

Clinical Improvement by EquMet in patient with type 2 diabetes (T2D) and poor compliance of diet therapy

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Abstract

The case is 75-year-old male with previous hypertension and dyslipidemia. For recent 10 years, he has been treated for Type 2 diabetes (T2D), slight cerebral vascular accident (CVA) and mild cognitive impairment (MCI). His clinical problem included poor compliance of diet therapy. After he started EquMet (Equa + Metformin), his glucose variability became stable. HbA1c value decreased from 9.1% to 6.7% for 18 months. EquMet is provided twice a day, in which it shows medical efficacy of decreasing nocturnal blood glucose surge. This effect may contribute clinical improvement of glucose variability. His clinical progress will be followed-up with attention.

Key words: EquMet (Equa + Metformin); Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes (VERIFY); low carbohydrate diet (LCD); cerebral vascular accident (CVA); mild cognitive impairment (MCI); imeglimin (Twymeeg)

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Introduction

Type 2 diabetes (T2D) has become medical and social crucial disease to be managed properly across the world [1]. International standard guideline for T2D has been announced from American Diabetes Association (ADA) in Jan 2023 [2]. Recent trend has been observed on some oral hypoglycemic agent (OHAs) which has each characteristic efficacy [3]. They include DPP4-i, oral GLP-1RA, SGLT2i and imeglimin (Twymeeg) [4]. Furthermore, some OHAs have been developed as combined OHAs in actual practice, in which DPP4-i and metformin as biguanide have been found.

From historical point of view, metformin has been the first-line agent for long years [5]. For convenient usage of metformin, the combination of vildagliptin (Equa) and metformin (EquMet) has been known. It has been investigated in large international studies as vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY) [6]. From several results of VERIFY for years, earlier combined treatment for future better glycemic control has been reported. Consequently, earlier intensified treatment has been brought novel paradigm shift, where it has been recommended by ADA and European Association for the Study of Diabetes (EASD) [7]. Authors et al. have our diabetic research group and continued diabetic reports for years [8,9]. Our medical fields cover meal tolerance test (MTT), low carbohydrate diet (LCD), Carbo-70g breakfast loading, continuous glucose monitoring (CGM) and OHA-related investigation [10,11]. Among them, we investigated clinical effect of EquMet in T2D patients for Pubtexto Publishers | www.pubtexto.com

seasonal changes during consecutive several years [12-399]. We have recently treated an impressive case which showed clinical efficacy for Equmet. Its clinical progress associated with related perspectives will be described in this article.

Case Presentation

Medical History

The case is currently 75-year-old patient with T2D. About 13 years ago, he was pointed out to have hypertension and dyslipidemia. He started to take anti-hypertensive agent (AHA) and statin agent in the neurosurgery (NS) department. After that, he was diagnosed as T2D 10 years ago, and began oral hypoglycemic agents (OHAs) in internal medicine department. He had the episode of cerebral vascular accident (CVA) 8 years ago. It was a small cerebral infarct in left thalamus, accompanied with slight hemiparesis in right hand and legs at that time. After that, he has continued Clopidogrel and Ezetimibe until now. His neurological symptoms have been almost relieved by continuous rehabilitation. He gradually showed some symptoms of mild cognitive impairment (MCI) from 6 years ago, and then he continued to have memantine until now.

Concerning his general status in the daily life, he cannot maintain the nutritional diabetic therapy so well. Then, his wife has been trying to take care of him for years. His compliance for taking medicine has been almost good due to wife's support, but compliance for diet therapy has been rather incomplete. Consequently, his clinical progress of HbA1c had been rather unstable (Figure 1). As regards to OHAs, he has been treated by EquMet LD (Equa + Metformin), canagliflozin, and glimepiride. From August 2021, he changed to

take from EquMet LD to EquMet HD, for increasing metformin. After that, his glucose variability has been improved. In April 2023, HbA1c was decreased to 6.7%. During recent 4 years, his neurological status, vitals and conversation have been stable.

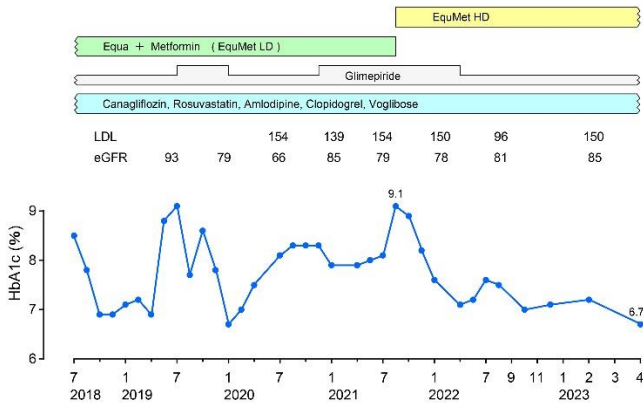


Figure 1: Clinical progress of the case

Physical examination

He has regularly visited departments of diabetes and neurosurgery for years. His physical examination in August 2021 showed in the following: Consciousness, speech and verbal response were normal. Vitals were stable as BP 138/82 mmHg, pulse 84 /min, SpO₂ 97%. His head, neck, heart and lung revealed unremarkable. Abdomen showed flat, soft without abnormal bowel sound. For neurological examination, his gait has been almost unremarkable, without apparent hemiparesis, motor disturbance, or sensory disturbance. His physique showed height 60.6 cm, weight 59.7 kg and BMI 23.1 kg/m².

Laboratory tests

The results of laboratory exams and physiological tests in August 2021 were as follows: HbA1c 9.1%, 2-hour post-prandial blood glucose 237 mg/dL, TP 7.4 g/dL, Alb 4.4 g/dL, GOT 17 U/L, GPT 12 U/L, ALP 202 U/L (100-340), GGT 37 U/L (7-74), Uric acid 4.5 mg/dL, BUN 20 mg/dL, Cre 0.74 mg/dL, eGFR 79.0 mL/min/1.73m², Na 137 mEq/L, Cl 102 mEq/L, K 4.5 mEq/L, HDL 66 mg/dL, LDL 154 mg/dL, post-prandial TG 236 mg/dL, CRP 1.08 mg/dL, WBC 8400/μL, RBC 5.26 x 10⁶ /μL, Hb 16.5 g/dL, Ht 48.9 %, MCV 93.0 fL (80-98), MCH 31.4 pg (27-33), MCHC 33.7 g/dL (31-36), Plt 26.9 x 10⁴ /μL. Urinalysis: glucose (+), protein (-), urobilinogen (+/-), pH 6.0, ketone bodies (-).

Several exams

Chest X-P test showed negative. Electrocardiogram (ECG) revealed normal axis, pulse 76/min, ordinary sinus rhythm (OSR), and unremarkable ST-T changes. He underwent the exam of the mechanocardiogram and sphygmogram. The results in

June 2021 showed that ankle brachial index (ABI) were 1.11/1.02 in right/left, respectively. The result of cardio-ankle vascular index (CAVI) showed 8.2/8.3, bilaterally. The same exams in December 2022 showed the results as follows: ABI showed 0.99/0.96, associated with CAVI 9.1/9.3, in which PEP, ET, R-AI and PEP/ET were stable compared with that of previous exam (Figure 2). Abdominal CT scan in September 2020 showed several findings. They were fatty liver, galls stone, thickened wall of gall bladder, atrophy of pancreas body, and colon diverticulum.

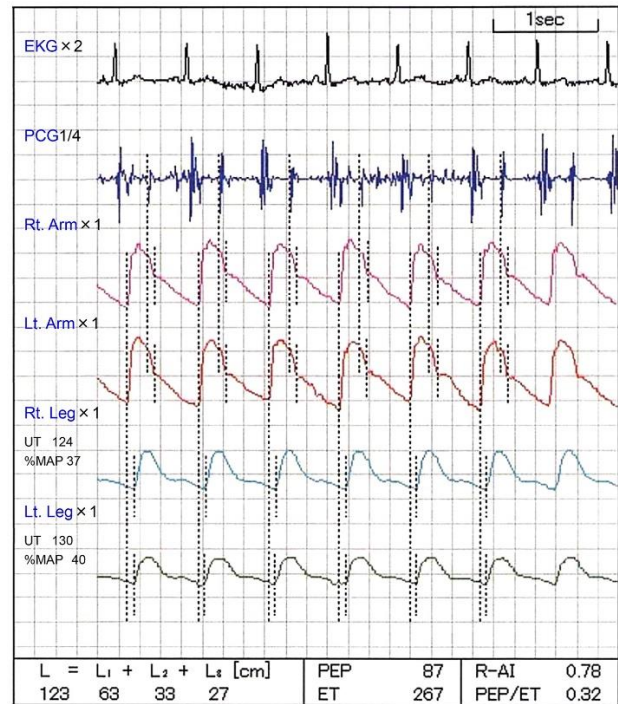


Figure 2: The exams of mechanocardiogram and sphygmogram

Brain MRI (magnetic resonance imaging) exam was conducted in June 2022, and its FLAIR (fluid-attenuated inversion recovery) findings are shown in Figure 3. Compared with the findings one year ago, no changes were observed for signal changes in the coronal radiatum and basal ganglia. A small hyperintensity in the left thalamus is slightly swollen from the previous time. No hyperintensities were found on DWI (Diffusion Weighted Imaging) and no new infarcts were observed. The lateral ventricle is slightly enlarged, but it has been almost the same as before.

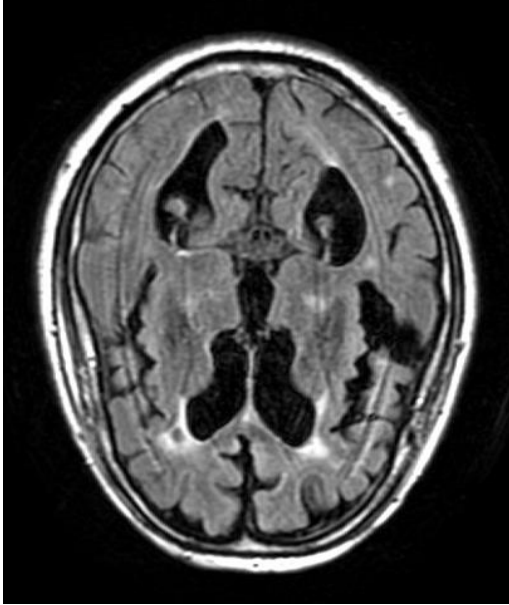


Figure 3: The finding of brain MRI

Clinical Progress

This case showed elevated HbA1c as 9.1 % in August 2021. Our diabetic team has investigated his daily situation in the light of meal, exercise and medicine intake with him and his wife. He was advised to keep clinical compliance, and he started EquMet HD instead of EquMet LD, where metformin doses were increased. After that, HbA1c value was gradually decreased to 7.1 % in April 2022. Consecutively, the doses of glimepiride were decreased. His glucose variability was relieved in April 2023, as HbA1c 6.7% (Figure 1).

From mentioned above, current case has had several continuous clinical problems. Several medical problems are summarized from bio-psycho-social points of view in the following. They are #1 hypertension, #2 dyslipidemia, #3 T2D, #4 CVA, #5 MCI, and #6 rather poor compliance of daily lives for meal and taking medicines.

Ethical standards

Current report is complied with the previous standard ethic guideline of Declaration of Helsinki. In addition, several commentaries are from the protective regulation associated with personal information. The related principle included the ethic rule about clinical practice and research. It is involved in the problems of human being. Certain guidelines have been proposed from Japanese government. They include Ministry of Education, Culture, Sports, Science Technology and also Ministry of Health, Labor and Welfare. The authors have established our ethical committee concerning the case. It was in Sakamoto Hospital, Kagawa, Japan. This committee included several hospital staffs and legal professional. They are hospital president, physician, Pubtexto Publishers | www.pubtexto.com

registered nurse, pharmacist and dietician. We have fully discussed about the current protocol and agreed enough for this protocol. Informed consent was taken from the patient by written document.

Discussion

Current case has several clinical problems, which can be summarized into 3 categories. They are i) Neurosurgery problems as CVA and MCI, ii) adequate glucose control with combined OHAs, and iii) poor compliance for diet habit. Some perspectives concerning these categories will be discussed in the order.

First, this case had medical problems of CVA and MCI. As his background, hypertension and dyslipidemia were from the 62 years old, diabetes from 65 yo, CVA from 67 yo, and MCI from 68 yo. These problems were developed from the exacerbation of arteriosclerosis. In contrast, he did not have obesity as BMI 23.1 kg/m². He was formerly diagnosed as MCI, in which Mini-Mental State Examination (MMSE) and Hasegawa's Dementia Scale-Revised (HDS-R) were applied [13,14]. They have been standard and prevalent exams for diagnosing MCI or dementia for long in Japan [15]. Consequently, MMSE and HDS-R have been useful and convenient in actual clinical practice [16]. In this case, mutual relationship was unlikely present between improving glucose control and managing situation for CMI. From a report, however, T2D becomes crucial risk factor for various symptoms in early dementia with odds ratio as 3.48 [17]. As regards to the diagnosis for cognitive impairment, related sensitivity and specificity were reported [18] MMSE showed 100% and 89%, respectively, z-score showed 100% and 89%, respectively, and combination of both exams showed 100% and 90%, respectively.

Second, this case was provided EquMet HD, which was effective leading HbA1c decrease. EquMet, a combination drug of vildagliptin and metformin, has undergone a large-scale clinical study of for newly diagnosed T2D patients. It was Vildagliptin Efficacy in combination with metfoRmIn for early treatment of type 2 diabetes (VERIFY) studies [6,19]. VERIFY was performed in 34 countries with 254 medical centers. As one of the DPP4-i, vildagliptin presented satisfactory efficacy by twice administration. It would be effective for stabilizing all-day blood glucose fluctuations [20]. Thus, EquMet seems to give improved glucose variability. Current case tends to have more carbohydrate in the supper. Consequently, EquMet may contribute much for the reduction of his nocturnal glucose surge.

Clinical efficacy of vildagliptin bid will present decreased value of mean amplitude of glycemic excursion (MAGE) [20]. Moreover, vildagliptin decreased MAGE for 20 mg/dL of blood glucose in six months [21]. Comparison of vildagliptin (twice) and sitagliptin (once) was conducted for clinical efficacy [22]. The compared results from each agent was 142 vs 153 mg/dL for 24-hour mean glucose, 111 vs 129 mg/dL for MAGE, 206 vs 223 mg/dL for highest

post-prandial supper, 484 vs 898 mg/min/dL for AUC in 3 hours after breakfast. Thus, vildagliptin intake twice daily would be larger benefits.

Third, his HbA1c values showed rather large fluctuation. Their reasons include the difficulty in maintaining a regular daily life, a favorable diet, and sometimes forgetting to take medicine. In other words, keeping good compliance was insufficient. His wife could confirm his taking medication, but she cannot manage his irregular meal style so much. Therefore, it was actually difficult to continue an ideal LCD method that does not raise blood glucose.

In order to improve diabetes management, some evidence-based daily lifestyle habit would be crucial. It focuses on the sequence, timing and composition of each meal. It seems to be beneficial habit to take balanced meals with lower consuming carbohydrate for diabetic patients and also healthy people [23]. Further, eating vegetable and protein components first in each meal can make glucose surge blunted. These methods can be applied easily in usual daily life. Concerning post-prandial glucose elevation, meal sequence of carbohydrate, protein and lipid would be important. Clinical effect of meat or fish before intake of rice, gastric emptying and changes in incretin secretion was studied [24]. The methods included some ways of rice before fish (RF), fish before rice (FR) and meat before rice (MR). As a result, glucose variability (15-240min) showed FR 1.94. MR 1.68 vs RF 2.77 mmol/L ($p < 0.05$). Time 50% of gastric emptying was FR 83.2 min, MR 82.3 min vs RF 29.8 min, ($p < 0.05$). Thus, meal sequence may play a crucial role for post-prandial glucose increase and delayed gastric emptying.

Systematic review for T2D was conducted for the effect of meal sequence and carbohydrate-later meal pattern (CLMP). The study included 8 trials with 230 cases for short and long-term changes [25]. Because of various protocols, results and judgment, significant differences were not observed for the changes in HbA1c, glucose value, insulin and GLP-1 values. Consequently, current review could not show significant proposal for meal sequence and CLMP. Fast eating habits may influence increased risk for obesity and diabetes. To investigate eating speed and meal sequence, 18 healthy female received experimental trials [26]. The protocol included i) vegetable first and carbohydrate first, ii) fast or slow eating, iii) test meal such as white rice, fried fish, broccoli and tomato. As a result, eating order by vegetable first and carbohydrate last can reduce post-prandial elevation of glucose and insulin response, even if eating was at fast speed.

Some limitation exists in the report. Current case revealed satisfactory effect of EquMet HD as the combination of DPP4-i and biguanide. This case has taken small doses of glimepiride for years [27], in which additional glimepiride as sulfonyl urea agent might play certain role for glucose variability. It would be

required to follow clinical progress from diabetic, neurological and general points of view.

In summary, case report of 75-year-old male with T2D and CMI was presented here. He showed satisfactory clinical effect of EquMet HD. This article showed certain perspectives concerning T2D, CVA, MCI and related matters. Current report would become hopefully useful reference for clinical research in the future.

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