



Rapid Decrease of HbA1c by Imeglimin (Twymeeg) in Patient with Obesity and Type 2 Diabetes (T2D)

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Abstract

The current case was 64-year-old male with obesity and type 2 diabetes (T2D). His weight was 49kg at 20 years and 69kg in 62 years old. He was diagnosed as T2D in Jan 2021 with HbA1c 9.4% and BMI 28.0 kg/m². He started super-low carbohydrate diet (LCD), and showed improvements of HbA1c 6.6% and 64kg for 5 months. In December 2022, he showed 7.4% and 71kg, and then imeglimin (Twymeeg) was initiated. He had remarkable improvement as 6.4% and 65kg in May 2023. Consequently, this novel oral hypoglycemic agent (OHA) seems to be clinically effective for obesity and T2D.

Keywords: Low carbohydrate diet (LCD); Imeglimin (Twymeeg); Oral hypoglycemic agents (OHAs); Trials of IMeglimin for Efficacy and Safety (TIMES); Japan LCD promotion association (JLCDPA)

Introduction

Various metabolic diseases have been prevalent and giving impact on public health in the world [1]. Among them, major diseases include type 2 diabetes (T2D), obesity, overweight, hypertension, fatty liver, and so on [2]. Adequate nutritional therapy would be required for the fundamental treatment of these diseases. Recent treatments for T2D and obesity include low carbohydrate diet (LCD), where long discussion was observed between LCD and calorie restriction (CR) [3]. LCD has been more known and popular associated with elevated understanding for LCD [4]. The ratio of US people applying LCD become twice in the latest decade. Some nutritional studies for daily meal were conducted, in which 57% of LCD performer were female and mean age was 48-67 years old [5].

Furthermore, several novel oral hypoglycemic agents (OHAs) have been introduced for diabetic practice and research. American Diabetes Association (ADA) has played the main role of diabetic management so far, and has announced standard treatment guideline in Jan 2023 [6]. The feature of T2D includes the decrease of beta-cell mass and increase of insulin resistance. This mechanism is involved in mitochondrial dysfunction [7].

Recently, imeglimin has been a novel OHA that has molecular similarity with metformin and possesses a unique mechanism of targeting mitochondrial bioenergetics [8]. It can decrease reactive oxygen species (ROS) production, and increase mitochondrial integrity and function, and improve the function and structure of endoplasmic reticulum (ER) [9]. Associated with large studies, imeglimin (Twymeeg) has shown beneficial glucose-lowering effects for diabetic various complications in T2D patients.

Authors and our clinical team continued actual medical practice and research for years [10]. A variety case reports have been presented concerning continuous glucose monitoring (CGM), meal tolerance test (MTT), LCD and treatment experiences with several OHAs [11]. Among them, beneficial effect of imeglimin (Twymeeg) has been found [12]. Recently, we experienced a T2D patient who was treated by Twymeeg associated with clinical efficacy. Its general clinical course and related perspectives will be described in this article.

History and Physicals

Current case is 64-year-old male patient with obesity, T2D and dyslipidemia. When he was 20 years old, his body weight was 49 kg. When he was 61 years old in January 2021, he was pointed

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out to show hyperglycemia with HbA1c 9.4% and elevated weight 69kg (Figure 1).

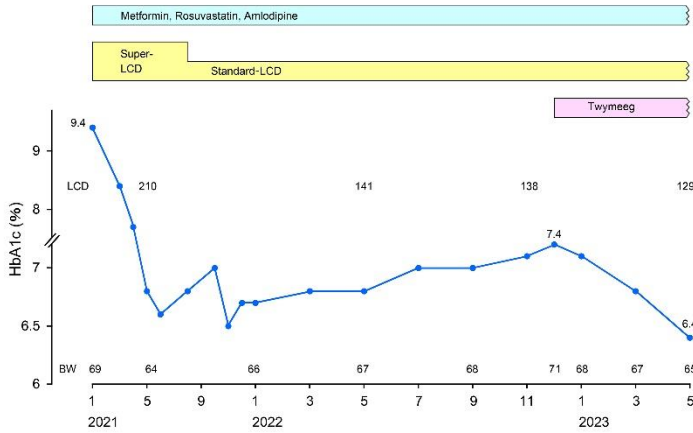


Figure 1: Clinical Progress with HbA1c, Weight and Treatment.

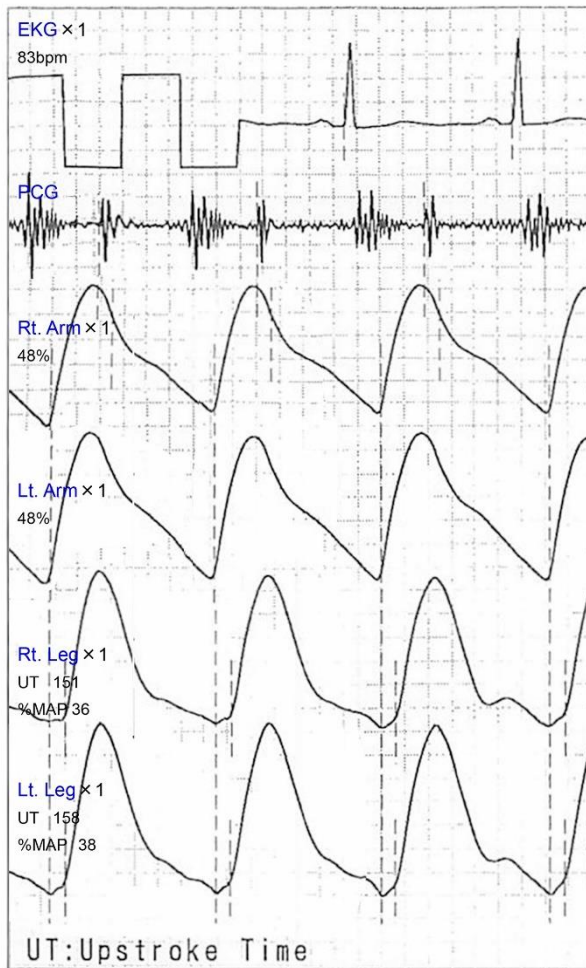


Figure 2: Mechanocardiogram and Sphygmogram.

At that time, his physique showed 157cm, 69kg and BMI 28.0. He was introduced to our diabetes department, and he was advised to start super-low carbohydrate diet (LCD) immediately.

Super-LCD means 12% of carbohydrate intake of total calory per day. Carbohydrate amount in his meal was restricted with continuous diet advise and therapy. His LCD treatment was successful, because he showed decrease of HbA1c from 9.4% to 6.6% and weight reduction from 69 kg to 64 kg for 5 months. Then, his diet therapy became standard LCD, in which carbohydrate intake was 26% in his total calory per day. His glucose variability and weight had been slowly worse until November 2022. His HbA1c was increased to 7.4% with weight 71kg in December 2022.

Several exams

Obtained laboratory data in November 2022 was in the following: HbA1c 7.2%, post-prandial blood glucose 276 mg/dL, AST 15 U/L, ALT 11 U/L, GGT 41 U/L, ChE 303 U/L (213-501), uric acid 6.1 mg/dL, Cr 0.90 mg/dL, BUN 12 mg/dL, LDL 138 mg/dL, HDL 45 mg/dL, post-prandial TG 375 mg/dL. WBC 7200 / μ L, RBC 4.05×10^6 / μ L, Hb 12.6 g/dL, Ht 38.4 %, MCV 94.8 fL, MCH 31.1 pg, MCHC 32.8 %, Plt 34.7×10^4 / μ L. Chest X-P revealed unremarkable, and electrocardiogram (ECG) showed within normal limits with no specific ST-T changes. He received the examination of mechanocardiogram and sphygmogram for arteriosclerosis (Figure 2). As the result, the ankle brachial index (ABI) showed 1.02/1.06 in bilateral sides of right/left, respectively. The result of brachial-ankle pulse wave velocity (baPWV) showed 1564/1649 in right/left foot, which was 1SD higher than average degree of age.

Medical Problems

From mentioned clinical course and laboratory exams associated with previous history and medication, his current medical problems in December 2022 can be summarized as follows:

- #1 Obesity (BMI 28.8)
- #2 T2D (HbA1c 7.4%)
- #3 Hypertension (Amlodipine)
- #4 Dyslipidemia (LDL 138 mg/dL)

Clinical Progress

In December 2022, his glucose variability became exacerbation as HbA1c 7.4% and increased weight 71kg. Then, we have decided to provide imeglimin (Twymeeg) for T2D. Consequently, his HbA1c was improved from 7.4% to 6.4% for 5 months, associated with weight reduction from 71kg to 65kg. During this period, the case visited regularly once per month. He stated that the appetite was moderately suppressed, and he was satisfied with eating small amounts. He did not change the degree of carbohydrate restriction as continuous same balance of meal content. As a whole, general amount of food intake was reduced. The changes in HbA1c and weight were apparent with linear

improvement. This clinical progress seemed to be effective by the administration of Twymeeeg.

Ethical standards

The case is complied with the ethical standard guideline of Declaration of Helsinki. Further, some comments were along with the usual regulation for personal information. This principle has been associated with the ethical rules for medical research and actual practice for human. Several guidelines were references from the official presentation of the Japanese government. These perspectives were from the Ministry of Health, Labor and Welfare, and also the Ministry of Education, Culture, Sports, Science Technology. The authors and collaborators established our ethical committee about this research. It exists in Kanaiso Hospital, Komatsushima, Tokushima, Japan. The committee has several required members, including the hospital president, physicians, radiologist, head nurse, pharmacist, nutritionist and legal professional. These members discussed in a satisfactory manner for this case, and agreed the protocol. Informed consent by written document was obtained from the case.

Discussion

As regards to the current case, several medical and characteristic problems are in the following. They are obesity, T2D, hypertension, dyslipidemia, clinical response of LCD and pharmacological response of imeglimin (Twymeeeg). In these perspectives, some points would be discussed, which are i) LCD, ii) imeglimin, iii) relationship among related atherosclerotic cardiovascular disease (ASCVD).

First, super-LCD method was so effective, and then he has the improvement of HbA1c from 9.4% to 6.6% for 5 months, associated with 5kg weight reduction. Authors and collaborators have continued LCD movement from medically and socially points of view. Three representative types of LCD were proposed and prevalent, which are petite-LCD, standard-LCD and super-LCD. They include carbohydrate ratio involvement as 40%, 26% and 12%, respectively [13]. These developments were conducted by our group of Japan LCD promotion association (JLCDPA). We have reported significant efficacy of super-LCD for thousands of patients with obesity and T2D. The results of weight reduction more than 10% was found in 26%, and more than 5% was found in about 58% [14]. From these medical effects, LCD seems to become one of the useful nutritional methods for obesity and T2D.

Second, the case presented clinically rapid and remarkable improvement by imeglimin. The results showed the decrease of HbA1c 1.0% and weight 6kg for 6 months. During this period, he did not change his actual diet method, which are standard-LCD style. Imeglimin showed mega clinical studies in many countries,

which were Trials of IMeglimin for Efficacy and Safety (TIMES) 1,2 and 3 [15]. From the reported results, clinically average HbA1c decrease was in the following: monotherapy -0.46%, add-on therapy of biguanides -0.67%, DPP4-i -0.92%, SGLT2i -0.57%, alfa-glucosidase inhibitor -0.70% from TIMES 2 [16]. Imeglimin has been known to have mechanism via mitochondrial pathway [17]. The characteristic results can be observed between GLP-1RA and DPP4-i. They have common pathway for pharmacological function, but both results were different as -0.12% vs -0.92% [18]. Consequently, the difference might bring the crucial key to uncover apparent mechanism of imeglimin [19]. Third, current case showed gradually decreased LDL-C level for the treatment period. For mega studies of imeglimin concerning the relationship of LDL-C and imeglimin, systematic review and meta-analysis of randomized clinical trials (RCTs) were conducted. It included 8 reports with 1555 T2D cases, where the data were from Cochrane Library, Pubmed, Google Scholar, Web of Science and Wiley. General effects revealed significant HbA1c decrease after administration of imeglimin. In contrast, it did not show significant impairment concerning HOMA-IR, HDL-C, triglyceride, LDL-C, which were $p > 0.05$ [20].

There are some limitations in current article. This case has been treated for LCD and imeglimin, where certain effective results were found in the clinical progress. However, various factors may be involved in the progress. Then, future situation would be carefully followed up, where we can evaluate some related biomarkers or factors.

In summary, current case is 64-year-old male patient associated with obesity and T2D. He showed remarkable clinical effect by the administration of imeglimin (Twymeeeg). Some discussion and perspective were described in this article, and future progress will be observed. Current report is hopefully evaluated to be useful in the future diabetic research and practice.

Conflict of Interest

The authors declare no conflict of interest.

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