

Diabetic patient with arteriosclerosis and cholelithiasis treated by imeglimin (Twymeeg) and vildagliptin/metformin (EquMet)

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Abstract

This case is 81-year-old male patient with type 2 diabetes (T2D), dyslipidemia, cerebral vascular accident (CVA), and cholelithiasis. His HbA1c increased to 8.8% in December 2022, and then oral hypoglycemic agents (OHAs) were changed to vildagliptin/metformin (EquMet) and imeglimin (Twymeeg). The add-on treatment was effective as HbA1c 6.6% in July 2023. By plethysmography for diabetic macroangiopathy, cardio-ankle vascular index (CAVI) showed for 10.3 to 12.1 with decreased ankle brachial index (ABI) as 0.72/0.88, indicating peripheral artery disease (PAD). International large studies for imeglimin showed effective add-on therapy by Trials of IMeglumin for Efficacy and Safety (TIMES) 1, 2 and 3.

Keywords: Cerebral vascular accident (CVA); Cardio-ankle vascular index (CAVI), Plethysmography, Peripheral artery disease (PAD), Trials of IMeglumin for Efficacy and Safety (TIMES)

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Introduction

Type 2 diabetes (T2D) has become a crucial disease in the light of health and medical aspects worldwide [1]. The management of T2D was presented by American Diabetes Association (ADA) in 2023 as the "Standards of Care in Diabetes" [2]. The fundamental therapy for T2D consists of nutrition, exercise and pharmacotherapy. For meal treatment, Low Carbohydrate diet (LCD) has been started by the doctors of Bernstein and Atkins in European and North American countries [3,4]. Its basic principle is from the fact that taking carbohydrate brings elevated blood glucose [5].

For T2D, carbohydrate 1g can increase blood glucose 3mg/dL. LCD has been prevalent for its actual efficacy [6]. Moreover, authors and collaborators began in Japan developing LCD medically and socially through Japan LCD promotion association (JLCDMA) [7]. As a matter of fact, three LCD methods have been introduced. They are petite-LCD, standard-LCD and super-LCD, that include 40%, 26%, and 12% of carbohydrate amount, respectively [8]. By applying these manners, LCD has become basic recommended diet therapy for T2D.

For decades, novel effective oral hypoglycemic agents (OHAs) were introduced to clinical practice with enough effects [9]. They are dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium-

glucose cotransporter 2 inhibitor (SGLT2i), and glucagon-like-peptide 1 receptor agonist (GLP1-RA). In addition, another novel OHA is imeglimin (Twymeeg) [10]. It seems to have novel mechanism through via mitochondrial pathway [11]. Then, it is known to have dual action of decreased insulin resistance and increased insulin secretion [12]. Authors et al. have continued clinical research for diabetes for years [13]. We have recently a meaningful T2D case with some characteristic aspects. Its general situation and related perspective would be presented in this article.

Case Presentation

Medical History

This case is an 81-year-old male patient with T2D and dyslipidemia for more than 6 years. He developed previously cerebral vascular accident (CVA) 4 years ago, and had the episode of cholelithiasis and elevated liver function test in September 2021. He has continued several OHAs for years. His HbA1c increased to 8.8% in December 2022, and then changed OHAs from Metformin and linagliptin to EquMet (Equa and Metformin). After that, HbA1c decreased 0.6% for two months. Furthermore, imeglimin (Twymeeg) was added from February 2023. Consequently, HbA1c decreased to 6.6% for 5 months (Figure 1).

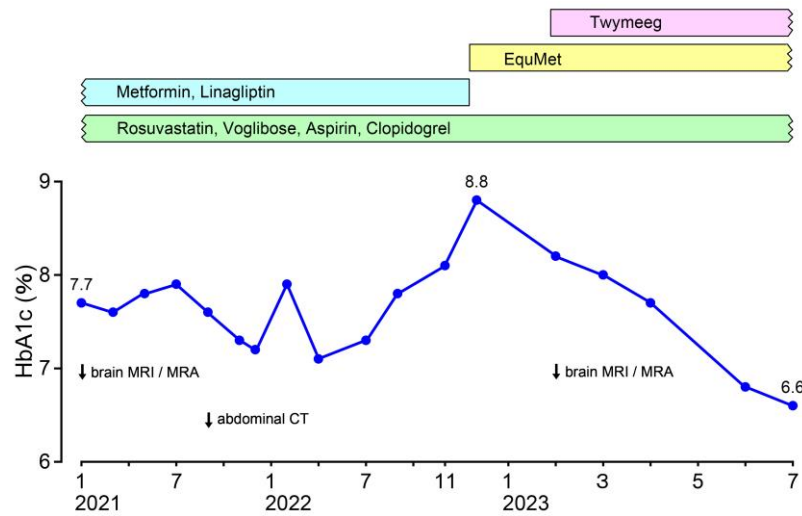


Figure 1: Clinical progress of HbA1c and treatment for T2D. EquMet and Twymeeg showed clinical effect.

Some exams

Physical examination revealed in the followings: vitals were BP 136/ 84 mmHg, pulse 72/min, SpO₂ 97%. Consciousness, speech and responses were normal. Unremarkable findings were observed in the heart, lung, and abdomen. Neurological tests showed no apparent sensory or motor abnormalities. His physique showed stature 150cm, weight 56.8kg and BMI 25.2 kg/m².

The results of laboratory tests in January 2023 were as follows: RBC 5.49 x 10⁶ /μL, Hb 13.9 g/dL, Ht 43.7 %, MCV 79.5 fL (80-98), MCH 25.2 pg (27-33), MCHC 31.7 g/dL (31-36), WBC 4300/μL, Plt 27.5 x 10⁴ /μL, uric acid 5.1 mg/dL, BUN 18 mg/dL, Cre 0.70 mg/dL, Na 144 mEq/L, Cl 104 mEq/L, K 4.4 mEq/L. Changes in laboratory data of lipids and liver function test are summarized in Table 1.

Table 1: Changes in laboratory renal and lipid data

		2020	2021			2022		2023	Units	
		Jul	Feb	Jun	Sep	Nov	Feb	Nov		Mar
Lipids	LDL	120	124	81		73		87	(mg/dL)	
	HDL	43	46	52		49		50	(mg/dL)	
	T-C	192	199	168		145		180	(mg/dL)	
	TG	144	143	174		114		214	(mg/dL)	
Liver	AST	60	61	68	126	33	55	87	40	(U/L)
	ALT	69	78	84	193	30	48	81	33	(U/L)
	ALP	232	254	117	283	144	264	101	102	(U/L)
	GGT	58	69	101	752	113	100	82	55	(U/L)

Chest X-P showed negative finding. Electrocardiogram (ECG) revealed pulse 76/min, normal axis, and ordinary sinus rhythm with unremarkable ST-T changes.

Plethysmography has been performed every year from 2020 to 2023. The values of cardio-ankle vascular index (CAVI) showed for 10.3 to 12.1 (Figure 2). The results of ankle brachial index (ABI) in July 2023 showed 0.72 in right and 0.88 in left, which indicates the presence of peripheral artery disease (PAD). ABI data in May 2022 were 0.73/0.91 about 1 year ago.

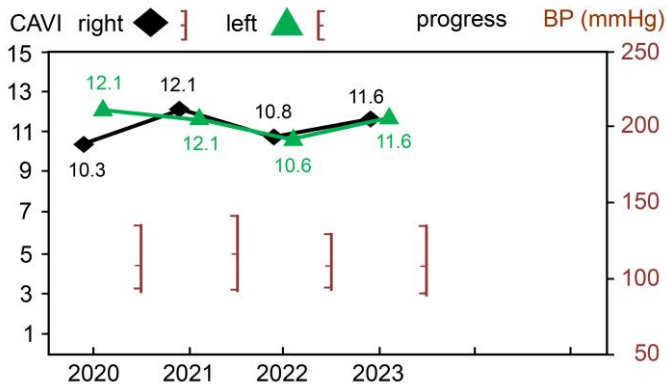


Figure 2: Changes in CAVI by plethysmography Arteriosclerosis is present from CAVI and ABI.

Radiological exams

Abdominal CT was conducted in September 2021. In the gall bladder (GB), several irregular high-density lesions were found. They were suggestive of cholelithiasis and sludge (Figure 3). Slight thickness of GB wall was observed. Liver showed fatty infiltration, and pancreas showed some fatty changes. Renal cyst and colon diverticula were observed. Otherwise, unremarkable findings were observed.



Figure 3: Abdominal CT scan Cholelithiasis and slight thickness of gall bladder exist.

Cerebral MRI and MRA was recently performed in Feb 2023, which was compared with those in Jan 2021. Both results showed almost no remarkable changes. DW1 MRI showed chronic infarction in the left frontal and left parietotemporal association areas (Figure 4a). The findings were almost the same as last time and no new DW1 hyper intensities were observed. Small lesion of the infarct of the corona radiata was also observed. As for MRA findings, stenosis was observed in the M1 region of the horizontal part of the left middle cerebral artery (MCA), and there was no change in the degree of stenosis

(Figure 4b). Distal vascular visualization has been preserved. Other than those findings, no other new changes were found.

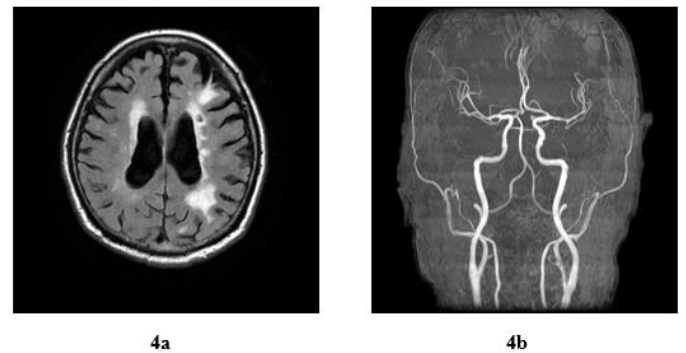


Figure 4: Brain MRI and MRA,

4a. infarcts are found in left frontal and parietotemporal areas
4b. stenosis is found in the M1 of middle cerebral artery (MCA).

Ethical consideration

The case was complied with the Helsinki Declaration as the ethical guideline. Moreover, some comments were presented by the basic regulation. The principle has included an ethic rule as to clinical research and practice. Some clinical problems as to human being have been present. This guideline was regulated by official Japanese Ministries that are Ministry of Health, Labor and Welfare and Ministry of Education, Culture, Sports, Science Technology. The authors and colleagues established the required ethical committee. It was present in Sakamoto Hospital, Kagawa prefecture, Japan. The committee includes several members that are hospital director, physician, neurosurgeon, registered pharmacist, nurse and also legal professional. The staffs discussed enough the content, and we have agreed the research protocol. We have obtained the informed consent of the document from the case.

Discussion

This patient showed some characteristic aspects. His problems include T2D, cholelithiasis, as well as previous slight CVA and PAD. For pharmacological treatment, EquMet and Twymeeeg were provided accompanied by clinical efficacy. Some discussion and perspectives are described in this article.

First, T2D presents the complications of microangiopathy and macroangiopathy. The latter includes CVA in the head and PAD in the extremities [14]. This case has previous medical problems of CVA, PAD and dyslipidemia, in which clopidogrel and rosuvastatin have been administered for long. LDL value has been decreased from 124 mg/dL to 73 mg/dL. Consequently, decreased LDL may contribute, at least in part, protective direction for macroangiopathy including CVA and PAD. From a systematic review, the administration of statins for patients with diabetes did not show apparent adverse effect [15]. From the data of post-marketing surveillance by FDA, lower rate values were recognized similar to other common agents for cardiovascular diseases [16]. Further, such dyslipidemia and

arteriosclerosis for years may cause the development of cholelithiasis.

Second, the case showed gradual progress of arteriosclerosis according to the plethysmography. CAVI values have been useful for evaluating the degree of arteriosclerosis, which have some factors influencing exacerbation [17]. The related factors are glucose control, blood pressure status, and LDL values [18]. Then, arterial stiffness can be evaluated by using the technique of pulse wave velocity (PWV) [19]. For recent years, Arterial stiffness index (ASI) has been convenient for arteriosclerosis. ASI can predict the exacerbation of isolated systolic hypertension associated with odds ratio as 1.30 [18]. Furthermore, LDL level for lipid profile may contribute arterial stiffness and also carotid intima-media thickness [20].

Third, current case has taken both OHAs of EquMet and Twymeeg, leading to clinical effects. For investigating EquMet efficacy, international VERIFY have been reported [21,22]. When compared the combined vildagliptin/metformin agents and metformin monotherapy, two groups were studied. If the applicants are more than 40 years old, add-on therapy revealed 46% reduction of risk degree of cardiovascular events [23].

Moreover, he took additional treatment of Twymeeg on fundamental EquMet administration. By Twymeeg intake, HbA1c showed remarkable decrease from 8.2% to 6.6% for 5 months. By international studies, clinical effects have been reported for administration of imeglimin, which is the Trials of IMeglimin for Efficacy and Safety (TIMES) 1, 2 and 3 [24]. Concerning the results, HbA1c reduction was found by monotherapy and also combined therapy. Obtained results were in the followings: -0.46% for monotherapy, -0.92% for DPP4-i, -0.67% for biguanides, -0.57% for SGLT2i, -0.12% for GLP-1RA, -0.70% for alfa-GI, -0.63% for insulin, and others [25]. From mentioned above, the case revealed remarkable HbA1c reduction by the combined treatment of these agents. However, large difference was detected between -0.92% for DPP4-i and -0.12% for GLP-1RA [26]. Both agents were known to show common route, but different efficacy will suppose another physiological mechanism [27]. Such novel mechanism of imeglimin may bring other pharmacological function with mitochondrial pathway [28].

Certain limitation may be present for this article. Medical effect of HbA1c reduction may be involved in combined intake of some OHAs, carbohydrate amount, and so on. The case is more than 80 years old, and has T2D with various complications. Then, future following up would be required with close attention.

In summary, 81-year-old male T2D with macroangiopathy was presented. He showed remarkable effect by EquMet and Twymeet for several months. It is expected that this report will become a useful reference for clinical practice and research.

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