93 (1.32–2.75)    | 0.235 |
| FBG, mmol/L              | 9.34 ± 3.27         | 9.10 ± 1.34         | 0.594 |
| FINS, μIU/mL             | 9.50 (5.98–14.37)   | 10.14 (5.25–14.94)  | 0.337 |
| HbA1c, %                 | 9.11 ± 1.46         | 9.03 ± 1.18         | 0.230 |
| HOMA-IR                  | 3.94 (2.47–5.93)    | 3.87 (2.27–6.02)    | 0.638 |
| HOMA-β                   | 55.13 (29.64–76.65) | 50.55 (29.80–74.81) | 0.289 |

Data are means ± SD unless indicated otherwise. TG, FINS, HOMA-IR, and HOMA-β are shown as medians (upper and lower quartiles). BMI: body mass index; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; FBG: fasting blood glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; HOMA-β: homeostasis model assessment of β-cell function.

**Table 2: Changes in metabolic parameters after metformin or exenatide treatment.**

| Parameters               | Exenatide (n = 106) | Metformin (n = 118) | P  |
|--------------------------|---------------------|---------------------|----|
| Body weight, kg          | −5.79 (−8.09 to −3.48) | −2.30 (−0.99 to −0.66) | 0.001 |
| BMI, kg/m²               | −1.99 (−2.85 to −1.14) | −0.83 (−0.99 to −0.66) | 0.000 |
| TC, mmol/L               | −0.58 (−1.00 to −0.15) | −0.35 (−0.52 to −0.19) | 0.252 |
| LDL-C, mmol/L            | −0.17 (−0.42 to 0.08) | −0.14 (−0.26 to −0.03) | 0.900 |
| HDL-C, mmol/L            | 0.06 (−0.02 to 0.13)  | −0.04 (−0.08 to 0.00)  | 0.358 |
| TG, mmol/L               | −1.26 (−2.07 to −0.45) | −0.03 (−0.31 to 0.26)  | 0.000 |
| FBG, mmol/L              | −2.62 (−3.89 to −1.35) | −2.17 (−2.51 to −1.73) | 0.321 |
| FINS, μIU/mL             | 0.63 (−1.19 to 2.46)  | −2.03 (−4.50 to −1.52) | 0.000 |
| HbA1c, %                 | −2.81 (−3.42 to −2.45) | −1.44 (−1.67 to −1.21) | 0.000 |
| HOMA-IR                  | −2.05 (−2.69 to −1.37) | −1.88 (−2.23 to −1.06) | 0.565 |
| HOMA-β                   | 33.01 (20.19–45.82)  | 14.03 (6.34–21.72)   | 0.002 |
| HbA1C < 7.0%, n (%)      | 84 (79.5)           | 75 (64.0)           | 0.033 |

Data are shown as difference (95% CI) versus baseline, except for HbA1C < 7.0%. BMI: body mass index; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; FBG: fasting blood glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; HOMA-β: homeostasis model assessment of β-cell function; HbA1C < 7.0%: the proportion of patients with HbA1C < 7.0% (53 mmol/mol).
with those of a meta-analysis, which demonstrated that GLP-1 receptor agonists contribute to a larger proportion of patients achieving HbA1c < 7.0% (53 mmol/mol) than metformin [17]. Thus, the results might suggest that for initial therapy in overweight/obese patients with newly diagnosed T2D, exenatide causes a better glycemic control than metformin.

Obesity is associated with T2D by inducing endoplasmic reticulum stress, chronic inflammatory state, and insulin resistance [2]. Our study demonstrated that exenatide and metformin individually caused a significant decrease in body weight. A greater weight loss was observed in the exenatide group compared to the metformin group. These results for metformin are consistent with those of our previous and other studies [9, 18]. Metformin leads to a moderate weight loss by several mechanisms, including increasing insulin sensitivity, decreasing gastrointestinal absorption of carbohydrates, and reducing ghrelin and leptin levels after glucose overload [19]. In addition, metformin increased circulating levels of active forms of GLP-1, which might be involved in the suppression of appetite [20]. In the present study, exenatide significantly decreased the body weight by 5.79 kg. Exenatide lowers body weight by slowing gastric emptying, promoting satiety, and decreasing food intake [12]. In addition, lifestyle intervention, especially diet control, can also effectively reduce the body weight in patients with T2D [21]. Due to the suppression of appetite, GLP-1 receptor agonist might exhibit a synergistic effect with life intervention and contribute to improved diet control and hence more weight loss. Notably, after adjustment for the decrease in body weight, no significant difference was observed in the reduction in HbA1c between the exenatide and metformin treatments. This suggested that the better hypoglycemic effect of exenatide on overweight/obese patients might be primarily associated with enhanced weight loss.

Insulin resistance plays a major role in the pathogenesis of T2D and its complications [2]. Metformin has been widely established as a strong insulin sensitizer [3]. The present study showed that exenatide and metformin similarly decreased insulin resistance in overweight/obese patients with T2D. The significant reduction in body weight is one of the key reasons for the improvement of insulin resistance of exenatide and metformin [22]. Both GLP-1 receptor agonist and metformin exerted some beneficial effects on insulin resistance indirectly by inhibiting oxidative stress and regulating lipid metabolism [23, 24]. Thus, it might suggest that exenatide is another insulin sensitizer that leads to amelioration of insulin resistance in obese patients with T2D.

Compared to the Western population, Asians with T2D showed a distinct β-cell dysfunction [25]. In the present study, both exenatide and metformin treatments significantly increased HOMA-β values, and the increase in the exenatide group was higher than that in the metformin group. The alleviation of glucose toxicity, rather than a direct drug effect, might underlie the HOMA-β improvement in the two groups [26]. However, after adjustment for the decrease in FBG, the increase in the HOMA-β value was still observed in the exenatide group than in the metformin group.
Previous studies showed that metformin indirectly increased β-cell function through decreasing glucotoxicity, lowering insulin resistance, inhibiting the formation of advanced glycation end products, and reducing oxidative stress [23, 26]. In addition to the similar capabilities of metformin, exenatide also displays some direct beneficial effects on islet β-cells [27–30]. A previous study showed that exenatide improved the insulin secretion of β-cells as compared to the insulin glargine in a similar glycemic control, and this effect was sustained after a 4-week off-drug period [28]. Animal studies have demonstrated that GLP-1 promotes the proliferation of β-cells and inhibits their apoptosis [29, 30]. Cell-based studies showed that GLP-1 enhanced the viability and inhibited the mitochondrial-dependent apoptosis in the PKC-dependent pathway [30].

Notably, our study has several limitations. The major limitation was that the present study was not a randomized controlled trial. In addition, our study also lacked accurate clamp techniques, to assess β-cell function and insulin sensitivity. Furthermore, the treatment duration was relatively short. Long-term observation of these treatments is needed to evaluate the persistence of beneficial effects over time. Moreover, the cost/benefit ratio is another aspect that should be considered. In terms of medical expenses, metformin might be more preferable for a lifelong treatment. Despite these limitations, one implication of the present study is that for a patient with newly diagnosed T2D, exenatide might contribute to a better effect on glycemic control, weight management, and β-cell function, which at least partly represents an avenue for investigation in the treatment of T2D.

In conclusion, for an initial therapy in overweight/obese patients with newly diagnosed T2D, exenatide causes a better glycemic control than metformin, whose mechanism might potentially be related to the better weight loss effect and amelioration of β-cell function.

Conflicts of Interest
No competing financial interests exist.

Acknowledgments
This work was supported by grants from the Capital Clinical Research Foundation of Beijing Municipal Commission of Science and Technology (no. Z161100000516069) to Guang Wang, and National Natural Science Foundation of China (no. 81600657), and Beijing Municipal Administration of Hospitals’ Youth Programme (no. QML20150308) to Jia Liu.

References
[1] L. Guariguata, D. R. Whiting, I. Hambleton, J. Beagley, U. Linnenkamp, and J. E. Shaw, “Global estimates of diabetes prevalence for 2013 and projections for 2035,” Diabetes Research and Clinical Practice, vol. 103, no. 2, pp. 137–149, 2014.
[2] A. J. Garber, “Obesity and type 2 diabetes: which patients are at risk?,” Diabetes, Obesity and Metabolism, vol. 14, no. 5, pp. 399–408, 2012.
[3] American Diabetes Association, “Standards of medical care in diabetes—2013,” Diabetes Care, vol. 36, Supplement 1, pp. S11–S66, 2013.
[4] G. Derosa, I. G. Franzetti, F. Querci et al., “Exenatide plus metformin compared with metformin alone on β-cell function in patients with type 2 diabetes,” Diabetic Medicine, vol. 29, no. 12, pp. 1515–1523, 2012.
[5] M. Diamant, L. Van Gaal, B. Guerci et al., “Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial,” The Lancet Diabetes and Endocrinology, vol. 2, no. 6, pp. 464–473, 2014.
[6] J. B. Buse, J. Rosenstock, G. Sesti et al., “Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6),” The Lancet, vol. 374, no. 9683, pp. 39–47, 2009.
[7] Chinese Society of Endocrinology, “Chinese expert consensus for the prevention and treatment of obesity in adults,” vol. 27, pp. 711–717, 2011.
[8] V. Bermudez, R. Cano, C. Cano et al., “Homeostasis model assessment (HOMA) as surrogate insulinization criteria in patients with type 2 diabetes,” American Journal of Therapeutics, vol. 15, no. 4, pp. 409–416, 2008.
[9] G. Wang, J. Liu, N. Yang et al., “MARCH2: comparative assessment of therapeutic effects of acarbose and metformin in newly diagnosed type 2 diabetes patients,” PLoS One, vol. 9, no. 8, article e105698, 2014.
[10] D. Russell-Jones, R. M. Cuddihy, M. Hanefeld et al., “Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study,” Diabetes Care, vol. 35, no. 2, pp. 252–258, 2012.
[11] A. P. Cotter, N. Durant, A. A. Agne, and A. L. Cherrington, “Internet interventions to support lifestyle modification for diabetes management: a systematic review of the evidence,” Journal of Diabetes and its Complications, vol. 28, no. 2, pp. 243–251, 2014.
[12] D. J. Drucker and M. A. Nauck, “The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes,” The Lancet, vol. 368, no. 9548, pp. 1696–1705, 2006.
[13] Y. G. Kim, S. Hahn, T. J. Oh, K. S. Park, and Y. M. Cho, “Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis,” Diabetes, Obesity & Metabolism, vol. 16, no. 10, pp. 900–909, 2014.
[14] Y. M. Cho, “Incretin physiology and pathophysiology from an Asian perspective,” Journal of Diabetes Investigation, vol. 6, no. 5, pp. 495–507, 2015.
[15] T. J. Oh, M. Y. Kim, J. Y. Shin et al., “The incretin effect in Korean subjects with normal glucose tolerance or type 2 diabetes,” Clinical Endocrinology, vol. 80, no. 2, pp. 221–227, 2014.
[16] W. H. Herman, K. M. Dungan, B. H. R. Wolfenbuttel et al., “Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes,” The Journal of Clinical Endocrinology & Metabolism, vol. 94, no. 5, pp. 1689–1694, 2009.
systematic review of 218 randomized controlled trials with 78,945 patients,” *Diabetes, Obesity & Metabolism*, vol. 14, no. 3, pp. 228–233, 2012.

[18] W. C. Knowler, E. Barrett-Connor, S. E. Fowler et al., “Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin,” *The New England Journal of Medicine*, vol. 346, no. 6, pp. 393–403, 2002.

[19] S. K. Thondam, A. Cross, D. J. Cuthbertson, J. P. Wilding, and C. Daousi, “Effects of chronic treatment with metformin on dipeptidyl peptidase-4 activity, glucagon-like peptide 1 and ghrelin in obese patients with type 2 diabetes mellitus,” *Diabetic Medicine*, vol. 29, no. 8, pp. e205–e210, 2012.

[20] E. Mannucci, A. Ognibene, F. Cremasco et al., “Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects,” *Diabetes Care*, vol. 24, no. 3, pp. 489–494, 2001.

[21] E. P. de Oliveira, A. C. Diegoli, J. E. Corrente, K. C. McLellan, and R. C. Burini, “The increase of dairy intake is the main dietary factor associated with reduction of body weight in overweight adults after lifestyle change program,” *Nutrición Hospitalaria*, vol. 32, no. 3, pp. 1042–1049, 2015.

[22] M. Sene-Fiorese, F. O. Duarte, A. E. de Aquino Junior et al., “The potential of phototherapy to reduce body fat, insulin resistance and “metabolic inflexibility” related to obesity in women undergoing weight loss treatment,” *Lasers in Surgery and Medicine*, vol. 47, no. 8, pp. 634–642, 2015.

[23] B. Batchuluun, T. Inoguchi, N. Sonoda et al., “Metformin and liraglutide ameliorate high glucose-induced oxidative stress via inhibition of PKC-NAD(P)H oxidase pathway in human aortic endothelial cells,” *Atherosclerosis*, vol. 232, no. 1, pp. 156–164, 2014.

[24] R. Barazzoni, M. Zanetti, G. Gortan Cappellari et al., “Fatty acids acutely enhance insulin-induced oxidative stress and cause insulin resistance by increasing mitochondrial reactive oxygen species (ROS) generation and nuclear factor-xB inhibitor (IxB)–nuclear factor-xB (NFkB) activation in rat muscle, in the absence of mitochondrial dysfunction,” *Diabetologia*, vol. 55, no. 3, pp. 773–782, 2012.

[25] A. Morimoto, Y. Tatsumi, K. Deura et al., “Impact of impaired insulin secretion and insulin resistance on the incidence of type 2 diabetes mellitus in a Japanese population: the Saku study,” *Diabetologia*, vol. 56, no. 8, pp. 1671–1679, 2013.

[26] R. Retnakaran and B. Zinman, “Short-term intensified insulin treatment in type 2 diabetes: long-term effects on β-cell function,” *Diabetes, Obesity & Metabolism*, vol. 14, Supplement 3, pp. 161–166, 2012.

[27] M. Zander, S. Madsbad, J. L. Madsen, and J. J. Holst, “Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β-cell function in type 2 diabetes: a parallel-group study,” *The Lancet*, vol. 359, no. 9309, pp. 824–830, 2002.

[28] M. C. Bunck, A. Corner, B. Eliasson et al., “Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes,” *Diabetes Care*, vol. 34, no. 9, pp. 2041–2047, 2011.

[29] J. Buteau, M. L. Spatz, and D. Accili, “Transcription factor FoxO1 mediates glucagon-like peptide-1 effects on pancreatic β-cell mass,” *Diabetes*, vol. 55, no. 5, pp. 1190–1196, 2006.

[30] L. Zhang, Y. Wang, J. Wang, Y. Liu, and Y. Yin, “Protein kinase C pathway mediates the protective effects of glucagon-like peptide-1 on the apoptosis of islet β-cells,” *Molecular Medicine Reports*, vol. 12, no. 5, pp. 7589–7594, 2015.