https://doi.org/10.33805/2690-2613.113
Volume 2 Issue 1 | PDF 113 | Pages 5

EDELWEISS PUBLICATIONS
OPEN ACCESS

Edelweiss Journal of Biomedical Research and Review

Case Report ISSN 2690-2613

Elderly Diabetic Patients with Effective Add-on Therapy of Dulaglutide as a GLP-1 Receptor Analogue (GLP-1 RA)

Yozo Takehisa[1] and Hiroshi Bando[1,2*]

Affiliation

[1]Hakuai Memorial Hospital, Heisei Medical Welfare (HMW) group, Tokushima, Japan
[2]Tokushima University/Medical Research, Tokushima, Japan
[*]**Corresponding author:** Hiroshi Bando, Tokushima University/Medical Research, Tokushima, Japan, Tel: +81-90-3187-2485, E-mail: pianomed@bronze.ocn.ne.jp

Citation: Takehisa Y and Bando H. Elderly diabetic patients with effective add-on therapy of dulaglutide as a GLP-1 receptor analogue (GLP-1 RA) (2020) Edel J Biomed Res Rev 2: 31-35.

Received: Aug 11, 2020
Accepted: Sep 03, 2020
Published: Sep 10, 2020

Abstract

Background: For diabetic treatment, Dulaglutide has been used and effective as a glucagon-like peptide-1 receptor analogue (GLP-1 RA). This report is to describe the various responses and to analyze dulaglutide administration in the elderly with DM. **Case presentation:** Two patients were Type 2 Diabetes Mellitus (T2DM) treated with add-on therapy of Dulaglutide. Case 1 is 81-year-old female is diabetic for 2 years, and on Metformin and Glimepiride as Oral Hypoglycemic Agents (OHAs). Her HbA1c was higher with 10.6% and she was started to given Dulaglutide 0.75mg. Remarkable efficacy was found in 3 months with HbA1c 6.7%. Value of LDL-C increased from 135 mg/dL to 158 mg/dL. Case 2 is 83-year-old male with 27 years of diabetes. He was on medication of Metformin and Glimepiride. His HbA1c persisted around 9.0%-9.4%, then he was provided Dulaglutide as add-on therapy. In 3 months, HbA1c decreased to 8.2% and LDL-C increased from 57 mg/dL to 116 mg/dL. **Discussion and conclusion:** Dulaglutide is a useful GLP-1 RA with once a week administration. There were some reports concerning LDL changes after dulaglutide therapy, showing that the changes may depend on the basal LDL value before the administration of dulaglutide. Dulaglutide may influence lipid metabolism. This report is expected to become reference in diabetic practice and research in the future.

Keywords: Dulaglutide, Glucagon-like Peptide-1 Receptor Analogue, Type 2 Diabetes Mellitus, Oral Hypoglycemic Agents, Heisei Medical Welfare.

Abbreviations: GLP-1 RA-Glucagon-like Peptide-1 Receptor Analogue, T2DM-Type 2 Diabetes Mellitus, OHAs-Oral Hypoglycemic Agents, HMW-Heisei Medical Welfare, eGFR-Estimated Glomerular Filtration Rate.

Introduction

Across the world, diabetes has been a major healthcare matter and given a burden for countries and districts socially and medically. Among them, estimated adults with Type 2 Diabetes Mellitus (T2DM) would be 415 million. Furthermore, there may be 200 million people with undiagnosed diabetes yet. Impaired glucose variability for long time brings T2DM patients macrovascular and microvascular complications. This pathophysiology will increase the risk of Chronic Kidney Disease (CKD) and Cardiovascular Disease (CVD). Consequently, improved achievement of glycemic control less than 7% of glycated hemoglobin (HbA1c) would be necessary. For fundamental therapy for diabetes, principle treatments in usual clinical practice include diet therapy and pharmacotherapy [1-5].

As to nutritional therapy for diabetes, former method of standard diet treatment was Calorie Restriction (CR). CR has been rather difficult to improve diabetic condition and to maintain CR for long. After that, Low Carbohydrate Diet (LCD) was introduced in practice medical region and health care field by Dr Atkins and Bernstein. LCD has become rather well-known for its clinical effects of glucose-lowering and weight reduction in Western countries. In contrast, authors and co-researchers had started LCD in Japan. We have developed three types of LCD-meal for everyone to understand and continue LCDs. These are petite-LCD, standard-LCD and super-LCL, including carbohydrate ratio of 40%, 26%, and 12%, respectively. Furthermore, we have established Japan LCD Promotion Association (JLCDPA) and developed social movement of developing LCD leading to healthy life for everyone. We have also continued diabetic research on glucose variability, Morbus (M) value, CR/LCD, Meal Tolerance Test (MMT) of CR/LCD, elevated ketone bodies in the axis of pregnant mother, newborn, umbilical cord and placenta. Thus, standard diet therapy for diabetes has been gradually changing from CR to LCD [6-11].

Regarding pharmacotherapy for diabetes, there have been long history and also standard therapeutic method recommended by American Diabetes Association (ADA) and International Diabetes Federation (IDF). Currently, several types of Oral Hypoglycemic Agents (OHAs) and injections have been available. Among them, it is metformin that has been evaluated to be the first provided OHA for T2DM. Primary care physicians and also diabetologists have provided metformin to T2DM patients for a fundamental OHA. It shows various beneficial effects, including low cost, safety, no hypoglycemia, weight neutrality and positive results for cardiovascular outcomes [12-14].

Consequently, there have been various discussions about add-on to metformin as first line of OHA. In the case of elderly diabetic, decreased Estimated Glomerular Filtration Rate (eGFR) has to be considered for first line metformin administration. Then, dulaglutide has been beneficial for an option of add-on therapy.

Another benefit would be clinical convenience for elderly, which can be administered once a week with satisfactory clinical efficacy in the diabetic practice. Its beneficial efficacy on glycemic control and weight control were maintained at 52 weeks and also 104 weeks. In the case of add-on treatment to sulfonylurea, administration of dulaglutide showed significant decreased HbA1c with satisfactory achieving target HbA1c levels. Furthermore, the beneficial point of dulaglutide is rather safer administration for diabetic patients with higher age and also CKD [15-17].

Authors have continued clinical practice for patients with diabetes, CKD, Non-Communicable Diseases (NCDs) and elderly having multiple medical and health problems for years. We have large complex medical association of hospitals, nursing homes, nursing college, international hospitals and others. It is called the Heisei Medical Welfare (HMW) group with more than 10000 beds, 15000 working staffs and 80 facilities [18-20].

HMW has specialized in convalescent and chronic medical care, and has developed many facilities for many years in Tokushima, Tokyo, Osaka, Indonesia, etc. It has important missions and functions such as saving all people, adequate Post-Acute Care (PAC) and Sub-Acute Care (SAC). Among our daily practice, we have experienced impressive elderly cases with T2DM. They have received standard therapy, but not been in satisfactory situation. We have started the administration of dulaglutide as add-on therapy, then their clinical progress showed improvement. From their responses in detail, we will discuss the dulaglutide administration in the elderly with DM and the adequate parameters or outcomes that can be assessed in their clinical courses in this article.

Case 1

Present History

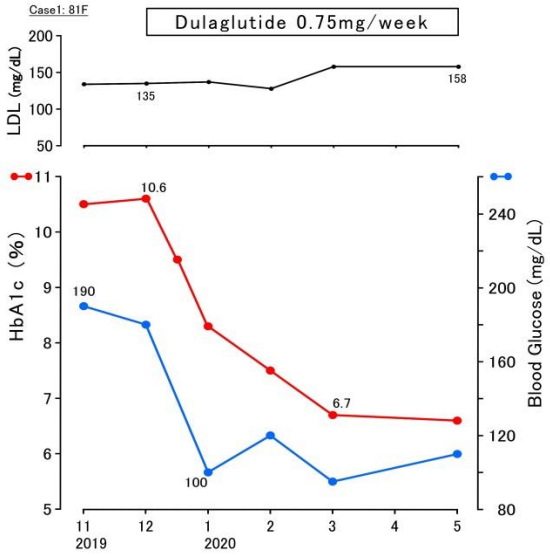
The case was 81-year-old female patient with the diabetic duration of 1 year. She had fatty liver and right total hip arthroplasty in 2014, followed by sometimes complaining of right ankle pain and right calf swelling. She received the operations of intraocular lens and has continuing eye drops, because of bilateral cataract, glaucoma, conjunctivitis and dry eye after 2015 until now. She was diagnosed with left peripheral facial nerve palsy and started rehabilitation and oral medication in 2018. After that, she was pointed out to have T2DM for annual health check-up in autumn, 2019. Then, she was provided metformin 500 mg, and glimepiride 1mg per day as OHA before dulaglutide administration.

Physicals and Labs

She has unremarkable findings for consciousness, vitals, and physical exams. She did not show progressed retinopathy or nephropathy, but slight neuropathy in the hands and feet. Her physique showed 156.9cm in height, 59.0kg in weight, Body Mass Index (BMI) 24.0 kg/m^2. Laboratory tests showed as follows: The fundamental peripheral blood and biochemical data were: WBC 5600/μL, RBC 4.44 x 10^6/μL, Hb 13.9 g/dL, Plt 15.2 x 10^4/μL, AST 36 IU/mL, ALT 63 IU/mL, r-GTP 120 U/L, BUN 28 mg/dL, Cre 0.7 mg/dL, Uric Acid 5.3 mg/dL, eGFR 63.2 ml/min/1.73m^2, HDL 66 mg/dL, LDL 135 mg/dL, TG 150 mg/dL, CPK 150 U/L (45-163). Data related diabetes were HbA1c 10.6%, pre-prandial glucose 190 mg/dL. Urine analysis revealed protein 15 mg/dL, 0.1g/dL for glucose and negative for occult blood and ketone bodies. Other exams showed unremarkable for ECG and chest X-P, age-related changes in head CT scan, old inflammatory changes in lung CT scan and fatty liver findings in abdominal CT scan.

Clinical Progress

The case with T2DM was provided Metformin 1000mg/day, Glimepiride 1mg/day as OHAs. However, her glycemic control was not satisfactory. Then she was started to be given Dulaglutide 0.75mg once a week by injection from December, 2019 as an add-on therapy for diabetes. After that, her glycemic variability showed remarkable improvement. Three months later, her HbA1c and fasting blood glucose was 6.7% and 95 mg/dL (**Figure 1**). As for clinical symptoms, she had no complaints concerning diabetes before and after Dulaglutide treatment. As regards to lipids, values of HDL-C and Triglyceride did not change significantly. In contrast, LDL-C showed a little elevated tendency by the administration of Dulaglutide. The treatment other than Dulaglutide was not changed. Currently, she has been on Metformin, Glimepiride, Fexofenadine 120mg/day and Dulaglutide 0.75mg/week. The treatment has been the same as before, with the addition of Dulaglutide.



Note: Upper: the changes in LDL, lower: the changes in HbA1c and blood glucose

Figure 1: Clinical progress of Case 1 (81F).

Case 2

Present History

The case was 83-year-old male patient. He was diagnosed as T2DM at the age of 56 years old, and treated for 27 years. Successively, he has suffered from arteriosclerotic diseases, including hypertension, hyperlipidemia and angina pectoris for years from 56 to 74 years old (2010). From 2011, he had various medical health problems, such as Gastroesophageal Reflux Disease (GERD) with lansoprazole, diabetic simple retinopathy, iron-deficiency anemia with dried ferrous sulfate, constipation with magnesium oxide and pneumonia during winter. Successively, diabetic control has not been satisfactory with HbA1c around 9% for last 1-2 years. He has been transferred to our hospital in May, 2019.

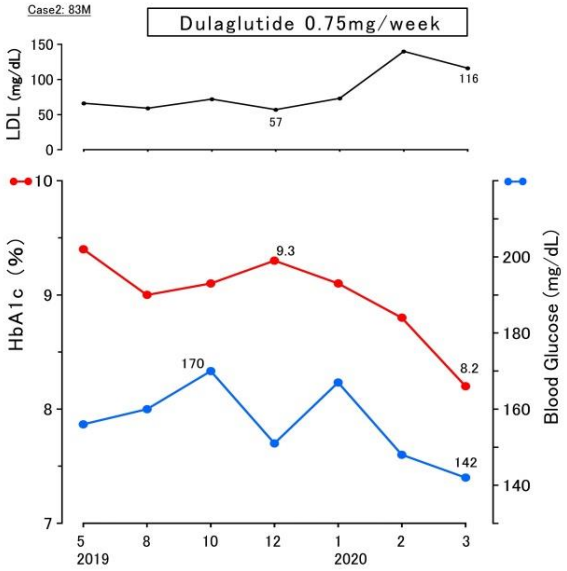
Physicals and Labs

He showed unremarkable findings for consciousness, vitals, lung, heart, abdomen and extremities. He showed a little numbness in the hands and feet. His physique showed 165.0 cm in height, 65.2 kg in weight, Body Mass Index (BMI) 23.9 kg/m^2. Blood tests including complete blood count and biochemistry were in the following: WBC 6500/μL, RBC 5.03 x 10^6/μL, Hb 13.7 g/dL, Plt 27.1 x 10^4/μL, TP 7.1 g/dL, Alb 4.5 g/dL, AST 16 IU/mL, ALT 11 IU/mL, r-GTP 22 U/L, BUN 18 mg/dL, Cre 0.8 mg/dL, Uric Acid 4.7 mg/dL, eGFR 69.9 ml/min/1.73m^2, HDL 81 mg/dL, LDL 66 mg/dL, TG 57 mg/dL, CPK 86 U/L (62-287). Data related diabetes were HbA1c 9.4%, pre-prandial glucose 156 mg/dL. Urinalysis revealed 30 mg/dL of protein, 1.0g of glucose g/dL, +/- of ketone bodies, negative occult blood, 0.1 mg/dl of

urobilinogen and pH of 5.0. He had unremarkable findings for ECG and chest X-P, prostate hypertrophy and colon diverticulum in abdominal CT scan.

Clinical Progress

He was provided pharmacotherapy for diabetes using OHAs. The HbA1c value persisted around 9.0%-9.4%, then he was started to be given Dulaglutide 0.75 mg once a week from December, 2019 as an add-on therapy for diabetes. After that, his HbA1c level decreased to 8.2% in March 2020 (**Figure 2**). As regards to lipid profile, LDL-C value showed increased tendency in 2-3 months, whereas HDL-C and TG showed no changes. As for clinical symptoms, he had not shown diabetic complaints before and after the administration of dulaglutide. His current medication has included Metformin 1000mg, Glimepiride 1mg, Ipragliflozin 50mg, Valsartan 80mg, rosuvastatin 2.5mg, rabeprazole 10mg and magnesium oxide 990mg per day. These medications were not changed for several months.



Note: Upper: the changes in LDL, lower: the changes in HbA1c and blood glucose

Figure 2: Clinical progress of Case 2 (83M).

Discussion

Recent developments of diabetic research and practice include the presence of Intestine Secretion Insulin (INCRETIN). Among them, Gastric Inhibitory Polypeptide (GIP) was identified by the purification of intestinal hormone and, Glucagon-Like Peptide-1 (GLP-1) with the incretin action was introduced. Successively, lots of investigations revealed the mechanism of GLP-1, and its physiological role includes various clinical functions. They are stimulating insulin secretion, inhibiting glucagon secretion, increasing glucose production and glucose uptake in the liver, reducing food intake through delay of gastric emptying and central nerve system. These developments have brought Glucagon-Like Peptide-1 Receptor Analogue (GLP-1 RA) and also Dipeptidyl Peptidase-4 Inhibitor (DPP-4i) into clinical practice for diabetic treatment. In particular, GLP-1 RA has been used for effective Anti-Hyperglycemic Agent (AHA), associated with lower risk of reverse effects and some weight reduction expected. There are a few kinds of GLP-1 RA introduced so far, with satisfactory efficacy [21-24].

Among several GLP-1RA, dulaglutide has been effective and useful for its one a week administration. As to add-on therapy for diabetic patients of poorly controlled OHA, comparison of Dulaglutide once-week and glargine once-day were investigated. T2DM (n=25) were randomly assigned into Dulaglutide and glargine groups and treated 52 weeks. From the studies of Continuous Glucose Monitoring (CGM) in both groups, they showed similar results of Mean Blood Glucose (MBG), Mean Amplitude of Glycemic Excursion (MAGE) and Standard Deviation of Blood Glucose (SDBG). These results suggested equivalent clinical efficacy for glucose variability [25].

Subcutaneous dulaglutide (Trulicity®) has been recognized as a GLP-1 RA, which has shown clinical efficacy for patients with T2DM for monotherapy or add-on therapy to other OHAs. Especially, it shows effects for high-risk patients, such as elderly, obese, those with Chronic Kidney Disease (CKD) as stage 3 or 4 and/or Atherosclerotic Cardiovascular Disease (ASCVD). It shows the effect of significant risk reduction for Major Adverse Cardiac Event (MACE), which includes nonfatal stroke, nonfatal myocardial infarction and primary composite outcome comprising CV death. As add-on therapy to Oral Hypoglycemic Agents (OHAs), there have been a series of AWARD studies, which stands for Assessment of Weekly Administration of LY2189265 in Diabetes. They include the add-on therapy to SGLT2 inhibitors, insulin glargine, glimepiride and others [26-29].

The add-on therapy of Dulaglutide has been used and investigated. There were several studies on phase 2 and phase 3 including cardiovascular meta-analysis, such as AWARD 1,2,3,4,5. Among them, AWARD 2 was based on the add-on therapy for Metformin and Glimepiride. Its protocol included 810 patients randomized to 3 groups, which were dulaglutide 1.5 mg, dulaglutide 0.75 mg, or glargine for 78 weeks. Baseline HbA1c (mean ± SE) was 8.1%, and HbA1c change at 52 weeks was-1.08 ± 0.06%, -0.76 ± 0.06%-1.08% and-0.63 ± 0.06% in 3 groups, respectively [30,31].

AWARD had 5 post-hoc, pooled analysis studies for dulaglutide administration weekly, in AWARD 1,2,3,5,6. Among them, dulaglutide 1.5mg was added to OHA. T2DM patients (n=1424) were investigated lipids changes for 6 months after dulaglutide therapy. There were no significant changes in HDL-C and triglycerides, but significant decrease of LDL-C as (-0.11 mmol/L [-4.2%], p=0.002). Furthermore, cases with higher baseline of lipids tended to show larger reduction in respective indices [32].

In this study, two elderly T2DM patients showed improved HbA1c values by the administration of dulaglutide. It is also noteworthy that changes in LDL were found to be higher than the previous values in the lipid profile. Therefore, the influence of dulaglutide for lipids will be described.

In previous report, dulaglutide therapy for 26 weeks brought significant decrease of LDL-C with no significant change in HDL-C. Such effects seem to be mediated by the alterations in the expression of genes and proteins, which are involved in lipid metabolism. In particular, the expression change of Adipocyte complement-related protein of 30 kDa (Acrp30) may be influenced. Acrp30 has a role of regulation for glucose and lipid homeostasis from several studies. The expression and serum levels of Acrp30 are reduced in patients with obesity and insulin resistance [33-35].

There was another recent report as to the lipid changes for administration of dulaglutide. The protocol was to switching therapy from sitagliptin 50 mg daily to dulaglutide 0.75mg weekly in T2DM patients. Clinical efficacy was observed in decreased HbA1c from 7.80% to 7.25% for 24 weeks. Further, the degree of decreased HbA1c (delta HbA1c) showed significant correlation with baseline HbA1c, fasting plasma glucose and Body Mass Index (BMI). Simultaneously, lipids profile was investigated. As a result, LDL-C was significantly decreased from 90.0 mg/dL to 78.6 mg/dL (p=0.0010), and HDL-C and TG showed no significant changes [36].

Among these, the correlation between the previous LDL value and decreased value of LDL (delta-LDL) shows a significant correlation. In other words, as the pre-LDL is higher, delta LDL becomes higher. Similarly, as the pre-LDL is lower, delta LDL becomes lower and/or becomes minus value. There are actual data of delta-LDL after Dulaglutide therapy. The results were that i) 6 cases (pre-LDL<70 mg/dL) showed increased LDL-C in all cases, ii) 21 cases (71 mg/dL<pre-LDL<100 mg/dL) showed increased LDL for 6 cases, and decreased LDL for 15 cases, iii) 6 cases (pre-LDL>101 mg/dL) showed decreased LDL-C in all cases. For the correlations of delta-LDL, significant correlation was found between delta-LDL and previous LDL (p=0.0012), but no significant correlation was found between delta-LDL and TG, AST, or ALT. These results suggest that lipid metabolism would be modified by the administration of Dulaglutide [36].

In this study, two subjects were elderly patients who were 81 and 83 years old. Their eGFR showed 63.2 and 69.9 ml/min/1.73m^2, which were more than 60 ml/min/1.73m^2 and were probably from age-related decline. One of the beneficial points of Dulaglutide would be possible administration to patients with CKD. There was a multicenter, open-label trial done at 99 sites in nine countries, which was AWARD-7 study [37].

Subjects were T2DM with CKD (stage 3-4), which were randomly assigned to three group of dulaglutide 1.5 mg, dulaglutide 0.75 mg, and daily insulin glargine. As a result, once-weekly dulaglutide showed glycemic control with similar degree of insulin glargine, associated with reduced decline in eGFR. Consequently, dulaglutide seems to be safe and effective for glycemic control for 3-4 stage CKD. In this perspective, stage 3 or 4 means that eGFR shows 30-59, 15-29 ml/min/1.73m^2, respectively. Consequently, dulaglutide can be used for patients with impaired renal function.

There are some limitations in this study. Subjects were 2 elderly diabetic patients, who showed improved glucose variability to Dulaglutide with some elevation of LDL values. We cannot suggest the mechanism of Dulaglutide for lipids profile from small numbers of clinical cases, but would investigate other elder cases successively. Furthermore, authors have continued comprehensive medical practice with chronic medical care for years. Each patient has various needs of adequate Post-Acute Care (PAC) and Sub-Acute Care (SAC), then we should deal with each problem from holistic point of view.

In summary, we described two diabetic patients treated by dulaglutide and some discussions concerning to GLP-1RA, lipids profiles and others. Some recommendations for dulaglutide administration may include elderly, subjects with CKD or decreased eGFR for expecting better clinical results. This report would be expected to become a reference for diabetic practice and research in the future.

Ethical Considerations

Current research has been basically conducted in compliance with the ethical principles presented on the Declaration of Helsinki. In addition, there was commentary for the Ethical Guidelines against the Research in the medical field for Human beings and also against the conduction of the Good Clinical Practice (GCP). Regarding the protection of human rights, some ongoing considerations were present. Furthermore, we applied adequately “Ethical Guidelines for Epidemiology Research” for the related guideline. These principles were originated from Japan by the Ministry of Health, Labor and Welfare and also by the Ministry of Education, Culture, Sports, Science and Technology.

As regards to the current subjects, the written informed consents from two patients were obtained. Moreover, we established the ethical committee for the clinical research in the Hakuai Memorial Hospital. The committee had several professional persons including the president, directors of the administration and pharmaceutical departments, the head nurse of the nursing department, and also related experts in the medical and legal specialties. There were fully and satisfactory discussion for the research content and conclusion confirmation that this study would be adequate without any problems and agreed with all participants.

Conflict of Interest

The author declares no conflict of interest. Relationship of related organizations would be explained. Dr. Takehisa has been the top director of HMW group with many hospitals, and a physician of Hakuai Memorial Hospital (HMH) which is one of HMW. Current cases are from HMH where Dr. Bando has been an advisor from diabetic and primary care points of views. Japan LCD Promotion Association (JLCDPA) was established for the development of LCD education by Dr. Ebe, Kyoto, Japan. Dr. Bando is one of the main members of JLCDPA and often gives lectures and advices for various opportunities.

References

1. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, et al. 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. a consensus report by the american diabetes association (ADA) and european association for the study of diabetes (EASD) (2019) Diabetologia 63: 221-228. https://doi.org/10.1007/s00125-019-05039-w
2. Shin JI. Second-line glucose-lowering therapy for type 2 diabetes mellitus (2019) Curr Diab Rep 19: 54. https://doi.org/10.1007/s11892-019-1171-0
3. International Diabetes Federation. IDF clinical practice recommendations for managing type 2 diabetes in primary care. 2017.
4. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of diabetes care (2019) Diabetes Care 4: 103-123.
5. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2020 (2020) Diabetes Care 43: 66-76. https://doi.org/10.2337/dc20-s006
6. Atkins RC. Dr. Atkins' new diet revolution (2002) Harper, United states.
7. Bernstein R. Dr. Bernstein's diabetes solution newly revised and updated (2007) Little Brown and Company, United States.
8. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, et al. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base (2015) Nutrition 31: 1-13. https://doi.org/10.1016/j.nut.2014.06.011
9. Ebe K, Ebe Y, Yokota S, Matsumoto T, Hashimoto M, et al. Low carbohydrate diet (LCD) treated for three cases as diabetic diet therapy (2004) Kyoto Med Associat J 51: 125-129.
10. Bando H, Ebe K, Muneta T, Bando M and Yonei Y. Effect of low carbohydrate diet on type 2 diabetic patients and usefulness of M-value (2017) Diabetes Res Open J 3: 9-16. https://doi.org/10.17140/DROJ-3-130
11. Muneta T, Kagaguchi E, Nagai Y, Matsumoto M, Ebe K, et al. Ketone body elevation in placenta, umbilical cord, newborn and mother in normal delivery (2016) Glycat Stress Res 3: 133-140. https://doi.org/10.24659/gsr.3.3_133
12. International Diabetes Federation.
13. Mauricio D, Alonso N and Gratacòs M. Chronic diabetes complications: the need to move beyond classical concepts (2020) Trends Endocrinol Metab 31: 287-295. https://doi.org/10.1016/j.tem.2020.01.007
14. Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis (2016) JAMA 316: 313-324. http://doi.org/10.1001/jama.2016.9400

15. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5) (2014) Diabetes Care 37: 2149-2158. https://doi.org/10.2337/dc13-2761
16. Weinstock RS, Guerci B, Umpierrez G, Nauck MA, Skrivanek Z, et al. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD5): a randomized, phase III study (2015) Diabetes Obes Metab 17: 849-858. https://doi.org/10.1111/dom.12479
17. Dungan KM, Weitgasser R, Perez Manghi F, Pintilei E, Fahrbach JL, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8) (2016) Diabetes Obes Metab 18: 475-482. https://doi.org/10.1111/dom.12634
18. Shimizu E, Takehisa Y, Bando H, Fujita M, Kusaka Y, et al. Effective SGLT2 inhibitor for patient with type 2 diabetes mellitus (T2DM) and depression (2020) Diab Res 2: 26-32. https://doi.org/10.36502/2020/droa.6160
19. Nishikori Y, Bando H, Yoshioka A, Fujita M, Kusaka Y, et al. Trials of Additional Effective Movements for Music Therapy Session for the Elderly (2020) Curr Res Complement Altern Med 4: 138.
20. Heisei Medical Welfare (HMW) group.
21. Kreymann B, Williams G, Ghatei MA and Bloom SR. Glucagon-like peptide-1 7-36: a physiological incretin in man (1987) Lancet 330:1300-1304. https://doi.org/10.1016/s0140-6736(87)91194-9
22. Smith EP, An Z, Wagner C, Lewis AG, Cohen EB, et al. The role of β cell glucagon-like peptide-1 signaling in glucose regulation and response to diabetes drugs (2014) Cell Metab 19: 1050-1057. https://doi.org/10.1016/j.cmet.2014.04.005
23. Gurung T, Shyangdan DS, O'Hare JP, Waugh N. A novel, long-acting glucagon-like peptide receptor-agonist: dulaglutide (2015) Diabetes Metab Syndr Obes 10: 363-386. https://doi.org/10.2147/dmso.s34418
24. Hedrington MS and Davis SN. Oral semaglutide for the treatment of type 2 diabetes (2019) Expert Opinion Pharmaco 20: 133-141. https://doi.org/10.1080/14656566.2018.1552258
25. Wang J, Li HQ, Xu XH, Kong XC, Sun R, et al. The effects of once-weekly dulaglutide and insulin glargine on glucose fluctuation in poorly oral-antidiabetic controlled patients with type 2 diabetes mellitus (2019) Biomed Res Int 2019: 2682657. https://doi.org/10.1155/2019/2682657
26. Scott LJ. Dulaglutide: A Review in Type 2 Diabetes (2020) Drugs 80: 197-208. https://doi.org/10.1007/s40265-020-01260-9
27. Ludvik B, Frias JP, Tinahones FJ, Wainstein J, Jiang H, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial (2018) Lancet Diabetes Endocrin 6: 370-381. https://doi.org/10.1016/s2213-8587(18)30023-8
28. Pozzilli P, Norwood P, Jodar E, Davies MJ, Ivanyi T, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9) (2017) Diabetes Obes Metab 19: 1024-1031. https://doi.org/10.1111/dom.12937
29. Dungan KM, Weitgasser R, Perez Manghi F, Pintilei E, Fahrbach JL, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8) (2016) Diabetes Obes Metab 18: 475-482. https://doi.org/10.1111/dom.12634
30. Weinstock RS, Guerci B, Umpierrez G, Nauck MA, Skrivanek Z, et al. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study (2015) Diabetes Obes Metab 17: 849-858. https://doi.org/10.1111/dom.12479
31. Giorgino F, Benroubi M, Sun JH, Zimmermann AG and Pechtner V. Efficacy and safety of once-weekly dulaglutide vs. insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2) (2015) Diabetes Care 38: 2241-2249. https://doi.org/10.2337/dc14-1625
32. Pavo I, García-Pérez LE, Tao Y, Thieu VT, Sattar NA, et al. Changes in lipid concentrations in patients with type 2 diabetes on once-weekly dulaglutide 1.5 mg: Post hoc pooled analysis of the AWARD trials (2018) Diabetologie und Stoffwechsel 13: 54-55. https://doi.org/10.1055/s-0038-1641919
33. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1) (2014) Diabetes Care 37: 2159-2167. https://doi.org/10.2337/dc13-2760
34. Li L, Miao Z, Liu R, Yang M, Liu H, et al. Liraglutide prevents hypoadiponectinemia-induced insulin resistance and alterations of gene expression involved in glucose and lipid metabolism (2011) Mol Med 17: 1168-1178. https://doi.org/10.2119/molmed.2011.00051
35. Tsao TS, Lodish HF and Fruebis J. ACRP30, a new hormone controlling fat and glucose metabolism (2002) European J Pharmacol 440: 213-221. https://doi.org/10.1016/s0014-2999(02)01430-9
36. Iwasaki T, Kessoku T, Higurashi T, Taguri M and Yoneda M. Low body mass index and old age are useful in predicting the hemoglobin A1c-lowering effect of switching from sitagliptin to dulaglutide in Japanese patients with type 2 diabetes mellitus: a single-center, open-label, single-arm, pilot study (2018) Diabetol Intern 9: 189-195. https://doi.org/10.1007/s13340-018-0348-0
37. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial (2018) The Lancet Diabetes Endocrinol 6: 605-617. https://doi.org/10.1016/s2213-8587(18)30104-9