



Remarkable Efficacy of Blood Glucose and Weight by Oral Semaglutide (Rybelsus) For Short Period

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Abstract

Background: Authors and researchers have continued clinical practice and research of diabetes and endocrinology for long. As a glucagon-like peptide 1 receptor agonist (GLP-1RA), oral semaglutide (Rybelsus) was applied to patient with type 2 diabetes (T2D) and investigated.

Case Presentation: Case is 51-year-old male patient with T2D for 8 years. His diabetic control was exacerbated to HbA1c 8.5% in autumn 2021, and then Rybelsus was administered for increasing doses of 3mg, 7mg, and 14mg per day. The results showed improvement of HbA1c 8.5% to 7.1% and weight 96kg to 91kg for 3 months.

Discussion and conclusion: Current remarkable effect may be from the characteristic benefit of Rybelsus. It is provided per os with 50-120 ml of water in the early morning, and after that at least 30 min of fasting time period is required. As fasting time is longer, the Rybelsus concentration in the blood and clinical efficacy become higher. The case has daily habit of no breakfast for long, and fasting time was about 3-4 hours. This situation may be one of the main reasons for remarkable efficacy. Current case will become an impressive reference for clinical effect of Rybelsus in patient with T2D.

Keywords: Glucagon-like peptide 1 receptor agonist (GLP-1RA); Oral semaglutide (Rybelsus); Oral hypoglycemic agents (OHAs); Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC); Japan LCD promotion association (JLCDPA)

Introduction

For practical guideline, Standards of Medical Care in Diabetes-2022 was recently presented from American Diabetes Association (ADA) [1]. Latest diabetic situation has been regularly announced from World Health Organization (WHO) including international situation [2]. Patients with type 2 diabetes (T2D) have been gradually increasing for developed and developing countries [3]. The fundamental methods for diabetic therapy include diet, exercise and medication [4]. Regarding pharmacological treatment, oral hypoglycemic agents (OHAs), insulin and other injectable agents have been used. Authors and researchers have continued clinical reports in the field of diabetes and endocrinology [5]. Among them, our group has proposed low

carbohydrate diet (LCD) and developed Japan LCD promotion association (JLCDPA) for decades [6]. We have also investigated detail situation of continuous glucose monitoring (CGM), meal tolerance test (MTT), analysis for insulin and C-peptide secretory response to carbohydrate intake and others [7]. Moreover, case reports were published including recent anti-diabetic agents of sodium-glucose transporter 2 inhibitor (SGLT2i) and also glucagon-like peptide 1 receptor agonist (GLP-1RA) [8,9]. In the area of diabetes and endocrinology, impressive topic includes clinical application of novel GLP-1RA [10]. It is oral semaglutide with brand name Rybelsus, which has been reported to show clinical usefulness and efficacy [11]. Furthermore, semaglutide has presented clinical effect of reducing body weight for a series of trials [12]. Authors have treated various situation of T2D

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patients. Recently, we have experienced a case who was provided Rybelsus, leading to remarkable improvement of blood glucose control and reduction of body weight. The general progress and some discussion will be described in this article.

Case Presentation

History & Physical

The patient is a 51-year-old male patient with T2D. In 2013, he was diagnosed to have T2D and he has been treated by some kinds of OHAs. The OHAs included metformin 1000mg and Ipragliflozin L-proline 50mg. In autumn 2020, his diabetic control was exacerbated to HbA1c 8.5%. Then, he was started to given dugulotide (Trulicity) 0.75 mg/week. Due to one-week injection, his HbA1c was decreased to 7.2%. However, glucose control became gradually worse (Figure 1).

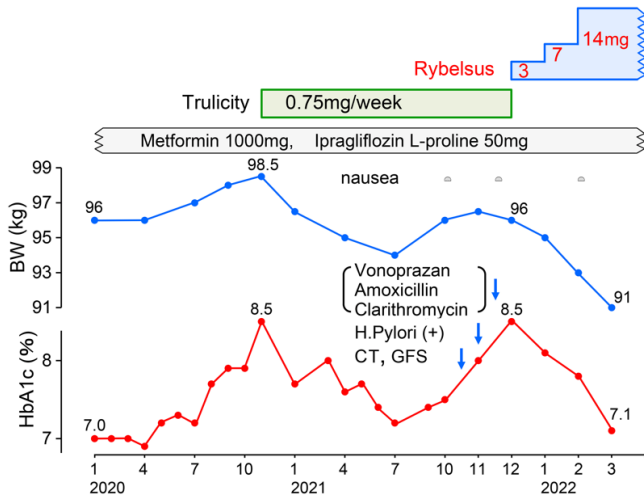


Figure 1: Clinical progress with changes in HbA1c, weight and treatments.

Several exams

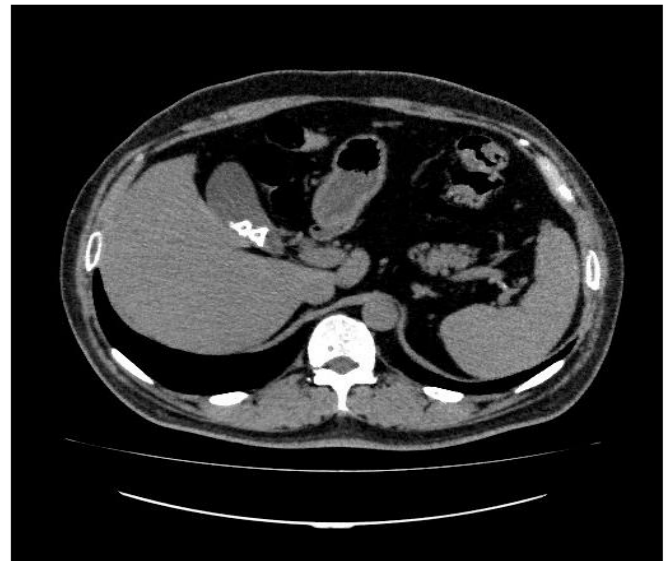
The biochemical results of Oct 2021 were summarized in the following: GOT 22 U/L, GPT 34 U/L, GGT 16 U/L, ChE 277 U/L (213-501), LDL-C 67 mg/dL, TG 211 mg/dL, HDL-C 51 mg/dL, BUN 12 mg/dL, Cr 0.96 mg/dL, eGFR 66 mL/min/1.73m², UA 5.2 mg/dL, RBC 5.34 x 10⁶ /μL, Hb 13.2 g/dL, Ht 43.5 %, MCV 81.5 fL, MCH 25.4 pg, MCHC 30.3 g/dL, WBC 5100 /μL, Plt 17.5 x 10⁴ /μL, serum Fe 29 mcg/dL, TIBC 377 mcg/dL, UIBC 348 mcg/dL, ferritin 13 ng/mL. For several tests for DM, HbA1c 7.5 %, post-prandial blood glucose 225 mg/dL, Urinalysis data were presented as protein (-), glucose (++) , urobilinogen (+/-). Chest X-P was negative for lung and heart, and ECG showed unremarkable. Occult blood in stool was negative twice, and no remarkable findings were observed in colonofiberscopic examination.

Clinical progress

He developed increasing HbA1c and occasional nausea from autumn 2021. He received the examination of abdominal CT scan and gastrofiberscopic examination (Figure 1). The results showed fatty liver, cholecystolithiasis (galls stones), right renal cyst, delayed gastric emptying (DGE), acute gastritis (C-3) with redness (Figure 2a,2b).



Figure 2: Abdominal CT scan.
2a: Fatty liver and slight delayed gastric emptying (DGE).



2b: cholecystolithiasis (gall stones).

Histological study of gastric mucosa showed the presence of Helicobacter pylori (H.Pylori). Then, he was given 7 days of medication for H. Pylori, including Vonoprazan, Amoxicillin and



Clarithromycin. His HbA1c increased to 8.5% in Dec 2021. Consequently, he was changed the diabetic therapy, which was from Trulicity to Rybelsus. The dose of Rybelsus was increased as 3 mg, 7mg and 14 mg for every 4 weeks. HbA1c values decreased from 8.5% to 7.1% for 3 months, associated with weight reduction from 96kg to 91kg. Concerning his symptom, he has noticed nausea in early Oct, mid Nov and early Feb associated with each improvement of 1-2 days.

Medical problems

From general history, examinations and clinical progress, medical problems can be summarized in the following. They are #1 T2D with successful control by Rybelsus, #2 fatty liver, #3 delayed gastric emptying (DGE), #4 gall stones, #5 Gastro Esophageal Reflux Disease (GERD) with treatment for H.Pylori, #6 dyslipidemia for taking medicine rosuvastatin 2.5mg for years, #7 arteriosclerosis for taking medicine of acetylsalicylic acid (Byaspirin) 100mg.

Ethical Considerations

Current investigation has been basically conducted along with the ethical principles of the Declaration of Helsinki. Further, partial commentary was according to the Ethical Guidelines for Research for Humans. It has been associated with Good Clinical Practice (GCP). Authors and collaborators related to this report have established an ethical committee for ethical considerations. It exists in the hospital including several professionals. They are the director, surgeon, physician, head nurse, pharmacist, dietician and legal specialty. We have discussed enough for adequate way, and the agreements were obtained for this study protocol. The informed consent associated with written agreement document were given from the patient.

Discussion

As to recent pharmacological therapy for T2D, several types of GLP-1Ras have been introduced so far [13]. These agents have different properties of duration of effect and molecular weight. There are also differences for providing methods and characteristics [14]. Some categories are present as follows. There are a) liraglutide and lixisenatide injection subcutaneous injection once daily, b) exenatide subcutaneous injection twice daily, c) duraglutide, exenatide and semaglutide subcutaneous injection once weekly, and d) oral semaglutide form that is investigated from the PIONEER studies (Peptide InnOvation for Early diabEtes tReatment). Concerning clinical efficacy of semaglutide, systematic review was found for 9890 patients in 11RCTs [15]. In comparison with liraglutide, empagliflozin and sitagliptin, semaglutide showed the priority of HbA1c decrease for 0.35% and weight decrease for 1.48kg. Moreover, it showed superiority

of all-cause mortality as odds ratio (OR) 0.58 and cardiovascular (CV) mortality as OR 0.55. For cardiovascular outcome trials (CVOTs) with 56004 cases, semaglutide had decreased OR of CV death than 4 GLP-1Ras, including lixisenatide (0.43), albiglutide (0.45), dulaglutide (0.46) and exenatide (0.47) [16].

Among several GLP-1RAs, semaglutide (Rybelsus) has been developed as the first oral agent. Its characteristics is the co-formulation of semaglutide peptide with the novel caprylate of the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) [17,18]. It can overcome the difficult situation for the absorption of the peptide in the acidic circumstance of the stomach. Concerning clinical efficacy of Rybelsus, CV safety was found to be non-inferiority to placebo group, and CV effect for Rybelsus seems to have similarity to that of subcutaneous injection of semaglutide [19]. Such evolution of GLP-1RA for oral intake will bring beneficial treatment for earlier management for many diabetic patients.

Oral semaglutide was applied to current patient with T2D. Clinical efficacy showed decreased HbA1c -1.4% and body weight -5kg for 3 months, which was satisfactory results. Some factors may contribute this improved situation. One is taking Rybelsus situation, when the patient wakes up in the morning [20]. The patient has regular daily life style with no breakfast for years. That is one of the reasons why we decided to give him Rybelsus. As a matter of fact, he has kept fasting about 3-4 hours after intake of Rybelsus every day [20]. Comparison study was conducted for food influence test. Area under the curve (AUC) and maximum concentration (Cmax) were compared between fasting and fed pre-med situation. As a result, AUC and Cmax were about 40% greater in fasting than fed pre-med situation, where P values were 0.082 and 0.080, respectively [21]. Consequently, intake of oral semaglutide in fasting with water 50-120cc and more than 30 minutes post-dose fasting seemed to be relevant in the clinical practice. These conditions for adequate amount were shown in the phase 3 trials. Furthermore, pharmacokinetics of oral semaglutide was investigated for fasting time period. As a result, the ratio AUC was 1.00, 1.98, 2.48, 3.33, and the ratio of Cmax was 1.00, 1.87, 2.30, 3.05, respectively, for 15, 30, 60 and 120 minutes [21].

From mentioned above, current case has longer fasting period after intaking of Rybelsus. Then, remarkable improvement of glucose variability and weight reduction may be found [22]. On the other hand, he showed nausea three times for 1-2 days during the clinical progress. Some adverse effects are reported so far [23]. The first episode of nausea may be from GERD with H. Pylori and/or gall stones. The second nausea may be from combined oral antibiotics treatment for a week. The third nausea was observed on the first day of 14mg of Rybelsus. Then, it may be from the adverse effect. However, the symptom was disappeared only 1 day. Authors asked the patient three possible

management including i) discontinue Rybelsus, ii) decrease the dose from 14 to 7 mg, iii) continue 14mg associated with anti-nausea agent, iv) continue 14 mg without other med. He decided IV) option, because he felt nausea only 1 day, and wants to intake Rybelsus with remarkable effect of -1.4% of HbA1c for 3 months. This case was provided injectable GLP-1RA (Dulaglutide), which showed insufficient clinical effect. Successively, oral GLP-1RA (semaglutide) was started, which showed sufficient efficacy. Thus, several hours fasting time period after intake of Rybelsus may be involved. Consequently, fasting time would be one of the factors that anticipates clinical improvement [24].

Some limitation exists in this report. The patient with T2D is 51 years old and only one case presented. His characteristics include i) usual habit of no breakfast, ii) longer fasting time period after intaking Rybelsus, iii) three times of nausea from possible three reasons, iv) delayed gastric emptying (DGE), v) satisfactory results of decreased HbA1c and weight and vi) no special adverse effect. Future follow up the detail clinical progress will be observed. In summary, T2D patient showed satisfactory clinical efficacy for Rybelsus. Some discussion and perspectives were presented from several points of view. This report will hopefully become a reference data for future practice and research in the diabetology.

Conflict of Interest

The authors declare no conflict of interest.

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