

Early elderly male with type 2 diabetes (T2D) changed from metformin to imeglimin (Twymeeg)

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Article Info

Article History:

Received: 29 January, 2023

Accepted: 02 February, 2023

Published: 05 February, 2023

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Abstract

Background: Imeglimin (Twymeeg) is latest focus of oral hypoglycemic agent (OHA).

Case presentation: Current case is 69-year-old male with type 2 diabetes (T2D) for 18 years.

Result: HbA1c value increased to 7.6% in Sept 2022, and then metformin 750mg/day was changed to imeglimin 2000mg/day. HbA1c decreased to 6.9% for 4 months.

Discussion and conclusion: Large study of Trials of IMeglimin for Efficacy and Safety (TIMES) showed beneficial efficacy for combined treatment of OHAs. Imeglimin has dual effects increasing insulin secretion and reducing insulin resistance. Perspectives concerning pharmacological effects of metformin and imeglimin are described in diabetic practice and research.

Keywords: imeglimin (Twymeeg); type 2 diabetes (T2D); Trials of Imeglimin for Efficacy and Safety (TIMES); oral hypoglycemic agent (OHA); Metformin

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Introduction

For recent years, type 2 diabetes (T2D) has become important disease for our medical social lives over the world. Latest guideline was presented by American Diabetes Association (ADA) proposed in Jan 2023 as "Standards of Care in Diabetes" [1]. The common purpose of elder T2D patients would be maintaining health associated with reducing several diabetic comorbidities. They include microangiopathy, macroangiopathy, and also atherosclerotic cardiovascular disease (ASCVD) [2]. The influence of T2D would be more crucial than before, and then appropriate protective management would be necessary for this urgent problem [3].

Basic principle of diabetic treatments include nutrition, exercise and anti-diabetic agents such as oral hypoglycemic agents (OHAs) [4]. For decade, novel OHAs were introduced to clinical practice associated with satisfactory pharmacological efficacy. They include dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like-peptide 1 receptor agonist (GLP1-RA) and sodium-glucose cotransporter 2 inhibitor (SGLT2i) [5]. Furthermore, latest topic would be imeglimin (Twymeeg), which shows dual function of elevated insulin secretion and reduced insulin resistance [6,7]. The detail molecule of imeglimin has similarity with that of metformin [8]. Metformin has been for years the first-line of OHA worldwide against the patients with T2D [9]. It was also prescribed by monotherapy or

combination treatment for T2D [10].

Authors have continued diabetic research and actual practice for years, associated with the proposal of low carbohydrate diet (LCD), meal tolerance test (MTT) and continuous glucose monitoring (CGM) [11]. Furthermore, we have applied effective OHAs to various T2D patients and reported the perspectives in the light of pathophysiology [12]). Imeglimin has shown additional fundamental and clinical benefits associated with mitochondrial metabolism [13]. As a matter of fact, administration of imeglimin has brought enough improvement of diabetic variability [14]. Authors' diabetic research group have experienced an impressive T2D male patient, who showed improvement by changing from metformin to Twymeeg. In this article, general progress and related perspectives are described.

Presentation of cases

Medical history

Current case is 69-year-old male with T2D. He was formerly diagnosed as T2D when he was 51 years old. After that he was provided with OHAs, his HbA1c has been almost stable around 5.8-6.8% for long. For recent years, he has given OHAs and anti-hypertensive agent (AHA) with stable situation. He has visited ophthalmology department in the university hospital every 6 months for checking stable condition of simple diabetic retinopathy. For his life style, he does not smoke or drink. He likes

to take carbohydrate food such as rice, bread and cakes. His current medical problems are i) T2D, ii) hypertension, iii) simple retinopathy.

Physicals and laboratory exams

His physical examination in Jan 2022 revealed the following: consciousness, speech and conversation are normal during the out clinic, his vitals are within normal limits including BP, pulse, BT, respiration and SpO₂ level, there were no remarkable changes in the chest, abdomen and extremities, and no neurological findings were found. He did not complain of symptoms or signs, vitals are normal ranges as pulse, BP, BT, respiration and SpO₂, unremarkable changes in the lung and heart, no symptom or signs of abdomen, neurological findings are intact. His physique was 157.6 cm in height and 74.0 kg in weight with BMI 29.8 kg/m².

Biochemical test showed following data: HbA1c 7.0%, fasting

blood glucose 165 mg/dL, TP 7.2 g/dL, Alb 3.8 g/dL, Na 139 mEq/L, K 4.8 mEq/L, Cl 103 mEq/L, RBC 5.00 x 10⁶ /μL, Hb 14.9 g/dL, Ht 44.6 %, MCV 89.0 fL (80-98), MCH 29.8 pg (27-33), MCHC 33.4 g/dL (31-36), WBC 5500/μL, Plt 11.4 x 10⁴ /μL, AST 25 U/L, ALT 32 U/L, ALP 90 U/L(38-113), γ-GT 40 U/L, Uric Acid 3.2 mg/dL, BUN 13 mg/dL, Cre 0.91 mg/dL, eGFR 63.5 ml/min/1.73m², HDL 41 mg/dL, LDL 99 mg/dL, TG 160 mg/dL, T-Cho 172 mg/dL, CRP 0.08 mg/dL.

Chest X-P showed unremarkable changes. Electrocardiogram (ECG) showed pulse 68/min, ordinary sinus rhythm, incomplete right bundle branch block (RBBB). He received the examination of sphygmogram and mechanocardiogram. As a result, ankle brachial index (ABI) presented 1.15/1.03 in right/left, respectively. The cardio-ankle vascular index (CAVI) showed 9.7/9.5 in right/left, respectively (Figure 1). For the detail analysis, the data of upstroke time (UT) and % mean arterial pressure (%MAP) were within normal limits.

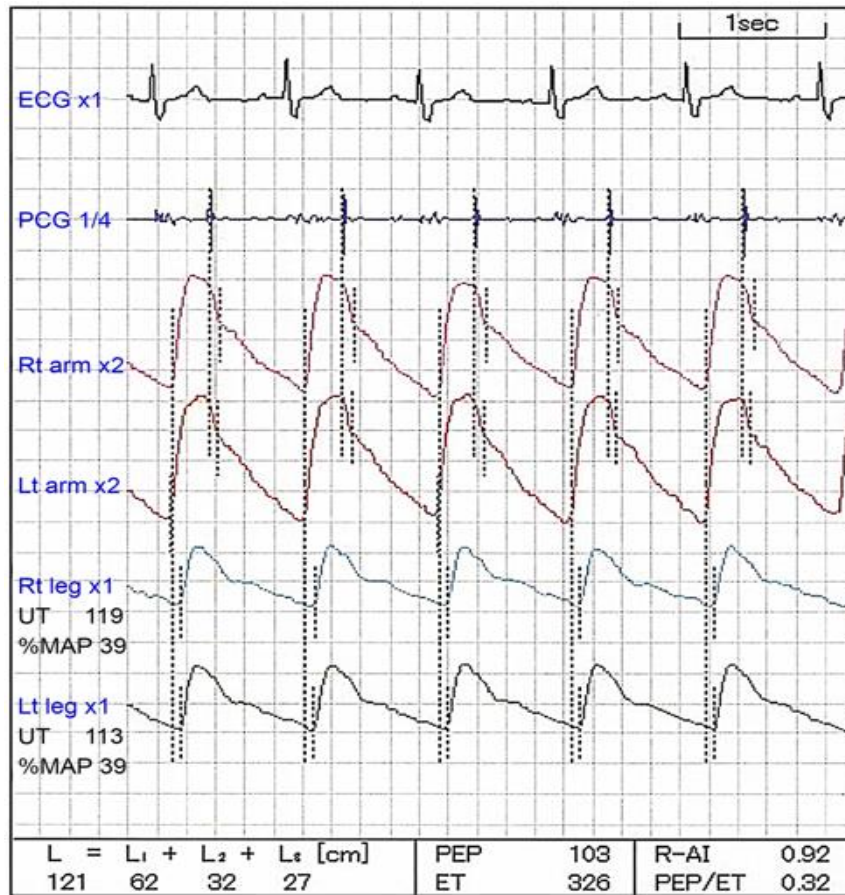


Figure 1: The results of sphygmogram and mechanocardiogram.

Clinical progress

HbA1c value increased from 7.0% to 7.4% from January to March 2022, and then metformin doses were increased from 500mg to 750mg per day (Figure 2). After that, HbA1c was decreased to 6.5% in June 2022. However, glucose control was

exacerbated as HbA1c 7.6% in Sept 2022. Consequently, medication was changed from Metformin 750mg/day to Twymeeg 2000mg/day. After that, HbA1c value decreased from 7.6% to 6.9% in 4 months. Concerning reverse effect of Twymeeg, unremarkable symptoms were observed. He can tolerate well for the current treatment.

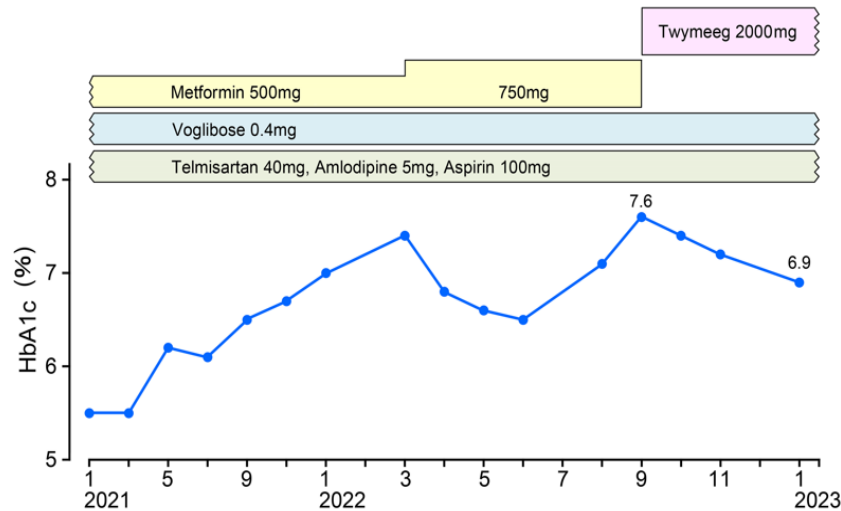


Figure 2: Clinical progress about changes in HbA1c and treatment.

Ethical standards

This case report was complied with the standard ethic guideline for previous Declaration of Helsinki. In addition, comment was associated with the standard protection regulation for personal information. The principle has been also along with the ethical rules for the clinically actual practice and the research for human subjects. Some guidelines have been from the official proposal of Japanese Ministry. This information has been from the Ministry of Health, Labor and Welfare (MHLW), Japan and also the Ministry of Education, Culture, Sports, Science Technology (MEXT), Japan. The authors of this report have established the ethical committee concerning this research, which has been present at Sakamoto Hospital in Kagawa, Japan. It has included professional medical and legal personnels, which has the hospital director, surgeon, physicians, nurse, pharmacist, registered dietitian and legal professionals. These members have discussed enough for the current case, and agreed for the protocol of the research.

Discussion

As to the usual treatment of T2D, there has been standard measure for pharmacology such as the proposal of the guideline from ADA [4]. However, some difference has been observed for the countries and districts. In Japan, Japan Diabetes Society (JDS) adopted the recommended consensus statement in 2023 [15]. From the JDS Committee on Consensus Statement Development, some changes were presented as the management of T2D in Asian region and Japan. Compared with Eastern and North American region, more DPP-4i agents were more prescribed and less metformin are prescribed in east Asia region [16]. The first-line antidiabetic medication for T2D patients would be DPP-4i in Japan, which shows different tendency in

comparison with that of United States (US). Furthermore, some situation would be related to this tendency, which has been the national health insurance system [17].

For diabetic pathology between Japanese and Western people, some characteristic differences are present. Westerners apt to have insulin resistance because of increased prevalence of higher BMI. In contrast, Japanese show both of reduced insulin secretion and increased insulin resistance, where Japanese diabetic patients include obese and non-obese about the similar prevalence [18]. These data were obtained from large RCT study of Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3) Group. Consequently, western countries and US pursue to decrease insulin resistance using biguanides, while Japan tends to lessen diabetic complications using DPP-4i [19]. Then, DPP4-I has become the first-line OHA about 40% of patients at clinics and hospitals in Japan.

When choosing the OHA for T2D patient, the evaluation of BMI would be required. Both measurement of BMI and abdominal circumference would contribute much for selecting OHA [20]. Excessive accumulation of visceral fat may exist in male or female with waist circumference of 85/90 cm or greater in Japanese criteria [21]. Consequently, T2D patients can be recommended to evaluate obese or non-obese [17], which contributes the selecting the adequate medication for two groups. Metformin is categorized in the usual medicine for obese group. However, it has showed comparable clinical effect in both of obese and non-obese patients in Japan [22]. Among various OHAs, imeglimin is the only agent that is included for both groups of OHA for obesity and for non-obesity categories [17].

In this case, glucose variability was improved as decreased HbA1c value for 4 months. It was not additional imeglimin prescription, but changed OHA from metformin 750 mg/day to imeglimin 2000mg/day. One of the reasons of selecting imeglimin would be

that the case was obese with expecting the dual effects of reducing insulin resistance and also increasing insulin secretion [23]. The case did not show any gastro-intestinal adverse events (GIAE) [24].

Imeglimin has shown beneficial effects for add-on treatment with other anti-diabetic agents. For standard data of imeglimin, large studies of Trials of IMeglimin for Efficacy and Safety (TIMES) were reported using TIMES 1,2, and 3. Monotherapy and combined therapy were compared in TIMES 2 [25]. For the changes in HbA1c, monotherapy showed -0.46% and combined treatments showed the following: DPP4-i -0.92%, α -glucosidase -0.85%, glinides -0.70%, biguanides -0.67%, SGLT2i 0.57%, SU -0.56%. Furthermore, GLP-1RA showed only -0.12%. DPP4-I and GLP-1RA have similar pharmacological route, but the results were different as -0.92% vs -0.12% (TIMES 3) [26]. From these results, different action function route may exist through mitochondria pathway, where detail pharmacophysiological mechanism will be hopefully clarified in the future [27].

From latest systematic review and meta-analysis, efficacy of imeglimin was reported [28]. Among 360 cases in 2 monotherapy studies, HbA1c change was -0.90% (-1.1 to -0.74%, $p < 0.0001$). By meta-analysis of 3 RCTs ($n = 574$), significant decrease of HbA1c 2000mg/day was -0.79% (-1.00 to -0.59%, $p < 0.0001$). On the other hand, monotherapy of metformin was investigated in previous trials. Among them, adequate protocol was found for the combination of monotherapy of sitagliptin and metformin [29]. Clinical response was influenced by baseline HbA1c. When mean baseline of HbA1c was $\geq 8\%$, reduction was -1.13% vs -1.24%, respectively. Daily doses of metformin may be related to the reduction of HbA1c value. Consequently, monotherapy and/or combined therapy of Twymeeg will be followed up in the future.

Some limitations may exist for the current report. This case showed clinical efficacy after changing medication from metformin to imeglimin. Various factors may influence clinical progress, such as meal habit, exercise and other stressors in his life style. Authors have reported the effects of Twymeeg for elderly T2D patients [30]. This novel OHA seems to have enough and safe results.

In summary, changed medication of metformin to imeglimin was presented for patient with T2D in this article. Imeglimin has been recently introduced to medical practice, and its monotherapy and/or combined therapy will be increased. Related research would be hopefully developed for further elucidation of pharmacological mechanism of imeglimin.

Conflict of interest: The authors declare no conflict of interest.

Funding: There was no funding received for this paper.

The authors declare that they have no conflicts of interest.

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