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PUBTEXTO

Early improvement of HbA1c, weight and low-density lipoprotein (LDL) for Type 2 diabetes (T2D) patient by Rybelsus (oral semaglutide)

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Abstract

Background: Latest topic for Type 2 diabetes (T2D) would be oral semaglutide (Rybelsus).
Case presentation: Patient is 74-year-old female with T2D. She showed 65.5 kg (BMI 28.7 kg/m^2) and HbA1c 7.4% in Feb 2022.
Results: She started Rybelsus 3-7mg/day, and then she had clinical effects as 58kg and 6.0% in June 2022, respectively.
Discussion: Rybelsus is characteristic for its clinical efficacy of improvement for glucose variability and body weight. Various data were from Semaglutide Treatment Effect in People with Obesity (STEP) and Peptide Innovation for Early diabetes treatment (PIONEER) studies. This report becomes hopefully useful reference for diabetic research.

Keywords: semaglutide (Rybelsus); Semaglutide Treatment Effect in People with Obesity (STEP); Peptide Innovation for Early diabetes treatment (PIONEER); glucagon-like-peptide 1 receptor agonist (GLP1-RA); sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC)

Introduction

Type 2 Diabetes (T2D) has become a more crucial health problem, and American Diabetes Association (ADA) has recently presented a standard diabetic guideline in Jan 2022 [1]. Regarding the number of T2D cases, it has increased very rapidly in developed and also developing countries [2]. The treatment principle of T2D would be nutrition, exercise and anti-diabetic medicine. For decades, several novel types of agents were introduced to clinical practice [3]. Compared to former situation, glycemic goals may become closer to the ideal levels because of the development of beneficial oral hypoglycemic agents (OHAs) [4].

As to nutritional treatment, calorie restriction (CR) was formerly usual method for diabetes and obesity. However, low carbohydrate diet (LCD) has been proposed for adequate method in Western countries [5,6]. Successively, LCD was developed broadly in Japan by our collaborators [7,8]. Authors have developed practical LCD method such as petite-, standard- and super- LCD methods [9]. We have applied LCD to lot of patients with T2D and obesity associated with high ratio of successful results [10].

For effective treatment for T2D and obesity, recent trends include the novel category of OHA, which is sodium–glucose cotransporter 2 inhibitor (SGLT2i) [11,12]. Another category of beneficial medicine would be glucagon-like-peptide 1 receptor agonist (GLP1-RA) [13,14]. In recent topic, oral type of GLP1-RA was successfully developed after vigorous research for long years, which is oral semaglutide (Rybelsus) [15]. Authors et al. have reported a T2D case treated with Rybelsus that showed remarkable reduction of HbA1c and weight [16]. We have various experiences of T2D patients so far, in which an impressive case was recently found. In this article, general situation and some perspectives would be described.

Case Presentation

History and Physicals

The patient is a 74-year-old Japanese female patient with obesity. She has received regular health check-up annually for 3 years. During 2019-2021, her BMI was 26.9-27.6 kg/m^2, and her HbA1c was 6.3%-6.5%, respectively. Her abdominal circumference was increased from 82cm, 84cm and 86 cm for 3 years. She was advised to reduce body weight, because of refraining from diabetic situation (Figure 1).

She was pointed out to have dyslipidemia as LDL 186 mg/dL in September 2021, and was started to be given Rosuvastatin

2.5mg/day. After 5 months later, she received blood chemistry examination. On February 2020, her physique was 151 cm in height and 65.5kg in weight with BMI 28.7 kg/m^2. Regarding her physical examination, she showed unremarkable consciousness, speech, vitals and neurological findings. Further, her lung, heart and abdomen revealed unremarkable abnormalities.

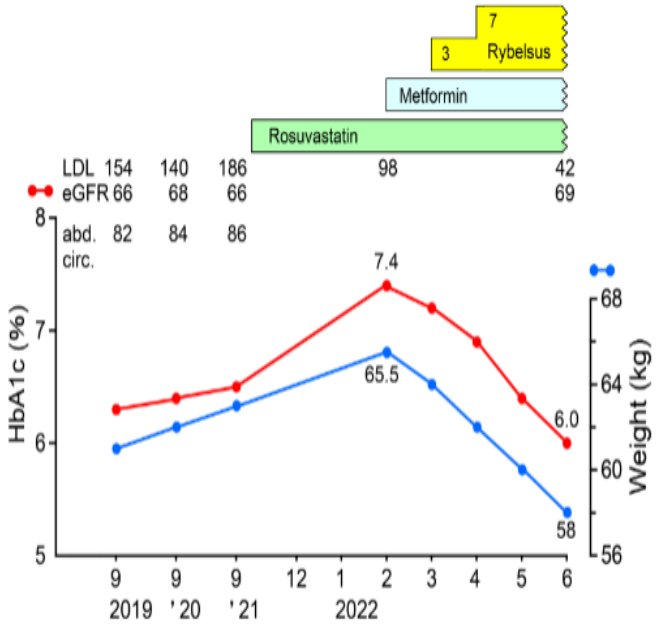

Figure 1: *Clinical progress of the case for a few years.*

Several Examinations

Her blood tests on Feb 2022 were in the following: AST 20 U/L, ALT 22 U/L, r-GT 10 U/L, LDL 48 mg/dL, TG 62 mg/dL, HDL 42 mg/dL, BUN 11 mg/dL, Cr 0.63 mg/dL, uric acid 3.6mg/dL, WBC 5000 /μL, RBC 4.23 x 10^6 /μL, Hb 12.8 g/dL, Ht 39.7 %, MCV 93.9 fL, MCH 30.3 pg, MCHC 32.2 g/dL, Plt 22.5 x 10^4 /μL, post-prandial blood glucose 195 mg/dL and HbA1c 7.4 %.

Other examinations were performed during Sept 2021 to Jan 2022. Chest X-ray showed negative results, and Electrocardiogram (ECG) were within normal limits without ST-T changes. She received the examination for peripheral artery disease (PAD). As a result, ankle brachial index（ABI）revealed 1.10 in right and 1.14 in left. The values of brachial-ankle pulse wave velocity (baPWV) were 1366/1508 for right/left, respectively. Detail result of heart function diagram (mechanocardiogram) and pulse wave chart (sphygmogram, plethysmography) is shown in Figure 2. They revealed normal ranges of % mean arterial pressure (%MAP) and upstroke time (UT).

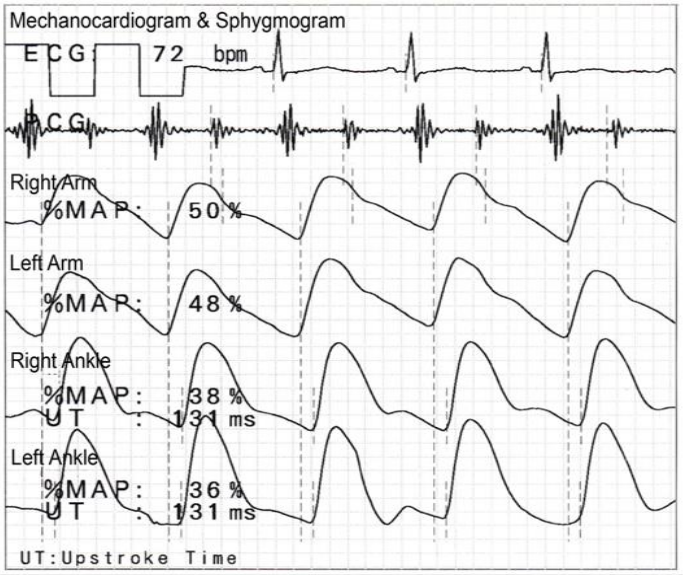

Figure 2*: The result of mechanocardiogram and sphygmogram.*

Clinical progress

The case has received regular health check-up once a year. In Sept 2021, her LDL-C was increased to 186 mg/dL, and then she war started to have rosuvastatin 2.5mg per day (Figure 1). When she checked biochemical examination in February 2022, her HbA1c was increased to 7.4%, and LDL was decreased to 98 mg/dL. She initiated to take metformin 500mg/day. Successively, she was provided oral semaglutide 3mg from Mar 2022, and 7mg from Apr 2022. Consequently, her HbA1c and body weight decreased 7.4% to 6.0%, 65.5kg to 58kg for 4 months, respectively.

Ethical Considerations

This report was basically conducted with ethics principles of the Declaration of Helsinki. Moreover, some commentary was along with the Ethical Guideline for Human Research. They are also consistent with the Good Clinical Practice (GCP). Authors and collaborators have established an ethical committee for the current investigation. The committee exists in the hospital associated with some professional members. They include the president of the hospital, surgeon, physician, pharmacist, dietitian, and legal specialty. For the meeting of the committee, enough discussion was conducted. As a result, fully agreements were provided according to this protocol. The document of the informed consent was taken from the patient.

Discussion

Among various medical agents for obesity, US FDA has so far approved several kinds of agents, such as semaglutide, liraglutide, naltrexone/bupropion, orlistat and phentermine/topiramate [11]. These agents contribute to influence of satiety and appetite to some degree. Among them, semaglutide administration weekly revealed clinical efficacy for obesity patients, in which symptoms of

gastrointestinal adverse events (GIAEs) are found. These results were from investigation from Semaglutide Treatment Effect in People with Obesity (STEP) [13]. In actual medical practice, some types of GLP-1Ras have been found [17]. They include i) once daily: liraglutide and lixenatide subcutaneously, ii) twice per day: exenatide subcutaneously, iii) once weekly: exenatide, duraglutide and semaglutide subcutaneously, iv) oral semaglutide as novel formulation that was due to the trials of Peptide Innovation for Early diabetes treatment (PIONEER) [18].

Among some kinds of GLP-1Ras, first oral agent would be developed as semaglutide (Rybelsus) [15]. It was possible by useful pharmacological technique with the application of absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) [19,20]. Pharmaceutical company Novo Nordisk could solve the difficult problem for peptide absorption from the gastric mucosa [15]. Actually, Rybelsus showed cardiovascular safety and effect, and it was similar to subcutaneous administration [21]. Thus, SNAC will possibly become evolutionary substrate for changing drug delivery system (DDS) drastically [22].

In the current case, 74-year-old female patient showed gradual increase of abdominal circumference, HbA1c and LDL-C for a few years. After rosuvastatin was administered to elevated LDL, the value was reduced in a short period of time with significant clinical effect. It is probably due to the situation that she has never taken any medicine for non-communicable disease (NCD) before and she took the medicine first time with enough sensitivity. Successively, her HbA1c increased rapidly in Feb 2020. Thus, she had the combined medical problems of obesity, diabetes and dyslipidemia. By the treatment of Rybelsus 3mg to 7mg per day, her clinical response was satisfactory without symptoms of gastrointestinal adverse event (GIAE). She can tolerate oral semaglutide well with clinical efficacy for reduction of HbA1c and body weight.

For reference, recent study is present that includes 11 RCTs with 9890 subjects [23]. They showed the superiority of semaglutide for HbA1c and weight for 0.35% and 1.48kg, in comparison with other agents of liraglutide, sitagliptin and empagliflozin. For actual data in average, each decrease was 0.89% and 2.99kg, respectively. Furthermore, these superiorities were calculated as odds ratio (OR). They showed 0.58 for all-cause mortality, 0.55 for cardiovascular (CV) mortality. There was another report with 56 thousand subjects from 7 CV outcome trials (CVOTs). As a result, semaglutide showed lower OR of less CV death as lixisenatide 0.43, albiglutide 0.45, dulaglutide 0.46 and exenatide 0.47 [24].

Some reports are found concerning the relationship with oral semaglutide and LDL-C. The efficacy of Rybelsus on lipid metabolism for T2D was investigated [25]. It was randomized, double-blind, crossover and single-centre trial, and 15 T2D case was enrolled. Fasting values of very low-density lipoprotein (VLDL) and triglycerides (TG) were significant lower in oral Rybelsus group vs placebo group, which was 20% vs 19%, respectively. Regarding effects of semaglutide on CV risk, combined analysis of SUSTAIN and PIONEER was investigated [26]. Hazard ratio (HR) for some factors could be compared with Semaglutide vs comparators groups. Among them, 3 risk group (low-5%, middle-50%, high-95%) showed HR as 0.45, 0.62, 0.84. In the group of middle CV risk, semaglutide vs comparator showed the following: Age 66 vs 67 years, eGFR 91.7 vs 94.1 mL/min/1.73m^2, systolic BP 137 vs 163 mmHg, HbA1c 7.2 vs 10.3% and LDL 3.2 vs 3.9 mmol/L (124 vs 151 mg/dL). Consequently, semaglutide could decrease the risk of MACE for broad T2D population [26]. As to anti-atherosclerotic efficacy of oral semaglutide, the first study will be start for emphasizing on CVD prevention [27]. The trial will be named as "Semaglutide Anti-atherosclerotic Mechanisms of Action Study (SAMAS)." For the protocol, outcome factors include carotid intima-media thickness, endothelial function, arterial stiffness, small dense LDL, HbA1c and high sensitivity C-reactive protein (hsCRP).

Some limitation may be present in this report. It is only one patient with T2D showing remarkable efficacy for the reduction of HbA1c and weight, associated with no GIAEs. The case would be naïve onset for T2D, and then the response for Rybelsus seems to be satisfactory. Successive clinical progress will be carefully followed up.

In summary, elderly female showed significant improvement of HbA1c and weight reduction by oral semaglutide (Rybelsus). It is expected that various factors related to this case will become useful reference for diabetic clinical practice and research.

Conflict Of Interest

The authors declare no conflict of interest

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