



# Effective Imeglimin (Twymeeg) Treatment for Diabetic Patient with Various Medical Problems

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## Abstract

Current case is 75-year-old patient with type 2 diabetes (T2D), hypertension, hyperuricemia, possible cerebral vascular accident (CVA), coronary heart disease (CHD), mild dementia, androgenetic alopecia (AGA) and reflux esophagitis (RE). He was given EquMet from August 2021 with stable situation, and HbA1c increased to 8.5% in April 2023. He started to take imeglimin (Twymeeg), and HbA1c decreased to 6.2% for 4 months with remarkable clinical efficacy. This case has various medical problems with several pharmacotherapy. Administering dutasteride for AGA may influence cognitive dysfunctions, and imeglimin may develop gastrointestinal adverse effect (GIAE). Some inter-relationships among them may be considered.

**Keywords:** Imeglimin (Twymeeg); Androgenetic alopecia (AGA); Dutasteride; Gastrointestinal adverse effect (GIAE); Japan LCD promotion association (JLCDPA)

## Introduction

From epidemiological point of view, global burden of type 2 diabetes (T2D) has been increasing for decades [1]. The elevation status of T2D will bring the increase of atherosclerotic cardiovascular disease (ASCVD) such as cerebral vascular accident (CVA), coronary heart disease (CHD) and peripheral artery disease (PAD) which are diabetic macroangiopathy. Concerning the treatment of T2D, adequate judgement and management has been presented by American Diabetes Association (ADA). ADA announced the latest standard care method on January, 2024 [2]. Furthermore, novel types of oral hypoglycemic agents (OHAs) have been introduced to medical practice. Among them, imeglimin has attracted attention for its clinical efficacy and functioning mechanism via mitochondria [3]. For T2D treatment, three main principles have been known, which are nutrition, exercise and medicine. The basic therapy would be adequate nutrition, where calorie restriction (CR) or recent low carbohydrate diet (LCD) has been applied. When ingesting carbohydrate, blood glucose always increase according

to the amount of carbohydrate [4]. From historical point of view, CR was formerly popular, and after that LCD has been evaluated for its clinical efficacy [5]. Especially, ketogenic LCD has also provided more actual effect through the energy production of ketone bodies [6]. LCD was initiated by Doctors of Atkins and Bernstein in western countries [7,8]. Successively, authors and collaborators have begun LCD in Japan, and developed LCD measure clinically and socially through Japan LCD promotion Association (JLCDPA) [9]. We have often educated many people and patients with T2D and obesity for adequate method of LCD in the usual lives. They are petite-LCD, standard-LCD and super-LCD, in which containing carbohydrate amount would be 40%, 26% and 12%, respectively [10].

Combining adequate nutritional treatment and pharmacological agents, T2D patients would be treated in satisfactory manner than before [11]. Our diabetic research team has continued holistic practice for patients with T2D, T1D, SPIDDM and life style-related diseases for long [12]. We have informed actual LCD measures and treated T2D patients with balanced daily treatment [13]. Recently, we have been in charge of an impressive T2D case associated with various medical problems and remarkable

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efficacy of imeglimin. In this article, general outline of the patient and some perspectives are presented.

## Case Presentation

### Medical History

The reported case is a 75-year-old male with T2D, hypertension and other medical problems. He has taken several kinds of oral medicines for years. He has been treated in some departments of internal medicine, urology and dermatology. Concerning recent treatment of T2D, he was treated by pioglitazone until summer 2021 (Figure 1). After that, it was changed to glimepiride associated with the addition of EquMet. His HbA1c level increased to 8.5% in May 2023, and then he was started to take imeglimin (Twymeeg). Successively, HbA1c value has been acutely reduced as 7.6%, 7.1%, 6.5% and 6.2% for consecutive 4 months.

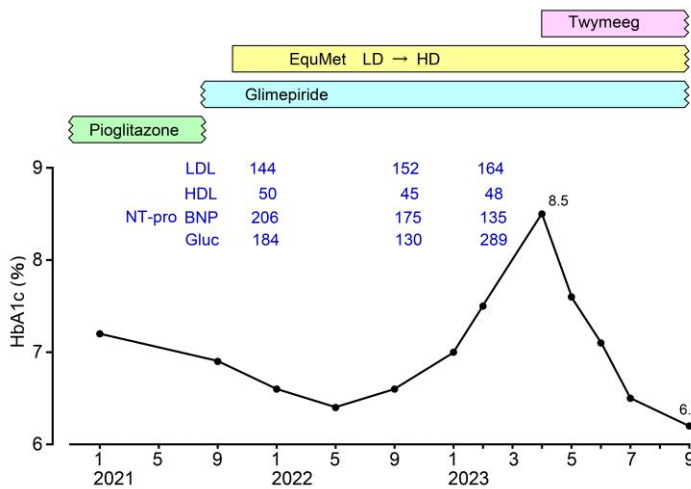


Figure 1: Clinical progress of the case.

### Several Exams

During his clinical progress, his laboratory results are summarized in Table 1. They have been stable, and unremarkable changes were found. Chest X-ray was negative. Electrocardiogram (ECG) showed ordinary sinus rhythm (OSR), in which Pulse 57/min, R-R interval 1.052 sec, P-R 0.169 sec. QRS 0.101 sec, QT 0.398 sec, axis -8 degree, SV1 0.79 mV, RV5 1.80 mV, R + S 2.59 mV (Figure 2). Findings are slight left axis deviation and counter-clock rotation.

### MRI and MRA examination

MRI and MRA exams were performed in September, 2021 (Figure 3). Selective atrophy of the hippocampus was somewhat conspicuous and consistent with the characteristics of Alzheimer's disease (AZ) [14,15]. Compared to the previous exam, small signal changes in the deep cerebral white matter and subcortex

were the same as before. There was no significant difference in the low signal level adjacent to the dorsal side of the left ventricular trigone on T2-weighted images, and no new vascular disorders or lesions were observed.

The nodules within the trigone of the bilateral lateral ventricles also have similar FLAIR hyperintensity under the ependyma of the trigone. No new high signals found on DWI. MRA shows decreased signal and irregularities in the left and right internal carotid arteries and left middle cerebral artery. The origin of the left internal artery is also slightly thin. These are about the same as the previous exam.

### Ethical Standards

This case complied with standard ethic guideline in Declaration of Helsinki [16]. Moreover, some comment is found for the information regulation. The principle has been observed in ethical rule as to medical practice and related research. Clinical various problems for human being have been present. Important guidelines have been valid from Japanese government, which are Ministry of Health, Labor and Welfare (MHLW) and Ministry of Education, Culture, Sports, Science Technology (MEXT). The authors et al. set up the ethical committee about current case study. It existed in Kanaiso hospital, Komatsushima, Japan. The committee consists of several hospital staffs. They are the president of the hospital, physician, registered nurse, pharmacist, nutritionist, and legal professional. These members have discussed the protocol with satisfactory situation. The required informed consent has been taken from the case with written document.

### Discussion

This case is a 78-year-old man who is characterized by T2D, as well as hypertension, coronary heart disease (CHD), cerebral vascular accident (CVA), dementia, urological and dermatological disease, and digestive health problems. Thus, he has various diabetic macroangiopathy, in which several medical treatments would be required [11]. His current situation seems polypharmacy, but his general condition has been stable.

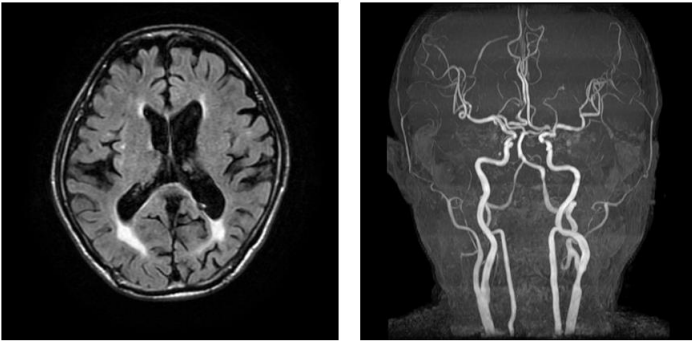
Medical problems and related pharmacotherapy would be summarized in the following. They are

- #1 T2D: EquMet (Egua and Metformin), imeglimin (Twymeeg), Glimepiride,
- #2 hypertension: cilnidipine,
- #3 hyperuricemia: silodosin,
- #4 dementia: galantamine hydrobromide,
- #5 CHD: bisoprolol fumarate,
- #6 CVA: aspirin,
- #7 androgenetic alopecia (AGA): dutasteride,
- #8 reflux esophagitis (RE): famotidine,

**Table 1:** Consecutive results of blood chemistry.

	2021 Sep	2021 Dec	2022 Jul	2023 Mar	2023 Jun	Units
<b>Liver</b>						
AST	28	22	16	19	17	(U/L)
ALT	34	12	10	17	11	(U/L)
GGT	12	11	22	26	21	(U/L)
<b>Nutrition</b>		6.3	6.6	6.8	6.4	
TP		4.0	4.1	4.3	4.2	(g/dL)
Alb						(g/dL)
<b>Lipids</b>						
LDL		144	152	164	146	(mg/dL)
HDL		50	45	48	48	(mg/dL)
TG		120	97	125	93	(mg/dL)
<b>Renal</b>						
BUN		15	14	14	13	(mg/dL)
Cre		0.73	0.72	0.77	0.66	(mg/dL)
UA		3.8	4.6	3.9	5.4	(mg/dL)
<b>CBC</b>						
RBC	393	437	464	509	466	(x10 <sup>4</sup> /L)
Hb	10.8	11.1	11.7	12.6	11.7	(g/dL)
WBC	52	47	54	75	63	(x10 <sup>2</sup> /L)
PLT	17.4	16.1	23.3	23.8	25.6	(x10 <sup>4</sup> /L)
<b>Metabolism</b>						
Glucose	376	184	130	289	133	(mg/dL)
HbA1c	6.9	6.9	6.6	8.0	7.1	(%)
NT-proBNP	222	206	175	135	141	(pg/mL)
CRP		0.02	0.06			(mg/dL)

**Figure 2:** Electrocardiogram.

**Figure 3:** Brain MRI and MRA.

a: MRI finding

b: MRA finding

Main medical problem in this case would be T2D associated with hypertension, hyperuricemia, CHD, CVA (#1,2,3,5,6). Further, he had dementia (#4) that is related with arteriosclerosis (#1,2,3,5,6). For anti-hypertensive agent (AHA), cilnidipine (#2) has been compared with amlodipine for years [17]. The former shows a little stronger effect for protecting renal function associated with hypertension than the latter [18]. There would be possible relationship between dementia and AGA (#4, #7) [19]. Dutasteride is known to have some adverse effect for recognition level [20]. By sensitivity analyses, younger cases and those with alopecia showed higher odd ratio of cognitive dysfunctions [21]. For GI tract complaints, these are possibly related to diabetic neuropathy and gastrointestinal adverse effect (GIAE) of imeglimin (Twymeeeg) (#1, 8, 9). This case did not feel GI problems after starting Twymeeeg.

Regarding actual treatment, some points are found corresponding to his clinical situation. It is known that SGLT2-i has some benefits for T2D, cardiovascular system and renal function. We have considered to give SGLT2-i to this case. On the other hand, certain disadvantage of SGLT2-i is present, such as increased urine output and higher risk of dehydration. In this case, mild dementia is observed in daily life, associated with prostate enlargement, frequent urination, slight CVA, and higher risk of dehydration in summer [22]. For these reasons, SGLT2-i was not administered. Our medical team will pay attention to these medical problems in his clinical progress.

From a prospective observational investigation, diabetic patients show 43% higher risk for Alzheimer disease (AZ), 43% higher of all kinds of dementia, and 91% higher of vascular dementia in comparison with those without diabetes [23]. In a well-known large study of Hisayama study, Japan. For 15-year study, diabetic people tended to have increased AZ, vascular dementia and all kinds of dementia compared with those of normal glucose tolerance [24]. This case was provided imeglimin (Twymeeeg) and other OHAs, who showed remarkable clinical effect. HbA1c value was reduced in short period. By the data of international

studies of Trials of IMeglimin for Efficacy and Safety (TIMES) 1, 2, 3, clinical response for monotherapy and combined therapy was reported [25]). They are 0.46% in monotherapy, 0.67% in biguanide, 0.92% in DPP4-i, 0.57% in SGLT2-i, and 0.56% in SU [26].

There is limitation in this article. Observed clinical effect would be due to Twymeeeg, other OHAs and continued LCD. However, other related factors may be present, which are involved in the daily life of the patient. Consequently, this case will be followed up with close attention.

In summary, 75-year-old T2D male patient was described in this case report. It showed clinical effectiveness of glucose variability. We hope that this document will be some reference for clinical research in the future.

### Conflict of Interest

The authors declare no conflict of interest.

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