



# Improved Glucose Variability by Imeglimin (Twymeeg) After Hypoglycemic Episode in T2D Patient

Bando H<sup>1,2,3,\*</sup>, Ogawa H<sup>3</sup>, Kobayashi H<sup>3</sup>, Nagahiro S<sup>3</sup>, Nakanishi S<sup>3</sup> and Watanabe O<sup>3</sup>

<sup>1</sup>Tokushima University / Medical Research, Tokushima, Japan

<sup>2</sup>Japan Low Carbohydrate Diet Promotion Association, Kyoto, Japan

<sup>3</sup>Yoshinogawa Hospital, Tokushima, Japan

\*Corresponding author: Bando H, Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan; Tel: +81-90-3187-2485; E-mail: [pianomed@bronze.ocn.ne.jp](mailto:pianomed@bronze.ocn.ne.jp)

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## Abstract

For latest topic, imeglimin (Twymeeg) shows clinical efficacy among several oral hypoglycemic agents (OHAs). The case is 79-year-old male with Type 2 diabetes (T2D) for long. He had hypoglycemic episode in Sept 2022, and then Glubes (mitiglinide/voglibose) was discontinued and EquMet (Vildagliptin/Metformin) was started in Oct 2022. His HbA1c increased to 8.3% in Jan 2023, followed by initiating Twymeeg. Clinical efficacy showed satisfactory degree for glucose variability as 7.3% for 8 weeks. He has body mass index (BMI) 22.0 kg/m<sup>2</sup>, and daily exercise habit. These factors may contribute diabetic improvement in addition to clinical efficacy of EquMet and Twymeeg.

**Keywords:** Imeglimin (Twymeeg); Glubes (mitiglinide/voglibose); EquMet (Vildagliptin/Metformin); 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]. Effective OHAs include alfa-glucosidase inhibitor ( $\alpha$ -GI), dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium-glucose cotransporter 2 inhibitor (SGLT2i), and so on. These OHAs show the beneficial clinical points that they do not suppress blood glucose levels lower than normal ranges. Furthermore, imeglimin (Twymeeg) has been in focus, in which it was recently introduced to clinical practice associated

with useful and safe efficacy [6]. It has presented similar molecule for metformin which has been the first line agent for T2D [7]. It has dual function for reducing insulin resistance and elevating insulin secretion [8]. As to imeglimin, large studies were reported that were TIMES 1 to 3 [9]. The abbreviation of TIMES means the Trials of IMeglimin for Efficacy and Safety, which shows the fundamental clinical data of imeglimin [10].

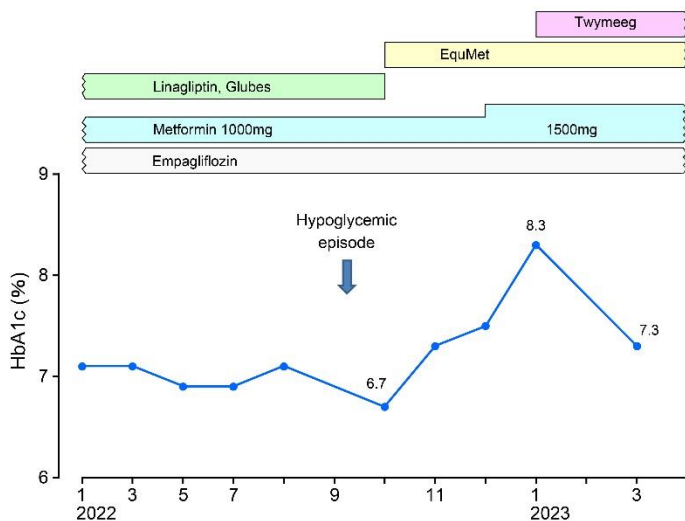
Authors et al. have been involved in diabetic clinical research for long. We have reported various actual diabetic matters concerning T2D. They include low carbohydrate diet (LCD), Carbo-70g loading test, meal tolerance test (MTT), continuous glucose monitoring (CGM) and so on [11,12]. Furthermore, various studies on OHAs were reported [13,14]. We recently had an experience to treat an impressive male patient with T2D. He had hypoglycemic episode and changed OHA from Glubes to Twymeeg. The detail clinical progress and some perspectives are described in this article.

## Case Presentation

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## Medical history

The case is 79-year-old male with T2D for about 12 years. He has been treated for several OHAs for years including empagliflozin, metformin, Linagliptin and Glubes (Figure 1). Glubes is the combination of mitiglinide and voglibose, and it was provided just before every meal. For social history, he worked as a craftsman until 65 years old and was retired. After that, he liked to play softball and also has become a general manager of a masters' softball league for long. He has been trusted by everyone around him. His HbA1c value had been stable until 2023 summer. However, he had hypoglycemic episode in autumn 2022. At that time, HbA1c was decreased to 6.7% in Oct 2022. Then, further evaluation was conducted in detail for his general and diabetic situation.



**Figure 1:** Clinical course for symptom, glucose variability and treatments.

## Physicals examination

His physical examination in Oct 2022 showed the following status: consciousness alert, conversation normal, vital signs within normal ranges, pulse 72 /min, BP 130/78 mmHg, SpO2 97%, respiration and temperature in normal range. His physique showed 165cm in height, 60kg in weight and 22.0 kg/m<sup>2</sup> in BMI.

## Laboratory examination

The data of the laboratory examination were in the following: HbA1c 6.7%, post-prandial blood glucose 174 mg/dL, RBC 4.63 x 10<sup>6</sup> /μL, Hb 14.4 g/dL, Ht 43.2 %, MCV 93.0 fL (80-98), MCH 31.2 pg (27-33), MCHC 33.5 g/dL (31-36), WBC 6300/μL, Plt 18.7 x 10<sup>4</sup> /μL, GOT 24 U/L, GPT 33 U/L, γ-GTP 15 U/L, Uric acid 4.3 mg/dL, BUN 19 mg/dL, Cre 0.70 mg/dL, eGFR 82.1 mL/min/kg1.73m<sup>2</sup>, HDL 48 mg/dL, LDL 131 mg/dL, TG 97 mg/dL. Urinalysis: pH 5.0, glucose (++) , protein (-), urobilinogen (+/-), ketone bodies (-), urinary Alb/Cre ratio 18.1 mg/g·Cre (0-

30). Electrocardiogram (ECG) showed ordinary sinus rhythm, pulse 68/min, normal axis, and no remarkable ST-T changes. Chest X-P was within normal limits.

## Clinical course

This patient had a hypoglycemic episode in Sept 2022 and blood chemistry exams in Oct 2022 showed no remarkable changes. Glubes may be associated with hypoglycemia, and then Glubes and linagliptin was replaced with vildagliptin. Medication was continued on EquMet that is combined agents of Vildagliptin and Metformin. In Dec 2022, metformin was increased from 1000 to 1500 mg per day. HbA1c value was elevated to 8.3% in Jan 2023, despite of increased doses of these agents. Therefore, imeglimin (Twymeeg) was initiated for recent novel OHA from Jan 2023. As a result, HbA1c decreased to 7.3% in a period of 8 weeks, suggesting its clinical usefulness for the improvement of glucose variability. During these periods, no changes were observed in the patient's diet and exercise status. No symptoms of gastrointestinal adverse effects (GIAE) were observed after administration of Twymeeg.

## Ethical standards

This report has been complied with the ethical guideline which is involved in the Declaration of Helsinki. In addition, several commentaries were along with the adequate regulation in relation to the personal information. Such principle was associated with ethical rule as to clinical practice and research for human. Some guidelines are proposed from Japanese government. This case includes the Ministry of Health, Labor and Welfare, Japan and also the Ministry of Education, Culture, Sports, Science Technology, Japan. The author and collaborators have established our ethical committee concerning the current case. It exists in the Yoshinogawa Hospital, Tokushima, Japan. The established committee includes several clinical hospital staffs and professional legal personnel. They include the director, internist in charge, nurse, pharmacist, dietician and legal professional. We have fully discussed as to the research protocol and have agreed for the proposed management.

## Discussion

Current case was characterized for some three diabetic perspectives. They are i) hypoglycemic episode in autumn 2022 which may be due to Glubes as combined OHA of miliglimitide and voglibose, ii) clinical effects of vildagliptin and increased metformin after changing OHA and iii) remarkable clinical effect of Twymeeg from Jan 2023 indicating -1.0% of HbA1c for 8 weeks. The discussion would be described in this order as follows.

Firstly, this case has experienced hypoglycemic episode, which may be due to the administration of Glubes [15]. This OHA is the combined mitiglinide and voglibose (M/V) which are  $\alpha$ -GI and a glinide drug. Its efficacy is generally expected to correct postprandial hyperglycemia. Combination tablets significantly reduced the mean amplitude of blood glucose fluctuations (MAGE) [16]. The Glycated albumin (GA)/HbA1c ratio is a simple and competent biomarker of postprandial hyperglycemia [17]. For the protocol, Glubes was started to give T2D patients who previously continued  $\alpha$ -GI. As a result, a significant decrease in the GA/HbA1c ratio was observed. Therefore, it is possible that postprandial hyperglycemia was improved as well as the decrease in HbA1c. Furthermore, GA/HbA1c ratio becomes a significant factor indicating cognitive decline [18]. From Hisayama study, elevated ratio suggested the atrophy of hippocampus and whole brain [19]. Consequently, Glubes seems to show protective efficacy on cognitive function for older T2D cases. In particular, Glubes seems to be comparatively broadly used in Japan, where larger T2D cases have less BMI values than those of Western countries [20].

Some clinical studies were reported as to fixed combined agents of mitiglinide and voglibose (M/V) (Glubes). Postprandial hyperglycemia was significantly reduced when M/V was administered compared to the standard protocol. As to safety assessment, unremarkable adverse events were observed, except short period of gastrointestinal symptoms. However, symptoms of hypoglycemia, changes in body weight, blood pressure, blood, urine, and others were not observed [21]. Post-prandial glucose (PPG) has been studied for glinide,  $\alpha$ -GI and DPP4-I through various pharmacological mechanism [22]. The comparison of sitagliptin and M/V were conducted. As a result, M/V showed significantly larger decrease of post-prandial glucose. HbA1c revealed no changes between them. Clinical effect was compared between M/V and linagliptin [23]. After 8 weeks, 2 kinds of MTT were conducted. Consequently, post-prandial AUC 0-120 of glucose was significantly smaller in M/V than linagliptin in both meal protocols. In contrast, 24-hour AUC and mean amplitude of glycemic excursion (MAGE) were similar in both groups. In conclusion, M/V improved more effectively than linagliptin in the case of T2D.

Secondly, clinical effects of vildagliptin and increased metformin from Oct 2022 were not enough. This seemed to be partly due to taking carbohydrates in three meals. When T2D cases continue taking carbohydrate, post-prandial glucose always increases which cannot be suppressed as the same levels of normal subjects. Recent comparative study is found [24]. Basal treatment was vildagliptin 100mg, and add-on therapy was conducted. Group 1 was +M/V, and group 2 was +gliclazide 1mg. As a result, group 1 showed significantly lower values for standard deviation of glucose, MAGE, M-value, and AUC. Hypoglycemia (<68mg/dL)

was not observed during the M/V phase, but occurred 0.35 times/day in group 2. In conclusion, group 1 resulted in more effective post-prandial glucose control and less episodes of hypoglycemia than group 2.

Thirdly, this case showed remarkable effect of Twymeeeg as HbA1c decrease (-1.0%) for short period. From various data of TIMES 1,2 and 3, HbA1c decrease was reported in monotherapy or add-on therapy [10]. The degree of HbA1c changes are as follows: -0.46% for monotherapy, -0.85% for  $\alpha$ -GI, -0.70% for glinides, -0.67% for biguanides, -0.92% for DPP4-i and -0.57% for SGLT2i. In contrast, less efficacy was found for GLP-1RA as -0.12% [9]. Both of DPP4-I and GLP-1RA have similar pharmacological route, and then the discrepancy may suggest another possible mechanism. In this case, his physique has been moderate with 22.0 kg/m<sup>2</sup> of BMI. In addition, he has daily habit of exercise such as softball [25]. These factors may contribute clinical improvement as well as add-on therapy of Twymeeeg.

Some limitation may exist in this report. Clinical efficacy of each OHA cannot be calculated precisely, because the case has continued add-on therapy for T2D. From the clinical course, however, Glubes (M/V) and Twymeeeg contributed enough for glucose variability. Further evaluation will be required for possible effect for each OHA.

In summary, 79-year-old male with T2D had hypoglycemic episode, followed by changing several OHAs such as EquMet and Twymeeeg. These add-on therapy showed improved clinical course associated with satisfactory HbA1c decrease. These data hopefully contribute future diabetic practice and research.

## Conflict of Interest

The authors declare no conflict of interest.

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