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Improvement of Obesity and Type 2 Diabetes (T2D) by Oral Semaglutide (Rybelsus) and Super-Low Carbohydrate Diet (LCD)

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Abstract

For novel oral hypoglycemic agent (OHA), semaglutide (Rybelsus) has been attracted attention. Patient is 41-year-old hospital staff with obesity, who was pointed out 7.7% of HbA1c with weight 101kg in June 2020. He continued petite-low carbohydrate diet (LCD) for 8 months with weight reduction 3kg. Successively, he applied super-LCD for 7-months and showed 7kg reduction and HbA1c 5.6% in Sept 2021. He took Rybelsus 3mg per os from Mar 2022 and showed 88kg and 5.5% in Nov 2022. LCD brought improvement of ALT from 97 to 27 U/L for 30 months. Thus, LCD and Rybelsus showed satisfactory clinical effect.

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); Peptide InnOvatioN for Early diabEtes tReatment (PIONEER)

Introduction

Across the world, clinical problems of obesity and type 2 diabetes (T2D) are crucial from various points of view [1]. The standard guideline was presented by American Diabetes Association (ADA) as Standards of Care in Diabetes-2023 in Jan 2023 [2]. Among them, recent topics include clinical introduction of various types of oral hypoglycemic agents (OHAs) for T2D and obesity [3]. Among them, these OHAs include sodium–glucose cotransporter 2 inhibitor (SGLT2i) for T2D, CKD and heart failure, dipeptidyl peptidase-4 inhibitor (DPP-4i), and oral route of glucagon-like-peptide 1 receptor agonist (GLP1-RA). Oral semaglutide has been developed, which seemed to show new era for novel peptide delivery [4]. It was approved by US Food and Drug Administration (FDA) in US that has been moderately used for actual medical practice [5].

In recent years, GLP-1RA has shown higher demands, because of anti-obesity agents for social needs [6]. Consequently, oral semaglutide and liraglutide have led to some shortage and then T2D treatment is so far prioritized [7]. Concerning clinical efficacy of oral semaglutide as Rybelsus, large studies have been conducted for SUSTAIN and PINONEER programs [8]. This fundamental investigation associated with clinical research had led to the results of PIONEER, which stands for Peptide InnOvatioN for Early diabEtes tReatment [9].

Authors and research group have presented lots of reports concerning diabetes and endocrine diseases. Among them, several themes were included, such as OHAs, diet therapy, meal tolerance test (MTT), Carbo-70g loading test, low carbohydrate diet (LCD), continuous glucose monitoring (CGM) and others [10,11]. Furthermore, recent studies were about the administration of oral semaglutide as brand name Twymeeg [12-14]. During our daily medical practice, we recently experienced an impressive patient with obesity and T2D. General clinical progress and related perspectives are described in this article.

Case Presentation

History and Physicals

The patient is a 41-year-old male working as a hospital staff for years. When he had annual health check in Jan 2020, HbA1c was 7.0% with 102kg in weight, 160cm in height and 39.8 kg/m^2 in BMI. After that, HbA1c increased to 7.7% with weight 101kg in June 2020, and then he was advised to start medical treatment

(Figure 1). He started nutritional therapy as petite-low carbohydrate diet (LCD), which includes 40% of carbohydrate amount per calorie calculation. Further, he initiated to take metformin 500mg per day. In Jan 2021, his HbA1c was 7.4% with weight 98kg. From his clinical progress, he was advised to start super-LCD meal every day. It means strictly limited LCD and has 12% of carbohydrate in the meal. His glucose variability and weight were improved 8 months later, showing HbA1c 5.7% and weight 91kg. Consequently, his nutritional therapy was changed from super-LCD to standard-LCD, which was 26% of carbohydrate in usual meal.

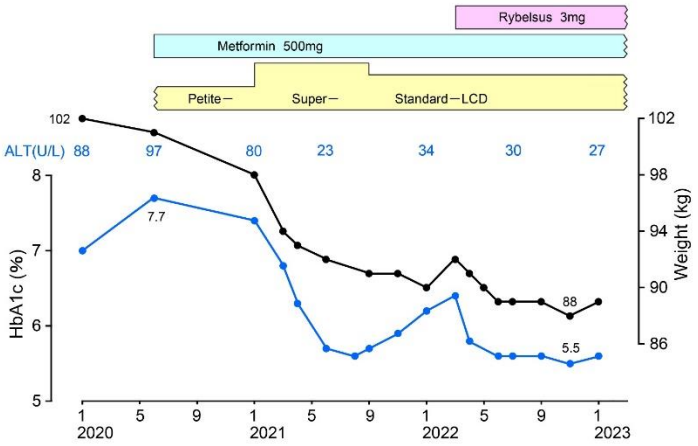

Figure 1: *Clinical progress with HbA1c, weight, biochemistry and treatment.*

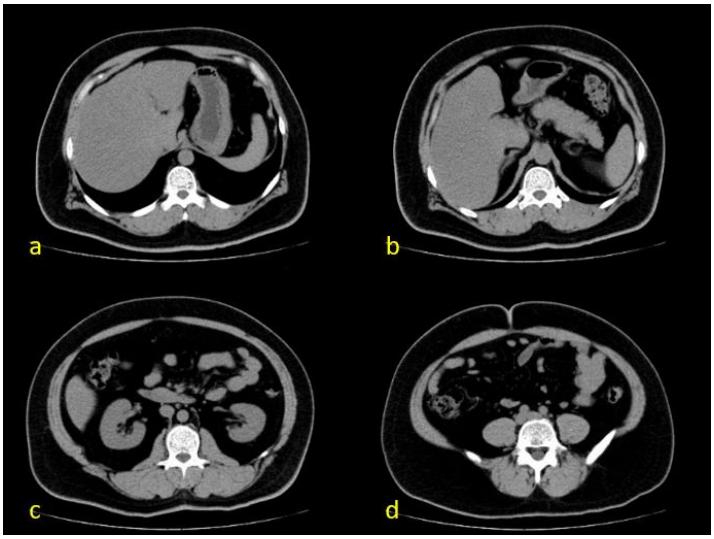

Figure 2: *Clinical progress with HbA1c, weight, biochemistry and treatment*

2a: Fatty liver and Retention of gastric juice is observed.

2b: Pancreas showed no remarkable changes.

2c: Bilateral kidneys were un remarkable.

2d: Visceral fat and subcutaneous fat were increased.

His physicals were as follows: His consciousness was alert and speech was normal. Vitals were stable with pulse 72, BP 132/ 85 mmHg, BT 36.4, respiration was normal with SpO_2 99%. He showed unremarkable findings as lung, heart, abdomen and neurological exams. Abdominal circumference was 114 cm.

The blood chemistry of health check-up in Feb 2022 showed as follows: Hb 14.6 g/dL, RBC 4.70 x 10^6 /μL, AST 19 U/L, ALT 34 U/L, GGT 38 U/L (-79), total-Cho 243 mg/dL, HDL-C 57 mg/dL, LDL-C 158 mg/dL, TG 141 mg/dL. Chest X-ray was negative, and ECG showed within normal limits.

Clinical progress

This case showed the improvement of HbA1c and body weight during June 2020 to Jan 2022. However, his HbA1c and weight have increased again as 6.4% and 92kg in March 2022. Consequently, he started to take oral semaglutide (Rybelsus) 3mg/day. His general situation was improved as HbA1c 5.5% weight 88kg and BMI 34.3 kg/m^2 in Nov 2022. His nutritional therapy was continued by standard-LCD. In Jan 2023, ALT as liver function showed reduced level of 27 U/L, associated with improved HbA1c and weight.

Concerning his radiological data, he received abdominal CT scan in Sept 2022. The results were shown in Figure 2, in which fatty liver, and retention of gastric juice, unremarkable changes in pancreas, unremarkable bilateral kidneys and increased visceral / subcutaneous fat were observed.

Ethical Considerations

This case study was carried out along with the ethical principles from the Declaration of Helsinki. Moreover, several comments were considered as the Ethical Guideline for Human Research and the Good Clinical Practice (GCP). Authors et al. have established the current ethical committee as to this report. This committee is present in our hospital with several professionals. They include the president of the hospital, physician in charge, head nurse, pharmacist, registered dietitian, and also legal specialty. Satisfactory discussion was conducted in their attendance. Consequently, agreement was fully given for the current protocol. The informed consent was obtained from the patient by the document.

Discussion

The current case is a 41-year-old man with obesity and T2D. His general situation was improved for HbA1c and body weight by continuing LCD and administration of imeglimin (Rybelsus). The important points for the discussion seem to be as follows: i) clinical effect of imeglimin, ii) super-LCD and weight reduction, and iii) improvement of complication such as fatty liver. The discussion will be described in this order.

First, several OHAs have been used for T2D in recent medical practice. Among them, a topic includes oral semaglutide

(Rybelsus) as GLP-1RA associated with clinical efficacy [15]. It was developed for continuous pharmacological research for 30 years [16]. Regarding the important aspect, it can be synthesized by sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) which is one of the absorption enhancers [17]. Because this peptide can be administered per os, it would be the important cornerstone for novel drug delivery system (DDS) in the future [18]. Further, clinical effects of Rybelsus include not only anti-diabetic efficacy but also beneficial efficacy on cardiovascular axis [19]. From mentioned above, peptide research field can develop associated with such SNAC matter [20]. For actual practice, Rybelsus was approved by United State FDA, EMA and PmDA [21]. Various evidence was reported by useful investigation of PIONEER [8].

Second, authors et al. have developed LCD development medically and socially for long through Japan LCD promotion association (JLCDPA) [22]. From historical point of view, Dr. Atkins has initiated LCD [23]. LCD has been known to be effective from the large investigation of Dietary Intervention Randomized Controlled Trial (DIRECT) [24]. Authors and collaborators have presented actually useful LCD meal methods [25]. Their type are super-LCD, standard-LCD and petite-LCD, in which carbohydrate amount ratio are 12%, 26% and 40%, respectively. When intake calorie is 1600kcal per day, carbo calories is calculated as 1600kcal x 0.12 = 168 kcal, and then 168kcal/ 4kcal (carbo 1g) equals 42g of carbohydrate a day.

Third, using super-LCD, we have achieved remarkable weight reduction in many cases of obesity and T2D [26]. Authors have applied these 3 types of LCD for various patients, and showed satisfactory results. Among more than 2900 cases, 25% cases have achieved more than 10% of weight reduction [27]. LCD has remarkably decreased serum level of triglyceride [28]. In addition, it shows improvement of fatty liver disease with the study of Randomized Controlled Trial (RCT) [29]. Furthermore, LCD may be involved in the ketogenesis and ubiquitination [30].

Limitations may the present in the current report. It is only one case with obesity and T2D for the improvement by Rybelsus and super-LCD. Future clinical progress would be carefully followed up, including macroangiopathy, microangiopathy and other complications [31].

In summary, rather younger male patient showed the decrease of HbA1c and weight. Clinical effects seemed to be from oral semaglutide and super-LCD. Current report becomes hopefully a useful reference for diabetic research in the actual practice.

Conflict of Interest

The authors declare no conflict of interest.

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