

Relieved Glucose Variability in Patient with Type 2 Diabetes (T2D) And Cerebral Vascular Accident (CVA) Treated by Zultophy and Equmet (Vildagliptin/Metformin)

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Abstract

This case is a 64-year-old male patient with cerebral vascular accident (CVA), hypertension and T2D. He developed diplopia, blurred vision and vertigo in January 2020, and was diagnosed as left abducens nerve palsy with CVA. Brain MRI in DW1 showed high intensity from the dorsal side of the tegmentum to the right side of the medulla oblongata of Pons. He was provided Zultophy accompanied with some efficacy. HbA1c increased to 8.8% in March 2023, and then intake of Twymeeg showed effect as 6.7% in June. The cardio-ankle vascular index (CAVI) showed elevation from 8.5 to 14.2 for 5 years.

Keywords: Cerebral Vascular Accident (CVA); Type 2 Diabetes (T2D); Imeglimin (Twymeeg); Cardio-Ankle Vascular Index (CAVI); Plethysmography

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Introduction

Across the world, type 2 diabetes (T2D) has been increasing for years. About 540 million T2D patients have been found according to the recent statistics by International Diabetes Federation (IDF) [1]. T2D shows various problems from medical and health points of view [2]. In particular, diabetes may present common developments of macroangiopathy and microangiopathy [3]. They include cerebral vascular accident (CVA), ischemic heart disease (IHD) and peripheral artery disease (PAD), which are atherosclerotic cardiovascular disease (ASCVD).

For adequate management for T2D, applicable measure has been announced from American Diabetes Association (ADA) in 2023 as the "Standards of Care in Diabetes" [4]. They presented several recommendations for nutrition, exercise and pharmacological therapies. Among them, novel oral hypoglycemic agents (OHAs) have been recently introduced to medical practice with clinical efficacy [5]. They include sodium-glucose cotransporter 2 inhibitor (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP-4i) and glucagon-like-peptide 1 receptor agonist (GLP1-RA). Furthermore, recent novel agent would be imeglimin (Twymeeg) [6]. Imeglimin has novel function via mitochondrial mechanism [7]. It has dual action of increasing insulin secretion and decreasing insulin resistance [8].

Authors and collaborators have continued medical practice and

diabetic research until now [9]. The related categories are obesity, metabolic syndrome (Met-S), T2D, ASCVD, low carbohydrate diet (LCD), meal tolerance test (MTT), chronic kidney disease (CKD), and others [10]. Moreover, our diabetic team has reported several cases treated by imeglimin with improvement of diabetic variability [11]. We recently experienced an impressive case that revealed some characteristic points for glucose variability. Its generalized status and some perspective will be described in this report.

Case Presentation

Medical History

The current case is a 64-year-old male patient with cerebral vascular accident (CVA), hypertension and T2D. He was diagnosed as hypertension and T2D about 10 years ago, and treated by nifedipine and oral hypoglycemic agents (OHAs). In recent 5 years, he was treated by linagliptin and insulin. He developed diplopia, blurred vision and vertigo in January 2020, and visited neurosurgery department of our hospital. From clinical point of view, he was diagnosed as left abducens nerve palsy accompanied by CVA. He was hospitalized and received further evaluation and treatment.

Several Examinations

Physical examination showed as follows: vitals BP 150/ 96 mmHg,

pulse 76/min, SpO₂ 97%, speech and consciousness were normal, and no remarkable findings were observed in the lung, heart, abdomen. Neurological tests revealed no apparent hemiparesis, motor or sensory abnormalities. His physique showed stature 181.8 cm, body weight 66.0 kg and BMI 25.2 kg/m².

The results of laboratory exams in Jan 2020 were in the following: HbA1c 9.0 %, pre-prandial blood glucose 205 mg/dL, RBC 4.83 x

10⁶ /μL, Hb 14.9 g/dL, Ht 44.5 %, MCV 92.2 fL (80-98), MCH 30.8 pg (27-33), MCHC 33.4 g/dL (31-36), WBC 8200/μL, Plt 25.0 x 10⁴ /μL, TP 7.9 g/dL, Alb 4.8 g/dL, GOT 19 U/L, GPT 24 U/L, ALP 244 U/L (38-113), Uric acid 5.3 mg/dL, BUN 22 mg/dL, Cre 1.18 mg/dL, Na 139 mEq/L, Cl 97 mEq/L, K 4.3 mEq/L, T-Chol 244 mg/dL, CRP 0.6 mg/dL. Changes in laboratory renal and lipid data was summarized (Table 1).

Table 1: Changes in laboratory renal and lipid data.

		2020 Feb	Sept	2021 March	Aug	2022 Aug	Nov	2023 Feb	May	Units
Lipids										
	LDL	-	150	98	108	58	30	73	58	(mg/dL)
	HDL	-	39	37	39	41	40	43	34	(mg/dL)
	T-C	244	242	165	183	128	143	154	154	(mg/dL)
	TG	-	263	150	178	145	364*	188	310*	(mg/dL)
Renal										
	Cre	1.18	1.01	0.91	1.12	0.95	-	1.25	0.89	(mg/dL)
	eGFR	49.7	59	65.8	53	62.5	-	46.1	66.8	(mL/ml/1.73m ²)

Chest X-P showed negative finding. Electrocardiogram (ECG) revealed pulse 74/min, normal axis, ordinary sinus rhythm without remarkable ST-T changes.

Radiological Exams

Cerebral MRI and MRA were performed in April 2022 (Figure 1a). Regarding MRI, DW1 high intensity was observed from the dorsal side of the tegmentum to the right side of the medulla oblongata of pons. For this area, the lesion of the infarct has been present from before. Signal changes in the left occipital lobe showed signs of chronicity and contraction, which was similar to previous finding. FLAIR images showed patchy hyperintensities in the cerebral white matter, including bilateral thalamus, basal ganglia, and cranial radiatum. Furthermore, the calcification of the cerebral falx has been observed.

In MRA, mild irregularity has been found in the left vertebral artery, that was similar to previous results (Figure 1b). The right vertebral artery is thinner than the left, that showed no changes compared to the previous time. Stenosis of the internal carotid artery siphon on both sides is observed. The anterior cerebral artery (ACA) showed signal unevenness, and the signal drop is observed at the left M1/2 bifurcation as before.

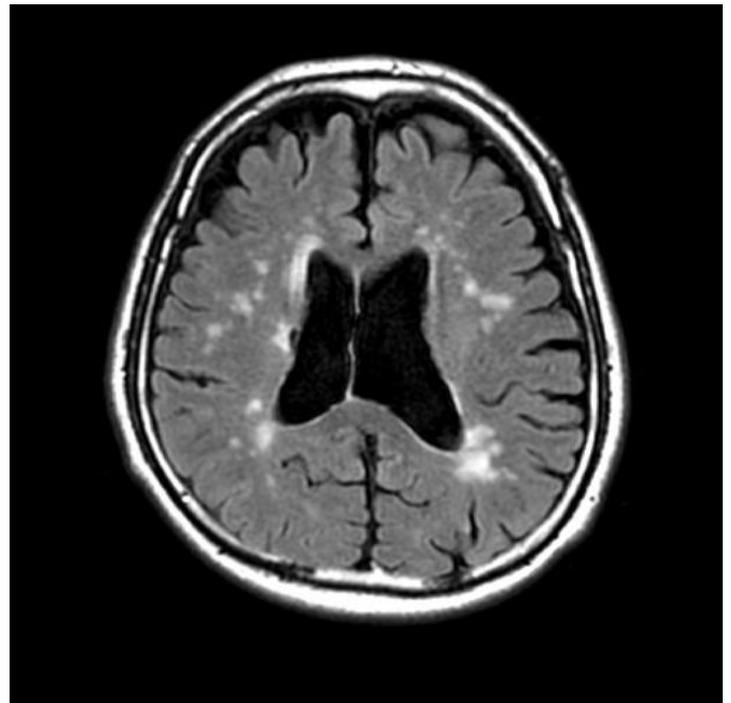


Figure 1a: Cerebral MRI.

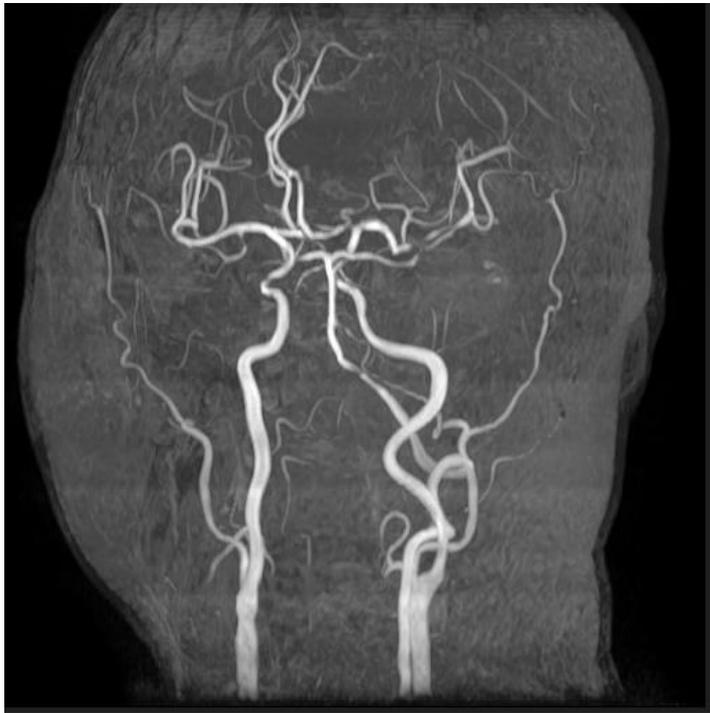


Figure 1b: Cerebral MRI.

Clinical Progress

The case was diagnosed as CVA, and started to take clopidogrel. In Jan 2021, HbA1c value increased to 9.6%, and then pharmacological treatment for T2D was changed from linagliptin and insulin to Xultophy (insulin degludec/liraglutide) (Figure 2). After that, glucose variability persisted unstable situation. In March 2023, he was provided imeglimin (Twymeeg) for further control of glucose profile. It showed satisfactory clinical efficacy for decreasing HbA1c from 8.8% to 6.7% for 3 months.

As the biomarker of arteriosclerosis, cardio-ankle vascular index (CAVI) has been measured by plethysmography from 2019 to 2023. The value of CAVI of left has been gradually increased from 8.5 to 14.2 during 5 years (Figure 3). For this period, HbA1c value had persisted moderately in higher degree.

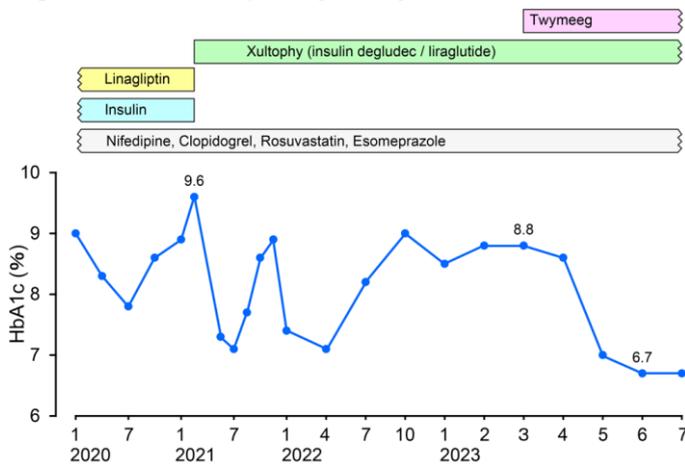


Figure 2: Clinical progress of HbA1c and treatment for T2D.

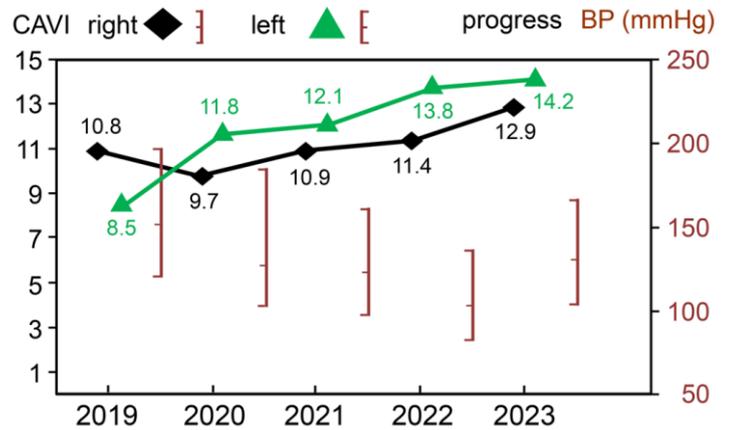


Figure 3: Changes in CAVI by plethysmography.

Ethical Consideration

This patient complied with the standard ethical guideline of human Helsinki Declaration. In addition, several comments were announced by the basic regulation. This principle included ethic rule concerning clinical research and practice. The recent principle included the ethic rule as to clinical practice and research. Some clinical problems as to human being have been present. The guideline is regulated by Japanese Ministries, which are the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science Technology. The authors and co-researchers have established the ethical committee. It exists in Sakamoto Hospital, Kagawa, Japan. This committee includes some staffs, which are hospital president, physician, neurosurgeon, pharmacist, head nurse and legal professional. These members fully discussed the protocol of the patient, and we agreed the research content. We obtained the document for the informed consent of the current case.

Discussion

This patient has several characteristic aspects. He had hypertension and T2D formerly, and developed cerebral infarction. CAVI values have showed gradual exacerbation for recent years. He was unable to limit his carbohydrate intake and was offered Xultophy and Twymeeg for glycemic control. Some perspectives are presented for these points.

Firstly, this case received annual exams of plethysmography, and presented gradual exacerbation of CAVI for years. The value of left CAVI increased every year from 8.5 to 14.2 during 5 years. It would be three main factors that influenced developed arteriosclerosis [12]. They are elevated HbA1c from unsatisfactory glucose control, elevated blood pressure from inadequate anti-hypertensive agents (AHAs), and elevated LDL from dyslipidemia [13]. Consequently, arterial stiffness has been regularly measured for the evaluation of developing arteriosclerosis by the exam of pulse wave velocity (PWV) [14]. Recently, Arterial stiffness index

(ASI) has been used for evaluating the developed arteriosclerosis in various situation. ASI seems to predict the aggravation of isolated systolic hypertensive state for 1.30 of odds ratio (OR), in which it increases to 2.20 of OR associated with the variability adjustment [13]. In addition, LDL in lipid profile influences the arterial stiffness and carotid intima-media thickness [15].

Secondly, this case could not keep satisfactory HbA1c values for years, because he continued to take moderate amount of carbohydrate in his daily life. By taking carbohydrate meal, blood glucose of T2D patient will increase with 3mg/dL per 1g carbohydrate [16]. Low Carbohydrate diet (LCD) has been begun by Atkins and Bernstein in North American and European countries [17,18]. Successively, LCD was evaluated for effective diet method [19]. Further, authors et al. in Japan have started LCD and developed LCD socially through various activities of Japan LCD promotion association (JLCDMA) [20]. From our method and protocol, three convenient diets have been prevalent. They are super-LCD, standard-LCD, and petite-LCD, including carbohydrate doses as 12%, 26%, and 40%, respectively. [21]. By applying these useful measures, LCD will be hopefully known and helpful in the future clinical practice.

Thirdly, HbA1c level was acutely decreased from 8.8% to 6.7% for 3 months by the administration of imeglimin (Twymeeg). His HbA1c reduction may be the combined effects of Xultophy (degludec and liraglutide, which are insulin and GLP-1RA) and Twymeeg. Clinical efficacy was found by the large international investigation, that is the Trials of IMeglamin for Efficacy and Safety (TIMES) 1,2 and 3 [22]. As to the results, HbA1c decrease was observed from monotherapy and add-on treatment. The reported effects were as follows: 0.46% in monotherapy, 0.63% in insulin, 0.12% in GLP-1RA, 0.67% in DPP4-i, 0.92% in SGLT2i, 0.67% in biguanides, 0.70% in alfa-GI, and so on [23]. From these findings, this case has showed moderate clinical efficacy of add-on therapy for Xultophy and Twymeeg. Large difference of clinical effect was observed between DPP4-i (0.92%) and GLP-1RA (0.12%) [24]. These two agents were believed to have common pathway, but different results would suggest possible novel physiological route [25]. It may be involved in pharmacological mechanism of imeglimin with mitochondrial pathway [26]. As to this report, some limitation may exist. Decrease of HbA1c would be from several factors including diet habit, exercise, therapy of Xultophy and imeglimin. The case has continued rather irregular meal habit taking moderate carbohydrate. Careful following-up would be continued associated with LCD and adequate pharmacological treatment.

In summary, 64-year-old patient with T2D, CVA, hypertension was reported. He was provided Xultophy and Twymeeg, which brought satisfactory decrease of HbA1c. This report hopefully becomes a reference for diabetic and arteriosclerotic problems in the future.

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