

# Acute Improvement of Glucose Variability by Oral Semaglutide (Rybelsus) and Low Carbohydrate Diet (LCD) In Type 2 Diabetes (T2D) Patient with Ophthalmic Operation

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## Article Info

### Article History:

**Received:** 31 July 2022

**Accepted:** 06 August 2022

**Published:** 08 August 2022

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## Abstract

**Background:** Oral semaglutide (Rybelsus) has been in focus as glucagon-like-peptide 1 receptor agonist (GLP1-RA).

**Case presentation:** Patient is 40-year-old male with diagnosed as type 2 diabetes (T2D). He complained of blurred vision in April 2022, and showed HbA1c 12.0%. He was transferred to university hospital for ophthalmic operation of proliferative vitreoretinopathy and our clinic for diabetic control. He was initiated Rybelsus 3mg/day and super-low carbohydrate diet (LCD) associated with normalized glucose profile in short period.

**Discussion:** This case showed satisfactory clinical efficacy for HbA1c 8.7% and 6.6% in 4 and 8 weeks, and weight reduction 6kg for 3 months.

**Keywords:** Super-Low Carbohydrate Diet (LCD); Oral Semaglutide (Rybelsus); Glucagon-Like-Peptide 1 Receptor Agonist (GLP1-RA); Sodium N-(8-[2-hydroxybenzoyl] amino) Caprylate (SNAC)

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## Introduction

In recent years, several kinds of oral hypoglycemic agents (OHAs) have been observed. Among them, Glucagon-like peptide-1 receptor agonist (GLP-1RA) is evaluated to be beneficial agent for type 2 diabetes (T2D), obesity, chronic kidney disease (CKD). For further developmental research of semaglutide, oral type of semaglutide as Rybelsus was produced [1]. It shows almost same clinical efficacy compared with injection type of semaglutide [2]. Rybelsus became the first medicine of oral possible agent once per day. It was already approved by United States Food and Drug Administration (FDA), which has been gradually prevalent in medical practice.

From pharmacological point of view, research for peptide administration via per os has been challenging for long [3]. For successful development of drug delivery technology by Novo Nordisk, oral semaglutide (Rybelsus) was approved by FDA, PmDA and EMA [4]. Basic investigation and applied clinical research have brought useful clinical studies of Peptide InnOvation for Early diabEtes tReatment (PIONEER) [5].

The recommended standard clinical management for diabetes mellitus has been presented by International Diabetes Federation (IDF) and American Diabetes Association (ADA). ADA announced latest guideline in 2022 [6]. Among latest pharmacological information, GLP-1RA and sodium-glucose cotransporter 2 inhibitor (SGLT2i) are included for effective agents

for diabetes [7]. In the light of actual clinical practice, Rybelsus is evaluated to be useful daily treatment, because it can be taken by oral route [8]. Authors' diabetic team have managed various patients so far, and presented some reports concerning oral semaglutide [9]. From our recent practice, we experienced an impressive case with T2D treated with Rybelsus. The general outline and some perspectives are described in this article.

## Case Presentation

### History and Physicals

The patient is a 40-year-old male with T2D. When he was 20s, his body weight was 108kg with body mass index (BMI) 35.2 kg/m<sup>2</sup>. He was diagnosed as T2D at the age of 30. He had OHAs a few years, but discontinued taking medicine. He did not remember the values of HbA1c at that time. During his 30s, he has not developed remarkable health trouble or problems. When he became 40 years, he has noticed blurred vision from early April 2022. Then, he visited ophthalmologist in late April and was diagnosed as bilateral diabetic proliferative vitreoretinopathy as well as left vitreous hemorrhage. The ophthalmologist in charge has introduced him to university ophthalmology department, and also to our diabetic department ASAP for urgent glucose control (Figure 1).

His physicals on first contact in early May 2022 were as follows: consciousness alert and speech is normal, vitals are pulse 68, BP 138/ 84 mmHg, BT 36.5, respiration normal, SpO<sub>2</sub> 99%, lung

vesicular no rale, heart regular rate rhythm, abdomen is soft and flat. Neurological exams were normoactive. His physique showed 175.1cm, 73.6kg, BMI 24.0 kg/m<sup>2</sup>, abdominal circumference 91.0 cm.

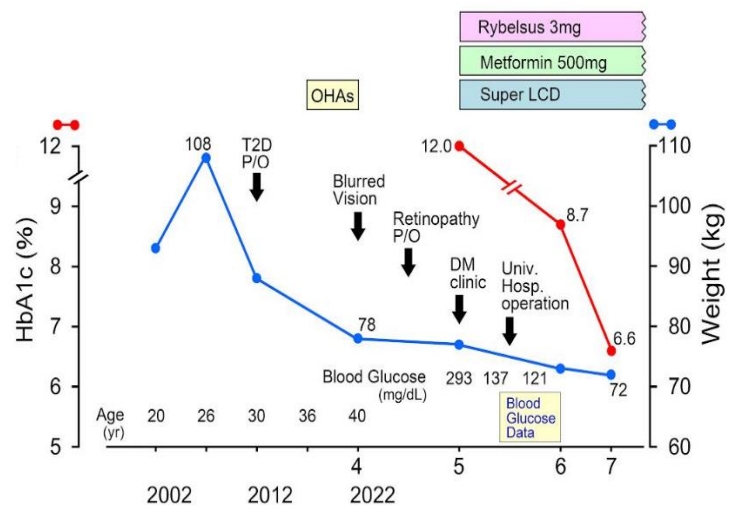
In early May 2022, a referral letter arrived from the ophthalmology department of university hospital. The basic situation is RV = 0.1 (1.5 x S -3.25D: C -0.50D A x 30), LV = 10cm / n.d. (n.c.). Proliferative vitreoretinopathy was observed in the left eye, which is complicated by vitreous hemorrhage. Vitrectomy will be planned as early period as possible. For the right eye, treatment for panretinal photocoagulation has already begun. Since the glycemic control of diabetes has not been achieved for many years, good glycemic control is required at an early stage.

### Several Examinations

The results of blood exams in April-June 2022 were as follows: AST 26 U/L, ALT 28 U/L,  $\gamma$ -GT 62 U/L (-79), ALP 84 U/L (38-113), TG 201 mg/dL, LDL-C 157 mg/dL, HDL-C 44 mg/dL, non-HDL-C 209 mg/dL, Cr 0.46 mg/dL, UA 7.1 mg/dL, WBC 4720 / $\mu$ L, RBC 4.71 x 10<sup>6</sup> / $\mu$ L, Hb 13.5 g/dL, Ht 40.8 %, MCV 86.6 fL, MCH 28.6 pg, MCHC 30.2 g/dL, PSA 0.76 ng/mL (-4.0). Other tests were conducted during April-June 2022. Urinalysis in June showed protein (+), occult blood (+/-), sugar (-) WBC (-), ketone bodies (++) . Occult blood in stool was negative twice. Chest X-ray showed no remarkable changes and Electrocardiogram (ECG) was within normal limits. Upper endoscopic examination showed negative results in stomach and duodenum.

### Clinical Progress

This case showed the exacerbation of T2D associated with proliferative diabetic retinopathy. The ophthalmology department of university hospital asked the author to provide urgent diabetic control such as using insulin treatment. The author has interviewed the patient carefully in detail, and judged that this case can understand and conduct super-low carbohydrate diet (LCD) perfectly. Then, this case started super-LCD and intake of oral semaglutide (Rybelsus) 3mg/day at once. Once week later, post-prandial blood glucose decreased from 293 mg/dL to 137 mg/dL, which was satisfactory progress (Figure 1). In middle May, he was admitted to the ophthalmology department of the university hospital. He was provided the operation for vitrectomy and photocoagulation successfully. As regard to blood glucose control, the daily profile of glucose data was summarized in (Table 1). Among these glucose data, 1-hour post-prandial glucose after breakfast kept around 130-140 mg/dL. The reason was that he did not take rice in the breakfast. Furthermore, 2-hour post-prandial glucose after supper kept around 140-180 mg/dL. He continued refraining from taking carbohydrate in his daily life. His body weight was 78kg in early April, and 72 kg in early July.



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

**Table 1:** Progress of blood glucose during pre- and post-operation.

Month	Date	breakfast post-prandial 60 min	daytime post-prandial	supper post-prandial 120 min	Hospitals Author or University
May	10		137		Author
	19	138		141	University
	20	140		134	"
	21	158		163	Eye Ope
	22	130		179	University
	23	131		194	"
	25	130		144	"
	27	121		200	"
June	2		121		Author

### Ethical Considerations

Current investigation has been conducted along with the ethical principles of the Declaration of Helsinki. In addition, some comments were consistent with the Ethical Guideline for Human Research and also the concept of the Good Clinical Practice (GCP). Authors and collaborators have set up our ethical committee concerning the case report. The committee exists in the hospital with some professionals. They include hospital director, physician in charge, pharmacist, dietitian, and legal specialty. During the meeting satisfactory discussion was conducted. Consequently, agreement was given as regard to the protocol. The informed consent was obtained from the patient.

### Discussion

For recent actual diabetic treatment, several types of GLP-1RA have been applied according to the situation of the patients [10]. The novel diabetic agent, oral semaglutide was developed by continuous research for 30 years [11]. For its important point, it could be synthesized using sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) that was an absorption enhancer [12]. As

this peptide was able to give through oral route, it will become the cornerstone for drug delivery system [13]. Moreover, the clinical efficacy of Rybelsus includes beneficial influence of cardiovascular aspect as well as diabetic effect [14]. Consequently, this pharmacological evolution will bring further development in the field of peptide research [15].

Current case showed remarkable weight elevation to 108kg at the age of 26 years. When he was 30 years old, his weight was 88kg and he was diagnosed as T2D. Significant weight gain from 20 years of age has been known to increase diabetes onset. Investigation of the relationship of weight gain from early adulthood and the presence of nephropathy in diabetic patients [16]. The protocol included 471 consecutive T2D cases and the changed degree compared with lifetime max weight and weight at 20 years ( $\Delta$ -BW-max-20y). This marker showed significant correlation with the degree of urinary albumin excretion (UAE). In order to predict the risk of diabetes, computational system was designed using multifarious physical examination [17]. The data was from 1.5 million diabetics and 0.39 million healthy people. A model of eXtreme Gradient Boosting (XGBoost) was made, that can distinguish the borderline of area under curve (AUC) of 0.8768.

Determination of the Weighted Decision Matrix (WDM) was conducted and analyzed for several biomarkers [18]. Among them, age and body weight showed closer relationships than height, BMI, sBP, dBP, urinary creatinine excretion. Furthermore, body-weight cycling (fluctuation) was evaluated by the calculation of average successive variability (ASV), which are analyzed with BMI and health-related outcomes [19]. This research was continued by 3678 cases for 16 years. As a result, clear relationship was not detected among ASV, weight and cardiovascular events. For predicting diabetes, various Machine learning (ML) techniques have been found. They include some Deep Learning (DL) algorithms for analyzing lots of factors for diabetes onset. Concerning ML and DL, several latest research for prediction of diabetes have been reported [20]. Such kinds of medical and computerized research will be developed in the future [21].

After this case visited university hospital, the ophthalmology department asked us to start diabetic control ASAP by using insulin. It was suggested that the eye doctor in charge thought indispensable insulin treatment. We interviewed him, and judged that he can continue perfect super-LCD [22]. Then, we decided to provide only LCD, metformin and Rybelsus. Actually, his glucose profile became suddenly normalized in short period. When he was admitted to the university hospital, his post-prandial glucose persisted in normal range (Table 1). Thus, hyperglycemia can be improved ASAP, just after super-LCD was initiated checked by continuous glucose monitoring (CGM) [23]. His HbA1c was initially 12.0%, decreased to 8.7% after 4 weeks, and 6.6% after 8 weeks. His body weight also dropped from 78kg to 72kg. He was

provided metformin and Rybelsus, which did not fall blood glucose below the normal range.

Concerning nutritional therapy, calorie restriction (CR) was previously standard way for obesity and diabetes. After that, LCD method has become adequate method in North American and Western countries [24,25]. Successively, the concept of LCD has been developed and recently accepted worldwide [26]. In Japan, authors and collaborators have initiated and developed LCD for years [27]. We have applied LCD to lots of obesity patients associated with satisfactory clinical efficacy of weight reduction [28].

Several limitations may exist in this report. It is only one case with T2D, ophthalmic operation for proliferative diabetic retinopathy, intake of oral semaglutide and LCD. LCD was effective for normalized blood glucose [29]. By successive continuation of these factors, he showed satisfactory results. However, longer clinical progress will be required for following up some aspects, such as HbA1c, retinopathy, body mass index (BMI), nephropathy and macroangiopathy [30]. In summary, younger male has showed significant improvement of glucose profile, HbA1c and weight reduction by the intake of Rybelsus. This report will be hopefully a reference for future diabetic practice and research.

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