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PUBTEXTO

Effect of imeglimin (Twymeeg) on pre-prandial glucose in patient with persisting post-prandial hyperglycemia

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Abstract

As recent topic for oral hypoglycemic agent (OHA), imeglimin (Twymeeg) shows clinical efficacy. Current case is 77-year-old female with type 2 diabetes (T2D) for years. HbA1c increased to 8.4% in Jan, 2023 and then Twymeeg was initiated. She has continued detail measurement of pre-prandial glucose 3 times a day, and these data were analyzed during Dec 2022 to Feb 2023. As a result, HbA1c decreased to 7.9% in 5 weeks, and pre-prandial level has decreased in satisfactory degree. In contrast, she kept intake of certain amount of carbohydrates in 3 meals as usual, and post-prandial hyperglycemia has been stable.

Keywords: imeglimin (Twymeeg); pre-prandial blood glucose; post-prandial blood glucose; Trials of IMeglimin for Efficacy and Safety (TIMES); oral hypoglycemic agent (OHA)

Introduction

In developed countries, type 2 diabetes (T2D) has been one of the most important life style-related diseases that should be controlled adequately [1]. For the screening methods of T2D, well-known markers include pre-prandial glucose, post-prandial glucose and HbA1c [2]. T2D has been for long managed along the standard guideline of diabetes, where American Diabetes Association (ADA) presented the "Standards of Care in Diabetes" in January 2023 [3]. Thus, the diagnosis and treatment for T2D have been conducted in the hospitals and clinics worldwide [4].

According to the standard guideline of oral hypoglycemic agents (OHAs), several types of OHAs have been actually used in the current diabetic practice and research [5]. Improved efficacy and safety were reported for multi-center studies of OHAs, including sodium–glucose cotransporter 2 inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP-4i), and so on. Among them, recent topic includes novel OHA as imeglimin (Twymeeg) associated with impressive pharmacological efficacy [6]. Its molecule is similar to metformin that has been the first-line OHA for T2D for long years [7]. Imeglimin has been known to show dual mechanism of increasing insulin secretary function and decreasing insulin resistance function [8]. There were some large investigation of TIMES 1,2 and 3 [9]. TIMES stands for the Trials of IMeglimin for Efficacy and Safety [10].

Authors and diabetes group have continued diabetic research for years including various matters concerning T2D. They covered continuous glucose monitoring (CGM), low carbohydrate diet (LCD), meal tolerance test (MTT), Carbo-70g loading test, and several reports providing OHAs [11,12,13]. We recently experienced a female elderly patient who revealed impressive clinical progress. The case showed frequent measurements for pre-prandial blood glucose before and after the administration of Twymeeg. Then, her general clinical course and some discussion will be shown in this article.

Presentation of cases

Medical history

Current case is 77-year-old female with history of T2D for 12 years. She was also treated for hypothyroidism and Gastro Esophageal Reflux Disease (GERD) for years. She has formerly received the insulin therapy until 2 years ago using insulin Humalog Mix75/25 twice a day. However, her HbA1c value was increased to 8.4%, and then, she was provided Xultophy combination injection FlexTouch. It included insulin degludec and liraglutide for 100 units/mL and 3.6 mg/mL, respectively. After that, glucose variability was improved to the level of 7.6% of HbA1c. Successively, her HbA1c persisted rather high. The reason would be from her diet habit. She liked to have rice, bread and noodles, and continued to take carbohydrate for years. In Jan 2023, her HbA1c was elevated to 8.4%, and then she received further evaluation of blood chemistry (Figure 1).

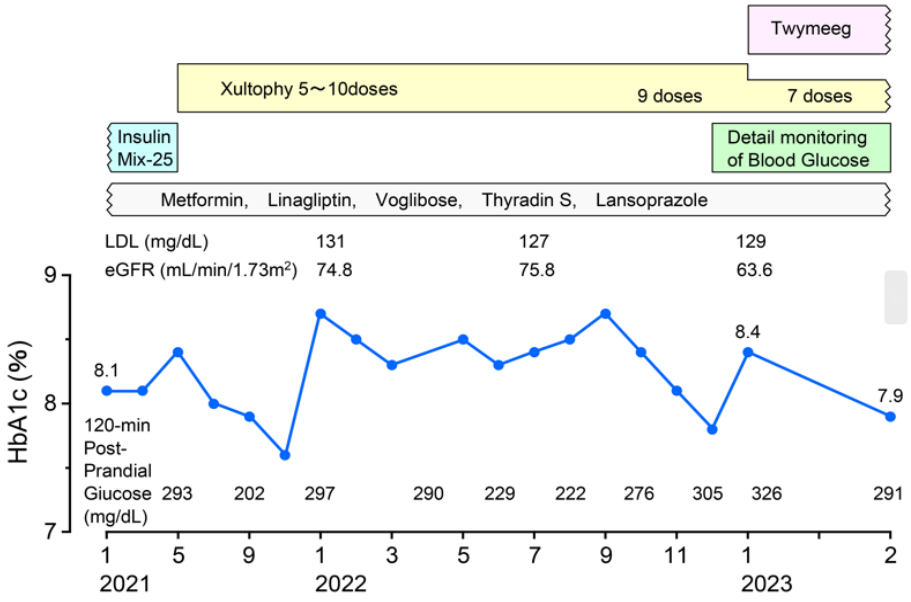

Figure 1: *Clinical progress for glucose variability and treatments.*

Physicals examination

Her physical examination in Jan 2023 showed the following status: consciousness is alert, conversation is normal, vital signs are within normal ranges with pulse 76 /min, BP 134/82 mmHg, SpO2 98%, temperature and respiration are normal. Physical examination was negative. Her physique has been unremarkable with height 159 cm, weight 51kg and BMI 20.2 kg/m^2.

Laboratory examination

The data of the laboratory examination were in the following: HbA1c 8.4 %, post-prandial blood glucose 326 mg/dL, RBC 4.28 x 10^6 /μL, Hb 11.2 g/dL, Ht 41.2 %, MCV 96.2 fL (80-98), MCH 26.1 pg (27-33), MCHC 27.1 g/dL (31-36), WBC 5000/μL, Plt 17.1 x 10^4 /μL, GOT 25 U/L, GPT 10 U/L, γ-GTP 21 U/L, Uric acid 2.2 mg/dL, BUN 20 mg/dL, Cre 0.67 mg/dL, eGFR 63.6 mL/min/kg1.73m^2, HDL 72 mg/dL, LDL 102 mg/dL, TG 74 mg/dL. Urinalysis: protein (-), glucose (++), urobilinogen (+/-), ketone bodies (-), pH 5.0, urinary Alb/Cre ratio 18.4 mg/g·Cre (0-30). Electrocardiogram (ECG) showed pulse 72/min, normal axis deviation, ordinary sinus rhythm and unremarkable ST-T changes. Chest X-ray revealed unremarkable changes.

Clinical Progress

This patient has continued to check pre-prandial glucose measurement three times a day for years. Her blood glucose variability was higher during Dec 2022, and then HbA1c increased to 8.4% in Jan 2023. Her meal always contains moderate amount of carbohydrates. Breakfast are bread, jam, yoghurt, and fruits in the morning including 60-70g of carbohydrates. For lunch and supper, carbohydrate amount would be about 60-90g of carbohydrates. Her lifestyle and meal pattern persisted for long.

Due to elevated HbA1c in Jan 2023, her pharmacological treatment has changed. Zultophy dose was reduced from 9 to 7 doses, and Twymeeg was started (Figure 2). Pre-prandial glucose values three times a day have been decreased than before. Pre-breakfast glucose kept mostly in the range of 71-110 mg/dL, and pre-supper glucose levels below 70 mg/dL can be observed. On the other hand, her three meals and carbohydrate amount were the same as before. After a month, HbA1c decreased from 8.4% to 7.9%, and post-breakfast glucose was 291 mg/dL as the same level as before. No symptoms of gastro-intestinal adverse effects (GIAEs) were noted after administration of Twymeeg.

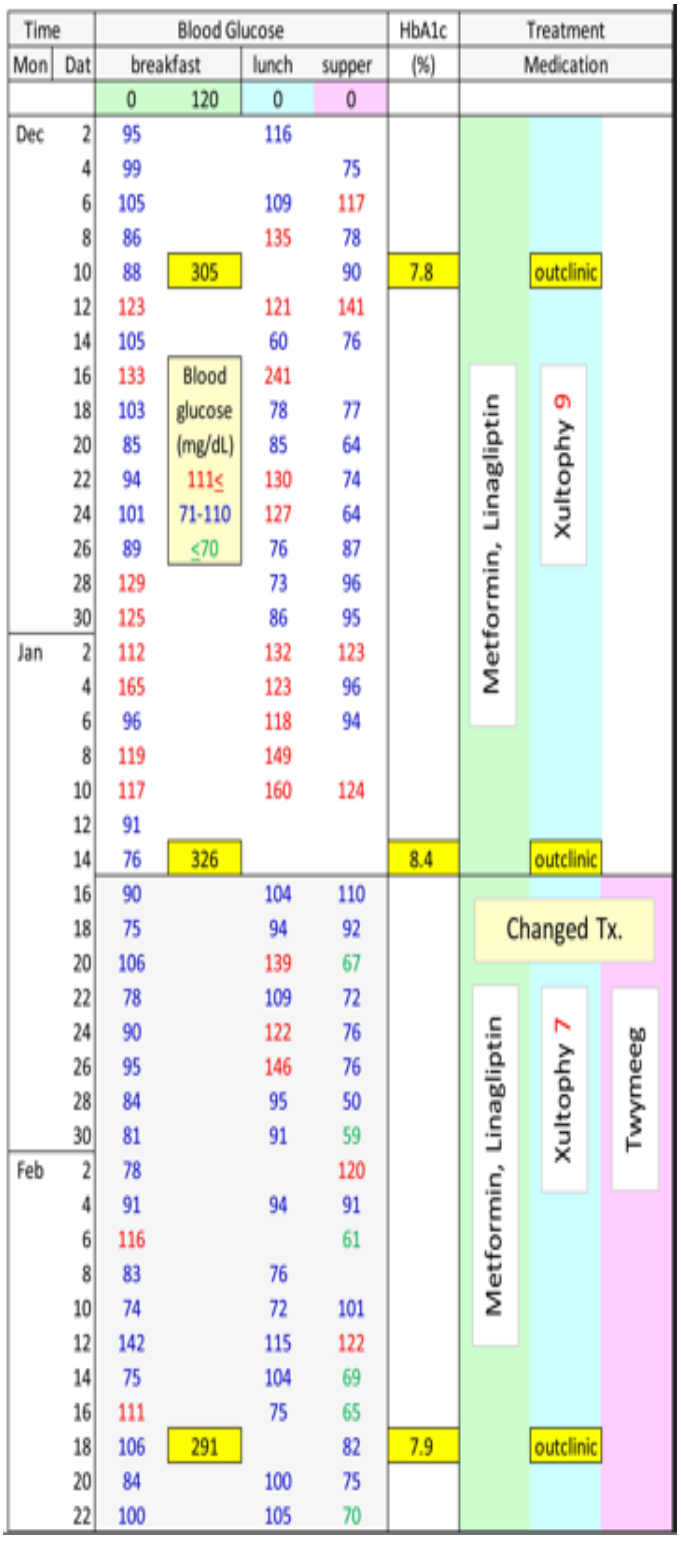

Figure 2: *Changes in pre-prandial blood glucose, HbA1c and treatments.*

Ethical standards

This article is complied with the standard ethic guideline that is from the Declaration of Helsinki. Further, some comments are along with the protective regulation related to personal information. The principle has been associated with the ethics rules concerning clinical research and practice which are for human being. Certain guideline is represented from Japanese government. It includes the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science Technology. The authors established currently the ethical committee regarding this case, that was present in Yoshinogawa Hospital, Tokushima, Japan. The committee had some clinical staffs and professional legal person, including hospital director, physician, pharmacist, nurse, nutritionist. We discussed enough concerning the protocol, and agreed for the research protocol.

Discussion

This case has been characterized for the following three points. They are i) the administration of Twymeeg lowered the pre-prandial blood glucose level, suggesting clinical effect in early period, ii) she has been monitoring blood glucose before meals three times a day perfectly for years, iii) Concerning her meal habit, she has continued to take certain amount of carbohydrates three times a day for long. These three points will be discussed in this order below.

Firstly, we examined the changes in pre-prandial blood glucose before and after administration of Twymeeg during Dec 2022 to Feb 2023. Before administration of Twymeeg, pre-prandial blood glucose distribution was almost 111 mg/dL or higher (red letters, Table 1). On the other hand, after Twymeeg administration, the range was 71-110 mg/dL (blue letters,). In this way, clinical effects were recognized in early period due to Twymeeg. Further, 120-min post-prandial blood glucose remained almost same around 300 mg/dL. One of the reasons for this would be that the amount of taking carbohydrates was at the same level [14].

Current case showed the decrease of HbA1c value from 8.4 to 7.9% for 5 weeks. For add-on therapy, Imeglimin was initiated for the previous treatments of metformin, linagliptin and Xultophy. Large study of TIMES 1, 2 and 3 compared clinical efficacy of monotherapy and combined therapy of imeglimin [10]. The data showed monotherapy (0.46%), SU (0.56%), glinides (0.70%), biguanides (0.67%), α-GI (0.85%), SGLT2i (0.57%), and DPP4-I (0.92%). Among these, DPP-4i had greatest effect. On the other hand, smallest effect was observed in the case of GLP-1RA, that was reported in TIMES 3 [9]. For GLP-1RA treatment as subcutaneous injection, combined effect showed only minus 0.12% of HbA1c. Both of these pharmacological routes are known to be common and/or similar between DPP4-I and GLP-1RA. However, large difference seems to be impressive.

Secondly, she has continued measuring every pre-prandial blood glucose for long. Formerly, she was treated mix-25 type insulin and she started monitoring three times a day. She can tolerate it well, and also multiple monitoring was not stressful for her. For 2 years, her treatment was changed into Xultophy injection once a day, and Twymeeg was added this time [15]. It was her perfect life style that

enabled the complete blood variability before and after administration of Twymeeg.

Thirdly, this case has continued the lifestyle for intaking of certain amount of carbohydrates for years. Then, her post-prandial blood glucose is always increased to certain degree. According to the standard biochemistry textbook, carbohydrate intake per os always elevates blood glucose values [16]. Among them, carbohydrate 1g increases blood glucose 3mg/dL in patient with T2D [17]. The case of normal person shows 1mg/dL elevation of blood glucose for carbo 1g [18]. In the case of patient with T1D, blood glucose elevates 5 mg/dL per ingestion of carbo 1g [19,20].

This case showed decreased HbA1c value and pre-prandial glucose level. Mutual relationship between blood glucose and HbA1c value has been reported as Nathan's equation [21]. The equation shows that [eAG (mg/dl) = (28.7 x HbA1c) -46.7, r^2=0.84]. Recent studies revealed the detail correlation between them, using several groups of hemoglobin and groups of higher/lower HbA1c [22]. It showed strong correlation between the groups. Furthermore, the relationship of HbA1c and glucose level is influenced by RBC turnover and glucose uptake. From the data of 0.94% of RBC turnover rate, usual RBC lifespan can be calculated for 106 days [23].

Some limitation may be present in the current report. Pre-prandial blood glucose was decreased, while post-prandial blood glucose seemed to be kept at the same levels. When considering the relationship of HbA1c and glucose values, both of pre-and post-prandial fluctuation has to be measured. Then, applying continuous glucose monitoring (CGM) can detect the detail glucose variability.

In summary, 77-year female with T2D showed clinical effect of Twymeeg by detail measuring pre-prandial blood glucose 3 times a day. She has kept the intake of certain carbohydrate amount for long, and post-prandial blood glucose seemed to be stable. These detail data will become hopefully useful reference in the future diabetic research.

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