



## Relieved Depressive State and Glycemic Control in Type 2 Diabetes (T2D) Patient Treated by Imeglimin (Twymeeg)

Masaki Okada<sup>1</sup>, Hiroshi Bando<sup>1,2ID\*</sup>, Noboru Iwatsuki<sup>1</sup>, Kazuki Sakamoto<sup>1</sup>, Tomoya Ogawa<sup>1</sup>

<sup>1</sup>Sakamoto Hospital, Higashi Kagawa city, Kagawa, Japan

<sup>2</sup>Tokushima University/Medical research, Tokushima, Japan

Corresponding Author: **Hiroshi BANDO, MD, PhD, FACP** [ORCID ID](#)

**Address:** Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan; Tel: +81-90-3187-2485; Email: [pianomed@bronze.ocn.ne.jp](mailto:pianomed@bronze.ocn.ne.jp)

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### Abstract

The patient is a 66-year-old female being treated for hypertension. She developed a cerebral vascular accident (CVA) in October 2019, and was subsequently diagnosed with type 2 diabetes (T2D) due to an HbA1c level of 9.8%. She began a low carbohydrate diet (LCD) and started taking oral hypoglycemic agents (OHAs) such as metformin and linagliptin. From July 2021, she occasionally experienced anxiety and palpitations, leading to a diagnosis of reactive depression (adjustment disorder). Despite treatment with etizolam as needed, these symptoms persisted. In December 2022, due to an increase in HbA1c levels to 7.7%, metformin was switched to imeglimin (Twymeeg). By April 2023, her HbA1c had decreased to 6.9%, and she reported a sustained sense of well-being without psychosomatic symptoms.

### Keywords

Low Carbohydrate Diet, Oral Hypoglycemic Agents, Reactive Depression, Adjustment Disorder, Imeglimin (Twymeeg)

### Abbreviations

LCD: Low Carbohydrate Diet; OHAs: Oral Hypoglycemic Agents

### Introduction

Non-communicable diseases (NCDs) have been prevalent in both developed and developing countries for several decades [1]. Type 2 diabetes (T2D) is a significant disease within the metabolic syndrome (Met-S) and requires proper management worldwide. T2D is associated with various comorbidities, including macroangiopathy, microangiopathy, and psychosomatic issues [2]. In January 2023, the American Diabetes Association (ADA) published the

"Standards of Care in Diabetes," providing guidelines for the adequate management of T2D based on evidence-based and patient-oriented approaches. These guidelines aim to improve T2D management from multiple perspectives.

In addition to North America, European countries have established standard and shared perspectives on diabetic management. The European Association for the Study of Diabetes (EASD) has also published

applicable guidelines for diabetes management [3]. Japan has played a leading role in the Asian region, and the Japan Diabetes Society (JDS) released a consensus guideline statement in 2023 [4]. The JDS Committee on Consensus Statement Development introduced some changes in diabetic practice. In East Asian countries, DPP-4 inhibitors (DPP-4i) are more prevalent than metformin as a first-line antidiabetic agent for T2D, unlike the situation in North America and Europe [5]. This variation may be related to the current national health insurance system [6].

Among the various oral hypoglycemic agents (OHAs) used in diabetic practice, a recent topic of interest is the introduction of the novel drug imeglimin (Twymeeg) [7]. Imeglimin combines the mechanisms of reducing insulin resistance and increasing insulin secretion. This innovative OHA has been developed in Japan and represents a significant pharmacological achievement. The molecular structure of imeglimin is similar to that of metformin [8], which has long been the first-line OHA for T2D worldwide [9]. Similar to metformin, imeglimin can be prescribed as monotherapy or as an add-on combined therapy for T2D [10]. Various reports on the clinical application and efficacy of imeglimin have demonstrated its beneficial effects [11]. Imeglimin is taken twice a day (bis in die, bid), resulting in improved glucose variability during both daytime and nighttime [12].

The authors and collaborators of this article have long been involved in diabetic practice and research. Their areas of expertise include low carbohydrate diet (LCD) in conjunction with meal tolerance tests (MTT), various OHA administrations, continuous glucose monitoring (CGM), and more [13]. Among these topics, effective OHAs have been provided, and several T2D patients have been reported [14]. Recently, the authors' diabetic group treated a female patient with T2D who showed improved glucose control after switching from metformin to Twymeeg. This article will describe the general clinical progress of the patient and provide some perspectives on the treatment.

## Presentation of Cases

### *Medical History:*

The patient is a 66-year-old female who is being

treated for hypertension with anti-hypertensive agents (AHAs). In October 2019, she experienced sudden muscle weakness in her left hand and leg, which prompted her transfer to the neurosurgery department of our hospital for further evaluation and treatment.

On physical examination, slight left hemiparesis was observed in the upper and lower extremities. Brain MRI revealed a small infarction lesion in the right brainstem. Brain MRA examination showed stenosis of the right middle cerebral artery (MCA) and left posterior cerebral artery (PCA) in the cerebral vessels. Laboratory examination indicated an HbA<sub>1c</sub> value of 9.8% (**Fig-1**), leading to the initiation of appropriate treatment for type 2 diabetes (T2D). Nutritional therapy in the form of a low carbohydrate diet (LCD) was recommended, and she was prescribed two oral hypoglycemic agents, metformin, and linagliptin.

Due to the successful implementation of LCD and the use of oral hypoglycemic agents, her HbA<sub>1c</sub> value decreased to 6.6% in April 2020, and her condition remained stable for approximately one year. However, in 2021, her HbA<sub>1c</sub>, ALT, and GGT levels showed moderate increases. In January 2022, her HbA<sub>1c</sub> had risen to 7.8%, and she was advised to continue with the LCD meal plan. While her glucose variability improved for a period, her HbA<sub>1c</sub> increased to 7.7% in December 2022. Taking into account her lifestyle, diet therapy, exercise, and other factors, the diabetic team decided to initiate treatment with imeglimin (Twymeeg) from December 2022. As a result, her HbA<sub>1c</sub> gradually decreased to 6.9% in April 2023, demonstrating satisfactory clinical efficacy. The changes in ALT, GGT, and LDL are depicted in **Figure-1**.

During her clinical progress, she developed another medical issue. From July 2021, she experienced occasional feelings of anxiety and palpitations. During this time, her HbA<sub>1c</sub> levels increased from 6.4% to 7.4%. She had difficulty adhering to the LCD and felt anxious about her unstable diabetic control. She sought help from the psychosomatic department of a municipal hospital and received a diagnosis of reactive depression. She experienced various symptoms, including insomnia, shoulder stiffness, headache,

# Case Report

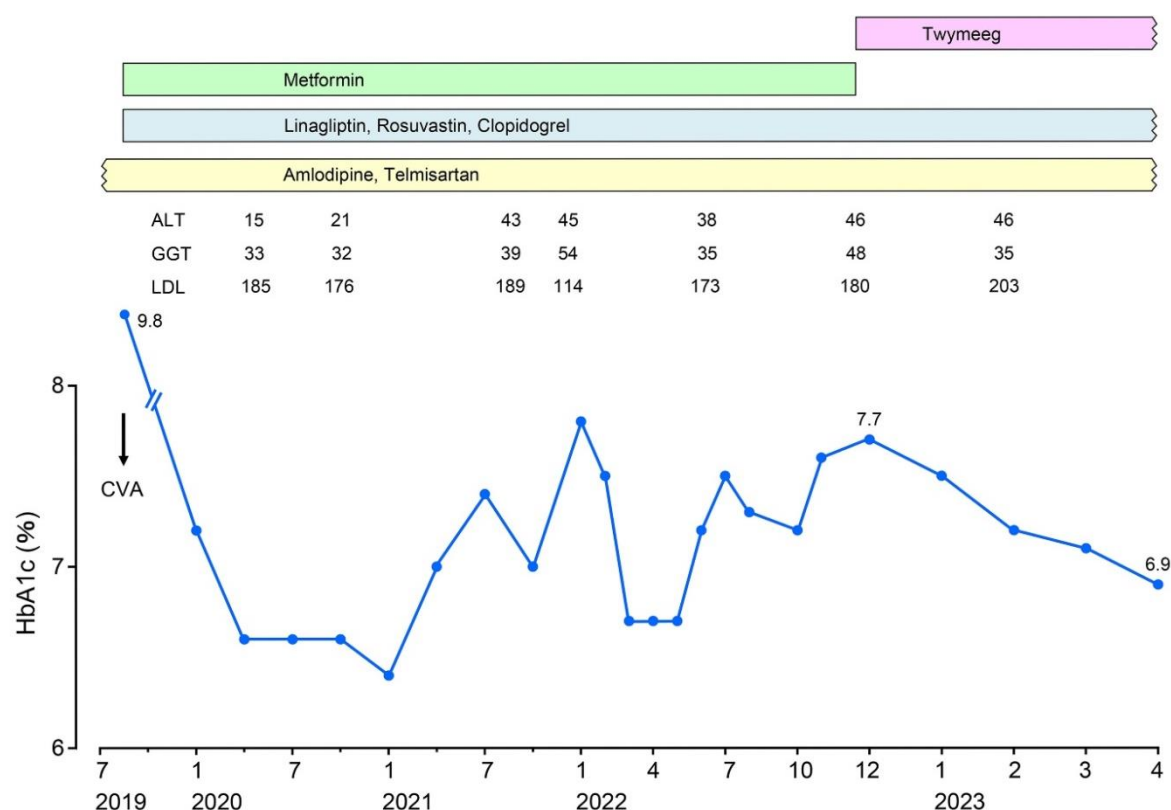


Fig-1: Clinical Progress About Changes in Hba1c and Treatment

general malaise, and dizziness. Etizolam 0.5mg was prescribed for her as needed (PRN). These symptoms persisted until December 2022. In response to the increase in HbA1c to 7.7%, metformin was replaced with Twymeeg. Over the course of four months, her HbA1c decreased from 7.7% to 6.9%, and she reported a sustained sense of well-being without psychosomatic symptoms.

## Physicals and Laboratory Exams:

During her physical examination in July 2021, the following findings were observed: The patient's level of consciousness and conversation were normal during the outpatient visit. Her vital signs, including pulse, blood pressure, temperature, and SpO<sub>2</sub> (oxygen saturation), were within normal limits. No significant changes were noted in the chest and abdomen upon examination. She exhibited normal walking and behavior, with slightly positive neurological findings of paresthesia (abnormal sensations such as tingling or numbness). Her physical measurements indicated a height of 160.7 cm, a weight of 61.7 kg, and a body mass index (BMI) of 23.9 kg/m<sup>2</sup>.

The results of biochemistry in July 2021 were in the following: HbA1c 7.4%, postprandial blood glucose 200 mg/dL, AST 26 U/L, ALT 43 U/L, GGT 39 U/L, Uric Acid 5.7 mg/dL, BUN 11 mg/dL, Cre 0.39 mg/dL, HDL 40 mg/dL, LDL 189 mg/dL, TG 295 mg/dL, T-Chol 288 mg/dL, CRP 0.06 mg/dL, TP 7.4 g/dL, Alb 4.5 g/dL, Na 141 mEq/L, K 4.0 mEq/L, Cl 100 mEq/L, RBC 4.27 x 10<sup>6</sup> /μL, Hb 13.7 g/dL, Ht 39.6 %, MCV 92.8 fL (80-98), MCH 32.0 pg (27-33), MCHC 34.5 g/dL (31-36), WBC 6900/μL, Plt 30.5 x 10<sup>4</sup> /μL, TSH 0.65 μIU/mL, free T<sub>3</sub> 2.8 pg/mL, free T<sub>4</sub> 1.2 ng/dL.

The patient's chest X-ray did not show any significant abnormalities. The electrocardiogram (ECG) revealed a pulse rate of 104 beats per minute with an ordinary sinus rhythm and tachycardia, but no ST-T changes were observed. She underwent mechanocardiogram and sphygmogram testing. The results showed an ankle brachial index (ABI) of 1.15 in both the right and left sides. The cardio-ankle vascular index (CAVI) was measured as 9.2 on the right side and 14.9 on the left side (**Fig-2**). Further analysis of the data indicated that both the % mean arterial pressure (%MAP) and upstroke time (UT) yielded negative results.

## Case Report

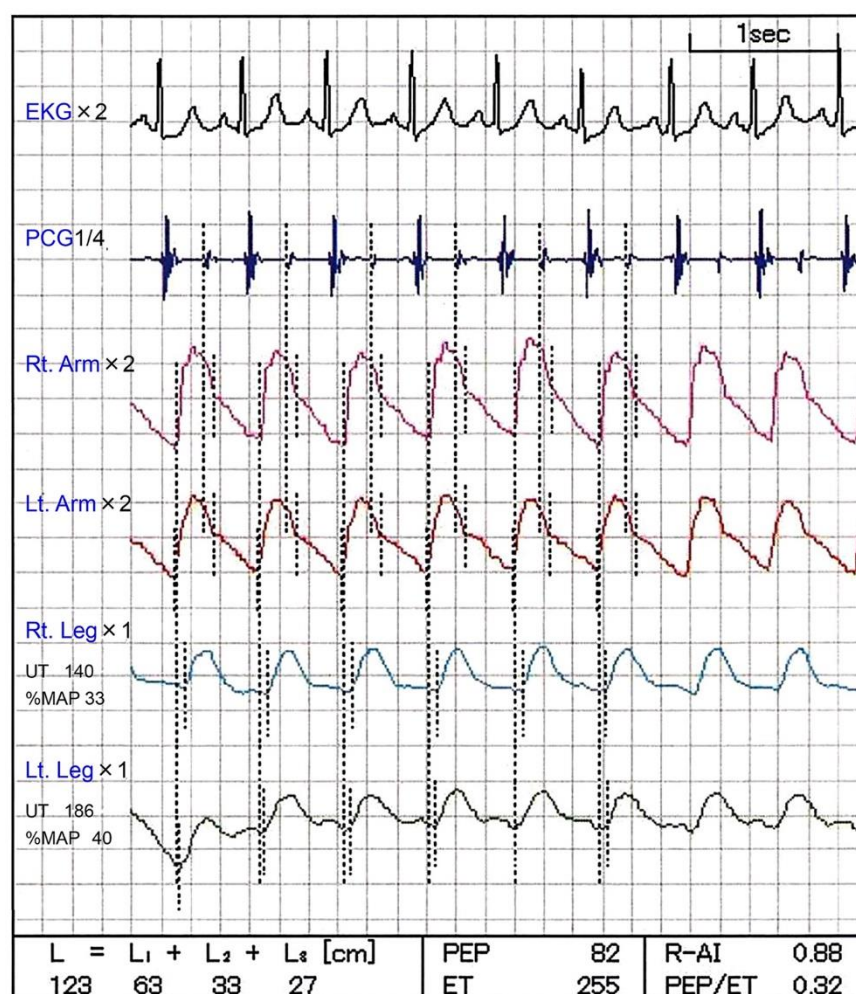


Fig-2: The Results of Mechanocardiogram and Sphygmogram

## Ethical Standards

The current case report adheres to the ethical guidelines outlined in the Declaration of Helsinki. Additionally, measures have been taken to protect the individual's personal information in accordance with relevant regulations. These principles align with the ethical rules governing clinical practice and research involving human subjects. Several guidelines have been established based on official presentations by the Japanese Ministry, specifically the Ministry of Health, Labor, and Welfare (MHLW), and the Ministry of Education, Culture, Sports, Science, and Technology (MEXT).

The authors and collaborators of this report have established an ethical committee specifically for this research at Sakamoto Hospital in Kagawa, Japan. The committee consists of professionals, including the hospital president, physicians, head nurse, registered

nutritionist, registered pharmacist, and a legal professional. These committee members thoroughly discussed the current situation and agreed upon the research protocol.

Informed consent was obtained from the patient through a written document, ensuring that the patient was fully aware of the nature of the research and voluntarily agreed to participate.

## Discussion

The patient was originally treated for hypertension for years. The existence of T2D was found as elevated HbA<sub>1c</sub>, when CVA was developed. Then she was treated by LCD and OHA of linagliptin and metformin. During the course, she developed reactive depression associated with various psychosomatic symptoms. She was treated with Twymeeg to improve her diabetic condition, which improved her glucose variability and

also relieved her psychological problems. Then, the clinical problems can be summarized as follows: #1 hypertension, #2 T2D, #3 dyslipidemia of elevated LDL, #4 CVA and continuing rehabilitation of lower extremities to slight degree, #5 reactive depression, #6 Twymeeeg administration and #7 improved diabetic status and relieved psychosomatic feeling.

This patient developed CVA (problem #4), where the etiology suggested arteriosclerotic cardiovascular disease (ASCVD) such as hypertension, T2D and dyslipidemia (#1, 2, 3). Changes in HbA1c, ALT and GGT seemed to be parallel, probably suggesting fatty liver. Furthermore, she was provided Rosuvastatin, but LDL has not been sufficiently lowered. Recently, some novel agents for dyslipidemia have been introduced to clinical practice, such as ezetimibe, pemafibrate and others [15,16]. These agents can contribute more for clinical efficacy by combination treatment with statins [17,18].

When the case visited the specialist of psychiatric department, she was diagnosed as reactive depression or adjustment disorder, which was related to #4, 5 [19]. The cause seemed to be some factors, including stressful daily rehabilitation for lower extremity, diabetic control, continuing LCD and limited daily life due to COVID-19 pandemic. From psychological and psychiatric points of view, reactive depression was used before, whereas adjustment disorder has been recently used [20]. The diagnosis of adjustment disorder was firstly appeared in DSM III. In this case, the stressor is defined as various stress in the daily life. It is not necessarily for overwhelming quality or quantity. Thus, such concept was recognized in modern society [21].

Current case had taken metformin before, and changed from metformin 500mg/day to imeglimin 2000mg/day. Metformin has been first-line OHA for T2D for long years, and imeglimin has similar molecular construction as metformin. Imeglimin can use the add-on treatment for all of previous OHAs. Their clinical efficacy has been reported from Trials of IMeglimin for Efficacy and Safety (TIMES) 1,2 and 3 [23,24]. The results were as follows: 0.46% in monotherapy, 0.92% in DPP4-i, 0.67% in biguanides,

0.57% in SGLT2i and 0.12% in GLP-1RA. Imeglimin has dual clinical effects for reducing insulin resistance and elevating the insulin secretion via mitochondrial mechanism [24].

As regards to the problem #6, current case showed improved glucose variability as decreased HbA1c. In this case, one of the reasons for starting Twymeeeg was that the case was not so obese, but existing ASCVD predisposition may contribute satisfactory clinical efficacy [25]. She did not feel any gastro-intestinal adverse events (GIAE) [26]. On the other hand, the case showed feeling healthier sensation in her daily life after starting imeglimin. The response may be from improved glucose variability, decreased daily value of mean amplitude of glycemic excursions (MAGE), reduced appetite before and so on [27,28].

As the problem #7, current case showed better healthy feeling after administration of Twymeeeg. It was associated with reduced nausea and other indefinite complaints. Previous reports showed some relationships between Twymeeeg intake and increased GIAE such as nausea [29,30]. From the large study of TIMES 1, some ratio of patients had felt GIAE [31]. Among various types of OHAs, Twymeeeg does not show higher incidence of GIAE so far [32].

Some limitation may be present in this report. The case is characteristic for the combination of T2D, other ASCVD diseases, and unstable psychosomatic trait such as reactive depression or adjustment disorder. We cannot diagnose whether the psychosomatic problem is one of the diabetic complications or not. For diabetic therapy, the combined treatment of imeglimin and metformin has been usually found in clinical practice. Then, add-on and other combined therapies will be possible according to the clinical progress in the future.

In summary, 66-year-old female has developed T2D and reactive depression during the clinical progress. Various perspectives were shown concerning diabetes, imeglimin and psychosomatic aspects. This article will hopefully contribute medical research and development as a useful reference.

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### Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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