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Remarkable Effects for HbA1c and Weight by Twymeeg (imeglimin) and EquMet in Type 2 Diabetes (T2D) Patient

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Abstract

The case is a 78-year-old male with type 2 diabetes (T2D) and hypertension treated by empagliflozin, metformin, amlodipine and telmisartan. HbA1c increased 5.4% to 7.4% in 2021-2022. By imeglimin (Twymeeg), HbA1c decreased to 6.3% for 8 months. Large studies were found as Trials of IMeglimin for Efficacy and Safety (TIMES) 1, 2 and 3. After that, HbA1c was elevated to 7.8% in April 2023. Then vildagliptin/metformin (EquMet) was started, and HbA1c decreased to 5.4% with 8kg weight reduction for 6 months. Thus, authors have continued to develop activities of low carbohydrate diet (LCD) through Japan LCD promotion association (JLCDPA).

Keywords: Imeglimin (Twymeeg); Trials of IMeglimin for Efficacy and Safety (TIMES); vildagliptin/metformin (EquMet); Low Carbohydrate Diet (LCD); Japan LCD promotion association (JLCDPA)

Introduction

Across the world, the number of the patients with type 2 diabetes (T2D) has been increasing due to the changes in usual lifestyle [1]. For its background, elevated prevalence of overweight, obesity and metabolic syndrome has been involved in the tendency [2]. American Diabetes Association (ADA) has recently presented the standard diabetic care in January, 2024 [3]. As to T2D therapeutic measures for T2D, some oral hypoglycemic agents (OHAs) have been recently developed to diabetic practice. Among them, imeglimin has been noticed attention for its novel clinical mechanism via mitochondria pathway [4].

Furthermore, diabetic research has brought effective OHA such as dipeptidyl-peptidase 4 inhibitors (DPP4-i). Recently, some OHAs shows the combined useful agents for convenient prescription in the actual medical practice. For example, the combined OHA has been known for vildagliptin/metformin as brand name of EquMet. It shows clinical efficacy by providing twice a day. Its large clinical studies were conducted for international levels, which was known as VERIFY [5]. It stands for vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes. Thus, intensified medication method had brought a new paradigm shift in the diabetic research and practice. Future adequate measure of diabetic pharmacology has been announced in North American and European regions for ADA and European Association for the Study of Diabetes (EASD) [6].

By taking carbohydrate per os, blood glucose value becomes elevated according to the carbo amount [7]. Historically, calorie restriction (CR) had been previously applied, but low carbohydrate diet (LCD) has been known to be effective nowadays for the treatment for T2D [8]. LCD was begun in health care region and medical care field by Bernstein and Atkins [9,10]. After that, authors et al. have initiated LCD in Japan, and successively developed LCD method socially and medically through our Japan LCD promotion Association (JLCDPA) [11]. We have broadly informed three types of useful measures of LCD for health and medical care region. They include super-LCD, standard-LCD and petite-LCD, where carbohydrate amount ratio is 12%, 26% and 40%, respectively [12].

In our diabetic research and practice experiences, we had a meaningful T2D male case, who showed remarkable clinical improvement by the administration of imeglimin and EquMet. His general clinical course and related discussion will be introduced in this report.

Case Presentation

Medical History

This case is a 78-year-old man with several diseases for years. He had been treated as hypertension, dyslipidemia and hyperuricemia for 10 years. In June 2018, he had noticed thirsty, general malaise and taste disorder and these symptoms persisted. He visited diabetic department of our hospital, and was diagnosed as T2D with the data of HbA1c 13.0% and post-prandial glucose 552 mg/dL. He has been treated by standard LCD nutritional treatment and pharmacological therapy of OHAs. They included amlodipine, telmisartan, empagliflozin, febuxostat and metformin. During Jan 2021 to February 2022, his glucose variability became aggravation with increasing of HbA1c 5.4% to 7.4% and weight gain from 85 to 93kg (Figure 1).

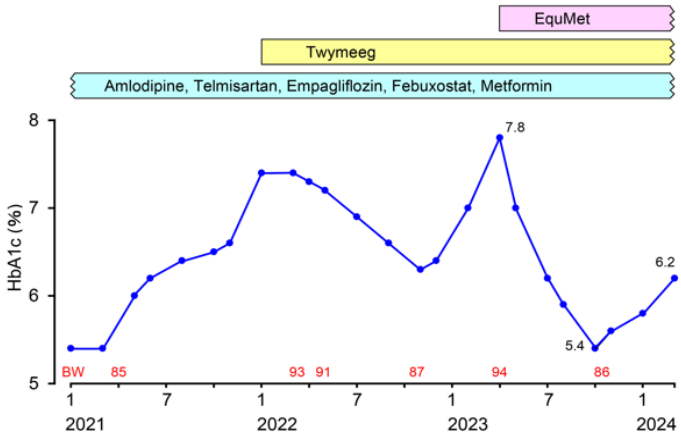

Figure 1: *Clinical progress of the case.*

Then, imeglimin (Twymeeg) was started and HbA1c value decreased from 7.4% to 6.3% for 8 months. However, HbA1c increased to 7.8% for peak for 5 months. In response to this aggravation of HbA1c, EquMet was added from April 2023. Clinical effect showed remarkable HbA1c reduction from 7.8% to 5.4% during 6 months. Simultaneously, his body weight was decreased from 94kg to 86kg. Thus, sufficient clinical efficacy was found.

Several examinations

Physical examinations in November 2023 revealed in the following: vitals, consciousness and speech were normal, his head, neck heart, lung, abdomen and neurological findings showed unremarkable. His physique showed height 167 cm, weight 87 kg, BMI 31.2 kg/m^2. The biochemical results in Nov 2023 showed in the followings: TP 7.1 g/dL, Alb 4.1 g/dL, AST 21 U/L, ALT 19 U/L, ALP 260 U/L (100-340), γ-GT 29 U/L, uric acid 5,9 mg/dL, BUN 11.7 mg/dL, Cre 0.71 mg/dL, eGFR 81.4 mL/min/1.73m^2, HDL 46 mg/dL, LDL 126 mg/dL, TG 147 mg/dL, glucose 118 mg/dl, HbA1c 5.6%, WBC 7600/μL, RBC 4.02 x 10^6 /μL, Hb 12.4 g/dL, Ht 39.6 %, MCV 99.0 fL (80-98), MCH 30.8 pg (27-33), MCHC 31.3 g/dL (31-36), Plt 30.8 x 10^4 /μL.

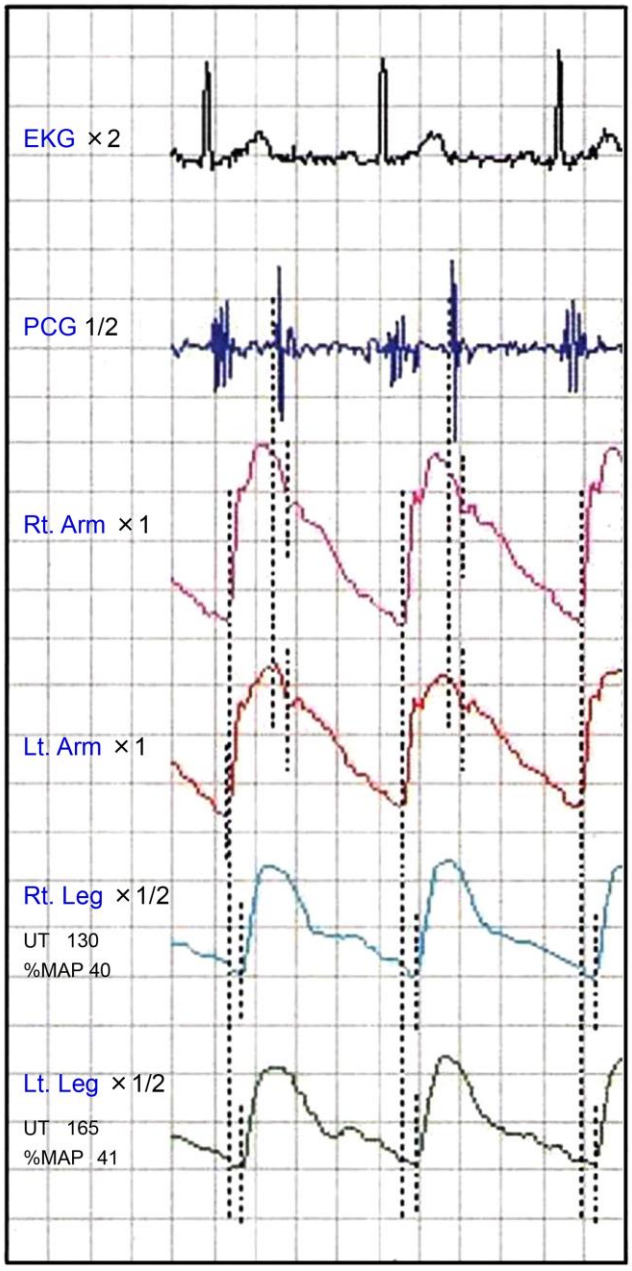

Figure 2: *Plethysmography examination.*

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As other physiological exams, chest X-ray showed unremarkable changes, and electrocardiogram (ECG) was ordinary sinus rhythm and no specific ST-T changes. Blood pressure pulse wave examination (plethysmography) was conducted. The ankle brachial index (ABI) showed 1.00/1.00 (right/left, normal range 0.91-1.40), and Cardio-Ankle Vascular Index (CAVI) showed 9.5/9.4 (R/L, 9.7+/- 0.9 for age), which were almost within normal range (Figure 2). For the reference, the standard values of ABI and CAVI are from the previous report [13].

Exams of MRI and MRI

Brain MRI and MRA examinations were conducted in April 2023 and compared with those in March 2022 (Figure 3). Cerebral atrophy and ventricular enlargement were approximately the same as last time, and no apparent lesions such as vascular disorders or masses were observed in the brain parenchyma. The enlargement of the cistern dorsal to the cerebellar vermis is also to the same extent. On MRA, tortuosity of the blood vessels is slightly noticeable, and a slight decrease in the signal of both vertebral arteries is observed. Otherwise, no new significant stenosis or aneurysm was observed.

Figure 3: *Brain MRI and MRA.*

Ethical Considerations

Current case was complied with the standard ethical guideline of Declaration of Helsinki [14]. In addition, some commentary was observed for the information regulation. This principle was observed in ethic rule regarding to the research and practice. Various clinical problem for human has been investigated. There was important guideline from Japanese government, which are originated from Ministry of Health, Labor and Welfare and also Ministry of Education, Culture, Sports, Science Technology. The authors and co-researchers have established the ethical committee for this case. It is in Sakamoto hospital, Kagawa, Japan. This committee included required hospital staffs. They were the director of the hospital, physicians, head nurse, pharmacist, dietitian, and legal professional person. The members discussed current protocol sufficiently. The informed consent was obtained from the patient by written document.

Discussion

Current case was 78-year-old male patient with T2D, hypertension, hyperuricemia and arteriosclerosis to some extent as aging process. He does not have apparent specific diabetic macroangiopathy such as cerebral vascular accident (CVA), ischemic heart disease (IHD), or peripheral artery disease (PAD) so far. Concerning microangiopathy, he has not complained of neuropathy, retinopathy or nephropathy. However, he has crucial medical problems of obesity with elevated BMI as 31.2 for metabolic syndrome, and has been treated by some effective OHAs [15].

This case showed significant HbA1c decrease from 7.4% to 6.3% for 8 months by the initiation of imeglimin (Twymeeg). In addition, weight reduction was observed from 93kg to 87kg during the same period. Otherwise, no particular changes of OHAs were found. From his clinical progress, pharmacological usefulness of Twymeeg was suggested. Diabetic efficacy for HbA1c by the combined therapy of OHAs were reported by international research projects of TIMES. It stands for the Trials of IMeglimin for Efficacy and Safety 1, 2 and 3 [16]. According to the summarized report, the reduction in HbA1c for each treatment was as follows: 0.46% for monotherapy, 0.57% for SGLT2-I, 0.92% for DPP4-I, 0.67% for biguanide, and 0.56% for SU [17].

Authors et al. have practiced clinical research for various diabetic patients [18]. Among them, educational cases with OHAs have been reported including EquMet [19]. We have treated and summarized T2D cases with EquMet for six years [20]. Through our important experiences, EquMet has shown clinical effect with decreased HbA1c. Current case also revealed remarkable efficacy of improving daily glucose fluctuation. As the sub-analysis of VERIFY studies, earlier combination of vildagliptin and metformin showed the decreased risk for macrovascular events [5,21]. In this case, hazard ratio (HR) was proved to be 0.71, indicating the predominance of EquMet from the initiation of treatment of T2D [5,21]. The comparison was investigated between metformin monotherapy and early combination of Equa (vildagliptin) and Metformin [22]. In VERIFY trials, two groups of young and late-onset T2D were compared. The analysis method has used statistical analysis plan (SAP) for VERIFY studies [21]. For its protocol, end point time was the period until treatment failure (TF) as HbA1c 7.0%. The result showed that early combined treatment developed the risk 46% vs 48%, in late-

onset *vs* young-onset group with significant difference, respectively. Then, treatment-naïve young group has brought improvement of early durability and late exacerbation of glycemic variability.

Some limitations are present in this report. Clinical efficacy may be involved in several factors, including imeglimin, vildagliptin, metformin, continuation of LCD and other related reasons. This is only one case with T2D treated by plural OHAs. Then, current case will be followed up with close attention in the future. In conclusion, 78-year-old men with T2D was reported in this article. It summarized clinical effects of imeglimin and vildagliptin/metformin. This report will become hopefully useful reference for developing diabetic research.

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