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Clinically Both Effects of Weight and Glucose Variability by Oral Semaglutide (Rybelsus) for Younger Female Patient with Type 2 Diabetes (T2D)

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Abstract

Background: Obesity and Type 2 Diabetes (T2D) are crucial problems worldwide. Oral semaglutide (Rybelsus) was introduced to medical practice for Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA). **Case presentation:** The patient is 24-year-old female with obesity (BMI 39.3 kg/m2), T2D and fatty liver. **Results:** She started and increased Rybelsus from 3mg, 7mg to 14mg/day each 4 weeks. She showed significant efficacy for 4 months as HbA1c 6.3% to 5.6% and weight 107kg to 103kg, without Gastrointestinal Adverse Events (GIAEs). **Discussion:** Rybelsus is provided just after waking up, and kept >30 min fasting period. Longer fasting time may contribute current effect.

Keywords: Type 2 diabetes, Obesity, Oral semaglutide, Weight.

Abbreviations: T2D-Type 2 diabetes, GIAEs-Gastrointestinal Adverse Events, EMA-European Medicines Agency, CKD-Chronic Kidney Disease, DKD -Diabetic Kidney Disease, MACE-Major Cardiovascular Averse Events, LCD-Low Carbohydrate Diet, MTT-Meal Tolerance Test, CGM- Continuous Glucose Monitoring, OHAs- Oral Hypoglycemic Agents, GERD- Gastro Esophageal Reflux Disease, GCP- Good Clinical Practice, STEP - Semaglutide Treatment Effect in People with Obesity, GLP-1RA-Glucagon-Like Peptide 1 receptor agonist, PIONEER-Peptide Innovation for Early diabetes treatment.

Introduction

Obesity has been one of the crucial problems worldwide, especially for younger generation [1]. It includes broader problems from medical, social, environmental and public health points of view [2]. For younger people, obesity may bring metabolic and cardiovascular impairement which would give grave influence for long life [3]. Consequently, several strategies will be required for the treatment for obesity, including lifestyle intervention, pharmacological treatment and other methods. As recent statistics, 38.2 million children <5 years old are obese or overweight [4]. Formerly, obesity problem was considered the matter of high-income countries, but recently it is found in also low-/middle-income countries. Approximately half children <5 years with obese or overweight have lived in Asian region. For the treatment of pediatric patients with obesity, pharmacotherapeutic agents had not approved by European Medicines Agency (EMA) until 2020. However, EMA has decided to authorize the therapy in April 2021, for the application of Liraglutide as a Glucagon-Like Peptide Receptor Analog (GLP-1RA). Clinical effect and safety were analyzed for 251 cases for a randomized, double-blind trial. As a result, 26.1% of cases showed >10%, and 43.3% cases showed >5% of weight reduction associated clinical effect [3].

As one of GLP-1RA, semaglutide has been also effective for weight reduction and decreased daily profile of blood glucose [5]. It can also show clinical efficacy for delaying stomach emptying and suppressing appetite leading to lose weight. As long-acting GLP-1RA, semaglutide can be applied for two ways, which are injection once-weekly and oral formulation once-daily. Thus, it is only agent of GLP-1RA that can be administered per os [6]. Oral semaglutide intake should be conducted for empty stomach when waking up. Furthermore, it has wide range of beneficial efficacy, including diabetic complication, cardiovascular outcomes, Chronic Kidney Disease (CKD) or Diabetic Kidney Disease (DKD), and non-alcoholic steatohepatitis [7]. Consequently, these clinical mechanisms of semaglutide would possibly extend to other beneficial function and indications. Obesity and Type 2 Diabetes (T2D) are closely correlated, and these combination will cause a variety of diabetic complications. They include impaired function of several organs, such as heart, kidney, nerve and macro-/ micro-angiopathy [8-10]. In recent medical situation of COVID-19 worldwide, the combined situation will become higher risk for patients with obesity and T2D [11,12]. As mentioned above, GLP-1RA has beneficial efficacy on obesity and T2D, by controlling appetite and stomach emptying [13,14]. Furthermore, it shows advantageous effects

for decreasing mortality and Major Cardiovascular Averse Events (MACE) in comparison with other regimens [15].

Authors and collaborators have developed diabetic clinical research especially for Low Carbohydrate Diet (LCD) [16, 17]. Furthermore, various reports were presented such as Continuous Glucose Monitoring (CGM), Meal Tolerance Test (MTT), Sodium-Glucose Transport Protein 2 Inhibitors (SGLT-2i), GLP-1RA and others. Among our medical practice, we have experienced an impressive young female patient with obesity, T2D and fatty liver. By applying oral semaglutide, she showed remarkable clinical efficacy. Her general clinical progress and some related discussion would be described in this article [18-20].

Case Presentation

History and physical: The patient is a 24-year-old female patient with Type 2 diabetes (T2D). She was diagnosed as T2D three years ago. After that she was provided Oral Hypoglycemic Agents (OHAs) and her HbA1c was almost stable 6.5% to 7.2%. The important problem has been obesity for years. When diagnosed as T2D, her body weight was 114kg. After that, she was advised to continue Low Carbohydrate Diet (LCD) and weight was decreased to 110kg. From Jan 2020, her weight has been stable about 107-109kg **(Figure 1)**.

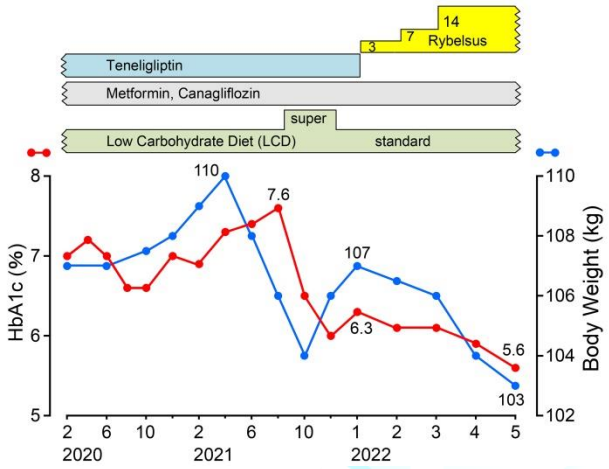

Figure 1: Clinical progress of the case with HbA1c, body weight and treatment.

As to her physical examination on Jan 2022, her physique showed 165cm in height, 107 kg in weight with 39.3 kg/m^2 of Body Mass Index (BMI). The consciousness is alert, speech is normal, and neurological findings were unremarkable. Her lung, heart, abdomen and orthopedic problems are negative.

Several exams: Biochemical laboratory tests were conducted in Feb 2022. The results were as follows: WBC 8300 /μL, RBC 6.02 x 10^6 /μL, Hb 13.0 g/dL, Ht 45.7%, Plt 36.6 x 10^4 /μL, AST 24 U/L, ALT 35 U/L, r-GT 34 U/L (-86), LDL 142 mg/dL, TG 148 mg/dL, HDL 61 mg/dL, BUN 16 mg/dL, Cr 0.50 mg/dL, uric acid 5.3 mg/dL. Other examinations were conducted during 2021-2022. Chest X-P and ECG (Electrocardiogram) were unremarkable. She has continued to reveal abnormal liver function tests, which were followed up every 4 months **(Table 1)**. The data showed the elevation of AST, ALT, g-GTP until June 2021, and they were normalized after Oct 2021.

Medical Problems and Medicine: From previous history and situation, medical problems and related medication can be summarized in the following.

- **T2D:** She has three years of T2D, and has been provided Metformin 1000mg, Canagliflozin 100mg, Teneligliptin Hydrobromide Hydrate 20mg and voglibose 0.2mg per day.
- **Gastro Esophageal Reflux Disease (GERD):** She has slight upper Gastrointestinal (GI) symptoms for years, and then has taken nizatidine 150mg per day.
- **Fatty liver:** She revealed continuous elevated liver function tests including AST, ALT, r-GTP. According to abdominal echography, she had moderate fatty liver. Since she is young, abdominal CT scan was not performed. She did not have special medicine for fatty liver. By continuing LCD, taking Canagliflozin as SGLT2i and diabetic treatment, her liver function was followed up. Her elevated biochemical data was relieved in Oct 2021 (**Table 1**).
- **Obesity:** Three years ago, her body weight was 114kg at the maximum point. At that time, BMI was 41.9 kg/m^2. After that, BMI was decreased to 39.3 kg/m^2 in Jan 2022.

	Year	2020			2021			2022
	Month	2	6	10	2	6	10	2
AST	(U/L)	93	56	119	57	64	25	24
ALT	(U/L)	154	122	179	98	97	39	35
r-GTP	(U/L)	62	72	69	55	67	32	34
LDL-C	(mg/dL)	159	162	162	165	162	131	142
TG	(mg/dL)	91	117	156	102	131	148	148

Table 1: Clinical progress of abnormal liver function test in every 4 months.

Clinical progress: Her body weight and HbA1c were increased in Jan 2022, and then her OHAs were decided to change. She had been provided Teneligliptin for DPP4i, and then changed to oral semaglutide (Rybelsus) 3mg/day as GLP-1RA. After that, Rybelsus was increased to 7mg and 14 mg for each 4 weeks (**Figure 1**). As a result, HbA1c was reduced from 6.3% to 5.6%, and weight was also decreased from 107kg to 103kg for 4 months. Before increasing the dose of Rybelsus, she was informed of the possibility of GIAEs, but she did not feel any GIAEs during the period until 14mg intake per day.

Ethical Considerations: Current report has been basically conducted with principles of ethics. They include the Declaration of Helsinki, and also some commentary from Ethical Guideline from the Research for Human aspect. These contents were along with the Good Clinical Practice (GCP). Authors and collaborators had established hospital ethical committee for arguing several ethical matters. This committee has been present in Kanaiso Hospital including several related professional members. They are hospital director, surgeon, physician, pharmacist, nutritionist and legal specialty. During the meeting of the committee, enough discussion and perspectives were conducted. As a result, agreements were provided according to the current investigation. The informed consent was given with written agreement document from the patient.

Discussion

As to applicable diagnosis and treatment of diabetes, American Diabetes Association (ADA) has presented standard guideline for medical care in Jan 2022 [21]. Recent recommendation for diabetic pharmacological OHAs include SGLT2-i and Glucagon-Like Peptide 1 receptor agonist (GLP-1RA) [22]. For the reason, GLP-1RA shows various beneficial efficacy for metabolic, cardiovascular and renal mechanism. Several types of GLP-1RAs have been prevalent in medical practice [23]. They have some categories as follows [24]: i) subcutaneous injection once a day (liraglutide and lixisenatide), ii) subcutaneous injection two times a day (exenatide), iii) subcutaneous injection once a week (exenatide, duraglutide and semaglutide), and iv) oral semaglutide formulation that was from Peptide Innovation for Early diabetes treatment (PIONEER) trials. As one of GLP-1Ras, semaglutide has been evaluated for various beneficial clinical efficacy [25,26]. Semaglutide includes two kinds of injective administration and

oral formulation [27]. In particular, Rybelsus as an oral semaglutide has been used for actual practice associated with pharmacological beneficial mechanism [28]. In addition, it shows benefits for significant improvement of glucose control and reduction of body weight [29]. Authors and our diabetic team have reported various diabetic patients treated with effective agents [30,31]. Among them, we have presented a recent report of a case with remarkable efficacy of Rybelsus [20].

Rybelsus shows clinical effect of weight reduction. Concerning anti-obesity agents, FDA of US approved some kinds of medicines, such as semaglutide and liraglutide, as well as orlistat, naltrexone/bupropion and phentermine/topiramate [31]. Once-weekly semaglutide revealed efficacy for obese people, and some Gastrointestinal Adverse Events (GIAEs) were found. Those data were from 1st to 3rd trials of Semaglutide Treatment Effect in People with Obesity (STEP) associated with simultaneous analysis of reduction degree [32]. In this case, remarkable decrease of HbA1c and weight was found after increasing dose of Rybelsus from 7mg to 14 mg/day. Some probable factors may contribute this clinical progress. She usually skips her breakfast for long as her lifestyle.

Rybelsus is administered just after waking up with 50-120mL of water followed by more than 30 min fasting [32]. Her fasting time period was rather long about 120 min. From previous analysis of fasting time, clinical efficacy of Rybelsus would increase as the fasting time becomes long [33]. These data were obtained by the investigation of PIONEER 2 and 3 [34,35]. Semaglutide concentration in the blood was analyzed for time period from 4 hours to 24 hours, and fasting time in the case of 15, 30, 60, 120 min. As a result, the level is stable during 4-24 hours. As the standard level is set 1.00 at 15 min, concentration ratio for 4 hours would be elevated 1.67, 2.60 and 3.06 times in 30, 60 and 120 min, respectively [36]. Thus, fasting time period after intake would become crucial factor for clinical efficacy. Consequently, current case seemed to have enough blood concentration because of long fasting time period.

When Rybelsus is provided to diabetic patients, possible problem would be Gastrointestinal Adverse Events (GIAEs) [37]. This case did not feel any GIAEs, and it may be due to usual intaking of nizatidine 150mg/day for the treatment of GERD. From mentioned above, the case has been tolerated Rybelsus well and had significant efficacy for the improvement of weight, glucose control and fatty liver. Some limitation would be present for this report. The case is young female with high BMI, T2D, fatty liver and GERD. Rybelsus may contribute much for such combined medical problems. Fasting time period will be possibly in discussion for the personalized medical treatment for lifestyle, the severity of T2D, the degree of obesity, fatty liver and other factors. In summary, Rybelsus showed significant clinical efficacy for young female patient with obesity, T2D and fatty liver. This report will become hopefully a useful reference for personalized therapy in the future.

Conflict of interest

The authors declare no conflict of interest.

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