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PUBTEXTO

Significant effect of decreased weight and HbA1c by oral semaglutide (Rybelsus) for Type 2 Diabetes (T2D) patient

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Abstract

Background
Authors et al. have continued clinical diabetic research for years. Oral semaglutide (Rybelsus) has been applied to type 2 diabetes (T2D).

Case Presentation
Case is 53-year-old male T2D patient for 10 years. The HbA1c was increased to 7.2% in January 2023, and then Rybelsus was increased from 7mg to 14mg/day. HbA1c was decreased to 5.8% in Dec 2023 with 9kg weight reduction.

Discussion and conclusion
The blood concentration of semaglutide is determined by the fasting time after taking the drug in the morning. He carefully adjusted fasting time in 15-minute increments to ensure gradually rising its blood concentration.

Keywords: Oral semaglutide (Rybelsus); Type 2 diabetes (T2D); Glucagon-like peptide-1 receptor agonists (GLP-1 RAs); Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC); Gastro-intestinal adverse events (GIAE)

Introduction

Type 2 diabetes (T2D) has been a chronic and progressive disease associated with higher morbidity and death rates [1]. As a recent treatment for T2D, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are in focus and are widely applied to various aspects of T2D management. They include adequate glucose variability, weight reduction, decreased cardiovascular risk, and protection of renal function [2]. Among them, semaglutide is a well-established therapeutic measure with a remarkable effect on achieving clinically valuable goals. Oral semaglutide (Rybelsus®) has been a combination of semaglutide and sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), which is known as an absorption enhancer, helping the absorption of semaglutide through the gastric epithelium to a concentration-dependent degree.

Concerning the standard therapy for T2D, the American Diabetes Association (ADA) announced the guidelines for treating diabetes in 2023. Both the European Association for the Study of Diabetes (EASD) and the ADA presented a consensus report that indicated the importance of holistic management for T2D therapy. It emphasizes the applicable weight reduction control for improving clinical outcomes. Out of them, novel semaglutide has been evaluated for its very high effect on weight reduction and glucose-lowering results in recent T2D therapeutic measures [3]. Furthermore, the latest matter would be the clinical efficacy of semaglutide for obesity that is not T2D. It is also a social matter and a problem, and people with obesity show this application in some developed countries. A randomized, double-blind, comparative study was conducted for semaglutide and placebo groups for more than 1 year [4]. For both groups, the weight changes were -15.1% vs. -2.4%, and the ratios with weight reduction (>5%) were 85% vs. 26%. Consequently, this medical agent showed actual clinical effects for T2D and obesity, respectively.

Authors and collaborators have continued our diabetic practice and research for a long time, including type 2 diabetes (T2D), type 1 diabetes (T1D), and other types of diabetes such as slowly progressive insulin-dependent diabetes mellitus (SPIDDM) [5]. In the light of adequate nutritional therapy, we have developed useful low-carbohydrate diet (LCD) methods for everyone to apply to their ordinary lives [6]. Our activities have been continued along with those of the Japan LCD Promotion Association (JLCDPA) [7]. The recommended LCD measures include three types of patterns, which are petite-LCD, standard-LCD, and super-LCD [8]. These convenient healthy meal ways have been informed through various reports, books, seminars, and

internet sites [9]. Consequently, LCD has been evaluated as a simple and effective measure in order to provide balanced nutrition, exercise, and pharmacological therapeutics [10].

In our actual practice for various cases of diabetes, we have recently encountered a clinically impressive patient. The case was a 53-year-old male patient with T2D. He showed remarkable clinical efficacy in weight reduction and relieved glucose variability with the increased dose of oral semaglutide (Rybelsus). The general clinical progress and some perspectives are presented in this article.

Case Presentation

History & Physical

The current case is a 53-year-old T2D patient with 10 years of diabetic history. He has been provided with some types of oral hypoglycemic agents (OHAs) so far. The continued OHAs included Metformin, Rosuvastatin, and Ipragliflozin L-proline. His HbA1c had been rather stable until autumn 2021, but increased to 8.4% in December 2021 (Figure 1).

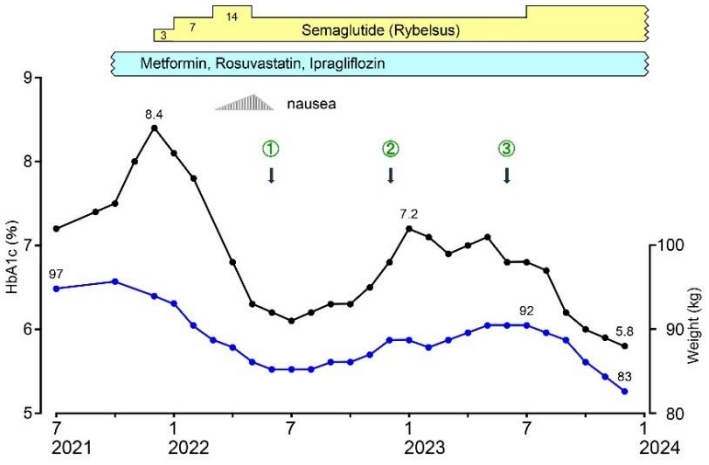

Figure 1: *Clinical progress of the case for years.*

Physical exams in June 2023 showed the following: Consciousness, vitals, and speech were unremarkable. The general status of the head, lung, heart, and abdomen revealed negative findings. His physique condition showed a height of 179 cm, a weight of 93kg, and a BMI of 29.0 kg/m^2.

During a few years, the case showed unremarkable results from laboratory biochemical examinations. It was summarized from June 2022 to June 2023 in Table 1. Furthermore, the chest X-ray revealed negative results for the heart and lung, and the ECG also showed unremarkable findings. Urinalysis findings were urobilinogen (+/-), glucose (++) and protein (-). For the gastrointestinal axis, occult blood in stool showed negative results, and a gastrofiberscopic exam showed unremarkable findings.

Table 1: *Changes in laboratory data for years.*

		1	2	3	Units
		2022	2022	2023	
		Jun	Dec	Jun	
Liver	AST	28	29	21	(U/L)
	ALT	34	41	30	(U/L)
	γGT	12	15	15	(U/L)
Lipids	LDL	45	51	47	(mg/dL)
	TG	137	100	103	(mg/dL)
	HDL	60	55	51	(mg/dL)
Renal	BUN	11	112	11	(mg/dL)
	Cre	0.85	0.96	0.84	(mg/dL)
	UA	4.6	5	5.1	(mg/dL)
CBC	RBC	541	538	522	(x10*4/L)
	Hb	13.5	13.1	13	(g/dL)
	WBC	52	55	54	(x10*2/L)
	PLT	23.2	27.4	22.2	(x10*4/L)
1,2,3: latest three exams, CBC: complete blood count					

As a biomarker of arteriosclerosis, plethysmography has been performed in 2018, 2020, and 2023 (Figure 2). The baPWV level in the right arm was increased from 1332 to 1518 cm/sec for 5 years. The normal range of baPWV is 1400–1800 cm/sec. The

ankle-brachial index (ABI) showed 1.20/1.09 (right/left) in 2023, which was within normal limits.

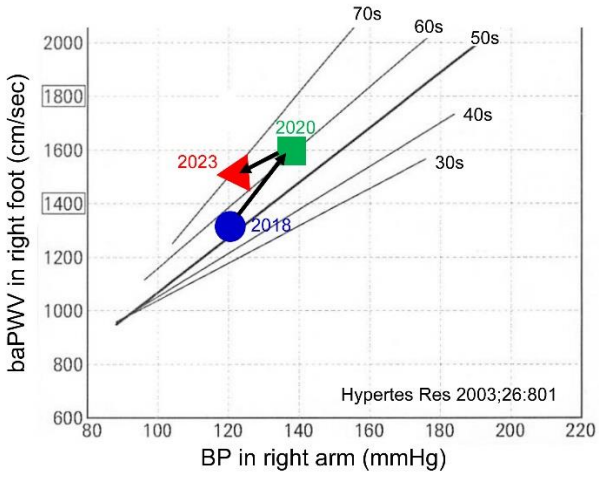

Figure 2: *Result of plethysmography for 5 years*

Clinical Progress

The case started with oral semaglutide (Rybelsus) at 3 mg/day at first. After that, he had an increased dose of 7mg and 14mg for half a year. During this period, HbA1c showed an acute decrease, suggesting a clinical effect. However, he had felt gastro-intestinal adverse effects (GIAE), such as slight nausea and abdominal fullness. Then, he hoped to decrease the dose from 14 mg to 7 mg in June 2022.

By decreasing the dose of semaglutide, his GIAE was relieved, associated with stable clinical progress for about a year. In July 2023, his HbA1c was 7.2%, and his weight was increased to 92kg. After consulting the case about this situation, he decided to change semaglutide to 14mg. As a result, HbA1c decreased to 5.8% with 9kg of weight reduction for half a year, indicating satisfactory clinical efficacy of Rybelsus during such a short period.

Ethical Considerations

The current investigation has been fundamentally conducted in accordance with the Declaration of Helsinki. In addition, some commentary was present according to the Ethical Guidelines for Research for Humans, which was associated with Good Clinical Practice (GCP). The authors et al. have set up an ethical committee for conducting ethical considerations. It was established in our hospital, including some professionals. They are the president, physician, pharmacist, head nurse, nutritionist, and legal specialty personnel. The members discussed in a satisfactory manner and reached agreements for the current protocol. The informed consent was obtained from the case by the written document.

Discussion

Among some types of GLP-1RAs, the first oral agent was developed as semaglutide (Rybelsus) [11]. It has impressive characteristics for the use of the novel caprylate of SNAC [12]. As to the clinical effect of Rybelsus, CV safety showed non-inferiority to the placebo group, and CV efficacy seems to show similarity to the subcutaneous injection route [13]. Thus, historical evolution for oral intake of GLP-1RA can provide satisfactory management for earlier treatment in diabetic cases [14].

As regards oral semaglutide, clinical indications include 3mg, 7 mg, and 14 mg once daily so far. Further investigation has been found for the higher dose methods of 25mg and 50 mg [15]. The randomized, multicenter, phase 3b study was conducted for 177 clinical sites in 14 countries, in which T2D adults (1606 applicants) and screening 2294 people received 3 doses of oral semaglutide. The results showed a mean HbA1c decrease of -1.5% for 14mg, -1.8% for 25mg, and -2.0% for 50mg. GIAE showed a mild-moderate degree, where the frequency was higher for 25mg and 50 mg than that of 14 mg.

In the light of the experimental animal, similar results were observed for oral semaglutide. As 14mg of semaglutide is for humans, 0.23 mg/kg of semaglutide can be applied to high-fat diet-induced obese (DIO) mice [16]. When this dose was given to DIO, it showed a rapid decrease in blood glucose and food intake. It also continuously decreased food intake amount and weight gain for three days for the experiment of DIO mice. When the dose was set at 0.7 mg/kg (42 mg for humans), the effect was observed to a slightly more potent degree. Consequently, the study protocol and result may suggest the DOI as a suitable model for investigating various mechanisms of anti-diabetes and obesity actions for oral semaglutide.

The current case showed some characteristic aspects. First, he showed a remarkable reduction in HbA1c and weight for the early stages of 2022, but he developed GIAE when the doses increased from 7mg to 14mg per day. It seemed to be from the acutely increased blood concentration of Rybelsus [17]. After decreasing the doses, GIAE was relieved shortly. Second, it was the successful management of an increased dose from 7mg to 14 mg in 2023. The clinical effect was remarkable for a decreased HbA1c of 1.4% and a decreased weight of 9kg in a short period of time. During this period, he modified the dosing regimen slightly to avoid GIAEs [18]. In other words, the blood concentration of semaglutide is determined by the fasting time after taking the drug in the morning. Therefore, he carefully adjusted his fasting time in 15-minute increments to ensure that the blood concentration rose slowly. It is thought that this method was clinically effective, with almost no remarkable problems [19]. Third, his arteriosclerosis was not a severe situation according to the results of the plethysmography for the last 5 years. His macroangiopathic and microangiopathic complications will be carefully followed up in the future.

Some limitations are observed in the article. This patient showed clinical effects for a remarkable reduction in HbA1c and body weight. However, not all patients can have such medical efficacy with oral semaglutide. Various factors may be involved, including

diabetic severity, carbohydrate intake amount, exercise status, anti-diabetic agents, and so on.

In summary, the current case revealed a satisfactory effect on glucose variability and weight. Related perspectives were shown in this article. The report is expected to provide a useful reference for future diabetic research.

Conflict of interest: The authors declare no conflict of interest.

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