



Clinical Perspectives of Luseogliflozin and Vildagliptin/Metformin (EquMet) in Patients with Type 2 Diabetes (T2D) and Renal Stone

Bando M¹, Hayami E¹, Abe H¹, Little M¹, Taiji M¹, Nishitani N¹ and Bando H²

¹Bando Heart Clinic, Tokushima, Japan

²Tokushima University / Medical Research, Tokushima, Japan

*Corresponding author: Bando H, Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan; E-mail: pianomed@bronze.ocn.ne.jp

Abstract

Case Presentation: This case is 71-year-old female with type 2 diabetes (T2D), dyslipidemia, obesity and fatty liver. She developed renal stone in 2016.

Results: During 2017-2018, HbA1c decreased to 6.5% by the administration of luseogliflozin and vildagliptin/metformin (EquMet). Related to her lifestyle situation, she cannot continue satisfactory nutritional treatment and exercise therapy.

Discussion: SGLT2-i would lead risk reduction of gout for T2D patients, and exert favorable effect in decreasing uric acid (UA). EquMet contributes improved glucose variability all day long. Elevated UA is associated with impaired beta cell function and insulin may act to decrease the excretion of UA.

Keywords: Atherosclerotic cardiovascular accident (ASCVD); Vildagliptin Efficacy in combination with metformin for early treatment of type 2 diabetes (VERIFY) vildagliptin/metformin (EquMet); Sodium-glucose co-transporter-2 inhibitor (SGLT2-i); Uric acid (UA)

Introduction

For decade, authors and co-researchers have continued clinical practice and research for Atherosclerotic cardiovascular disease (ASCVD). They include hypertension, type 2 diabetes (T2D), ischemic heart disease (IHD), chronic kidney disease (CKD) and other diseases [1]. In many patients with various medical problems, we have managed certain pharmacological treatments. From lifestyle point of view, nutritional treatment and exercise therapy would be necessary [2]. Consequently, Bando Heart Clinic has continued providing educational lifestyle modification for years. Among them, adequate amount of sodium would be recommended, which are effective for the control of blood pressure and ASCVD [3]. For prevention of ASCVD, predicting metabolic syndrome (MetS) has been crucial for identifying the risk degree for patients and giving preventive interventions [4].

On the other hand, T2D has been crucial medical and social problem across the world [5]. American Diabetes Association (ADA) has announced the latest guideline for T2D in Jan 2023

[6]. As to diet therapy for T2D and obesity, the recommended method has been changed from calorie restriction (CR) to low carbohydrate diet (LCD) [7]). Recent studies have revealed various evidence of predominance of LCD [8]). Furthermore, recent pharmacological development introduced novel oral hypoglycemic agents (OHAs) and useful combination of OHAs. Among them, the combined agent of vildagliptin/metformin (EquMet) showed clinical efficacy and evidence from large studies of vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY) [8]. This intensified prescription has brought paradigm shift in the diabetic therapy across the world, which has been from ADA and European Association for the Study of Diabetes (EASD) [9].

Authors and co-researchers have continued clinical practice and research for various ASCVD, in which T2D patients on EquMet were followed up 6 years [10]. In addition, another case on EquMet was analyzed in detail by high-technique radiological method of Curved Planar Reconstruction (CPR) [11]. Recently, we have experienced an impressive case who was treated by

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EquMet associated with several problems. Their general situation and related perspectives are described in this article.

Case Presentation

Medical History

The case is 71-year-old female patient with T2D and dyslipidemia for years. About 16 years ago, she was pointed out to have T2D, dyslipidemia, fatty liver, and obesity. She had been on OHAs for years, and HbA1c was around 7.8%. In 2016, she developed right back pain and hematuria, and then was diagnosed as right renal stone. The problem of urinary stone was excreted as itself after that. During 2017-2018, HbA1c decreased to 6.5% by the administration of luseogliflozin and EquMet. However, she complained of discomfort in the inguinal region. It was probably because of SGLT2-i intake every day. Then, the intake of luseogliflozin was decreased for every other day. After that, HbA1c value was elevated to some degree (Figure 1).

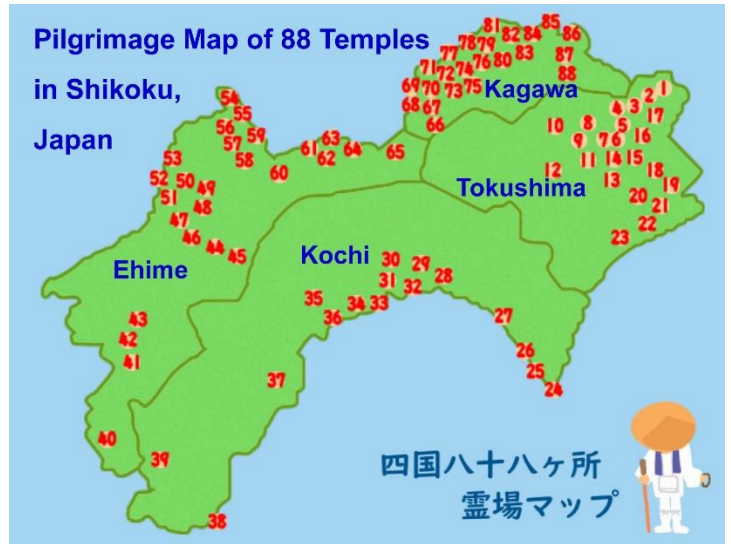


Figure 3: Pilgrimage map of 88 temples in Shikoku Island, Japan.

Physical examination

Her physical examination in July 2019 showed in the following: Consciousness and conversation were normal. Vitals of BP, pulse, respiration and SpO₂ 99% were in the normal range. Her head, neck, lung and heart showed negative. Abdomen showed a little distended and soft with unremarkable findings. Neurological examination was intact. Her physique showed height 151 cm, weight 65 kg, BMI 28.5 kg/m², and fat ratio of the body 35.7% by the analysis of the apparatus InBody.

Several examinations

Laboratory exams in July 2019 were as follows: TP 7.0 g/dL, T-Bil 0.5 mg/dL, AST 14 U/L, ALT 18 U/L, LDH 169 U/L, GGT 12 U/L, CPK 87 U/L, Uric acid 2.8 mg/dL, BUN 16 mg/dL, Cre 0.47 mg/dL, eGFR 98.4 mL/min/1.73m², Na 141 mEq/L, Cl 104 mEq/L, K 4.2 mEq/L, HDL 58 mg/dL, LDL 78 mg/dL, TG 106 mg/dL, T-Cho 151 mg/dL, LDL/HDL ratio 1.3, glucose 67 mg/dl, WBC 6000/μL, RBC 4.80 x 10⁶ /μL, Hb 14.7 g/dL, Ht 45.8 %, MCV 95.4 fL (80-98), MCH 30.6 pg (27-33), MCHC 32.1 g/dL (31-36), Plt 23.2x 10⁴ /μL.

As physiological exams in 2019, chest X-P was negative and electrocardiogram (ECG) showed normal axis, pulse 63 /min, ordinary sinus rhythm (OSR), and no remarkable ST-T changes. Regarding annual check of ECG, the results during 2019-2022 are shown in Figure 2. For latest 4 years, she did not develop unremarkable cardiovascular complaints, symptoms or signs.

The examination of carotid echocardiogram was performed in 2019. As a result, no plaque was found and no significant change was observed as a whole. The value of intima media thickness (IMT) was 0.78 mm and 0.70 mm in right and left carotid artery, respectively.

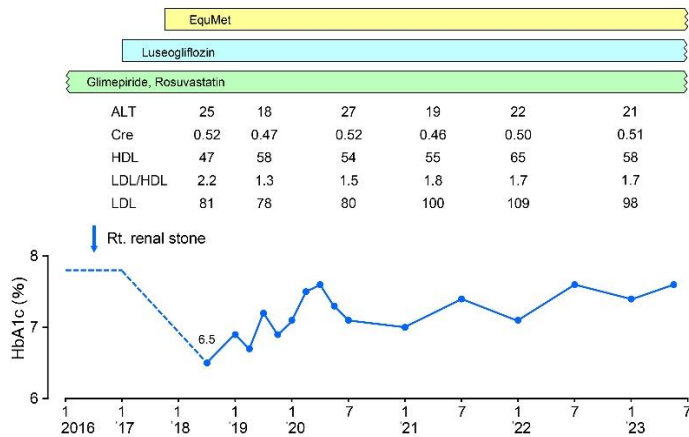


Figure 1: Clinical course of the case with HbA1c, laboratory data and treatment.

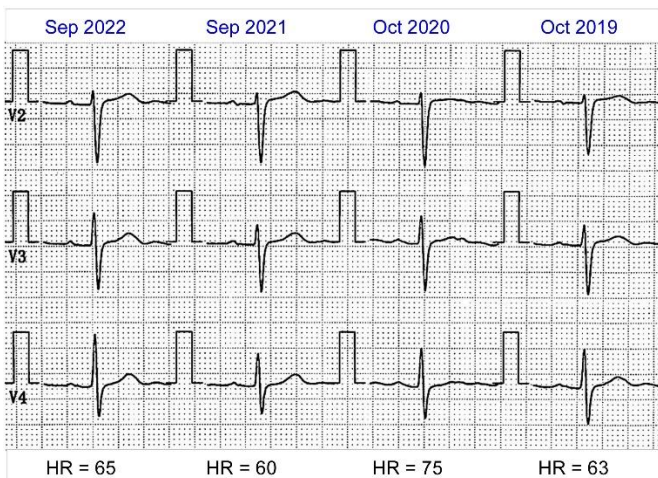


Figure 2: Consecutive ECG findings for 4 years.

Clinical course

This case has continued various behaviors and trials for diabetic treatments. They include three categories as nutritional, exercise and medicine during 2020-2023. Regarding diet therapy, she likes to eat rice, fruits, cakes, beer and so on. Then, our nutritionists always give lectures for adequate diet therapy. As to exercise therapy, she states that she always takes a walk around the house. Actually, her diet and exercise treatments seemed to be unsatisfactory.

One impressive episode for exercise therapy was observed. Japan has 4 main islands, which are Hokkaido, Honshu, Shikoku and Kyushu. The word “Shi+koku” means four + country, state, or prefecture. Tokushima is one of these 4 prefectures (Figure 3). Shikoku has pilgrim journey course visiting 88 consecutive temples, which takes 40 days for walking for 1400km. The important points would be that i) walking for long distance, ii) staying at cheap pilgrim lodgings, iii) interacting with other pilgrims for deep communication, and iv) thinking about our whole lives and relationship of other people with appreciation. She attended the pilgrim journey, but it was incomplete. The reason was that she moved by car and stayed high-class hotel with comfortable travel.

Concerning pharmacotherapy, she continued rosuvastatin as anti-hypercholesterolemia, and EquMet, Luseoglitflozin and glimepiride for OHAs. Her body weight has been almost stable for years. Several biomarkers for liver, renal, lipid and diabetes were followed up for 5 years, and these data were almost stable (Figure 1).

Ethical standards

This case report is complied with the ethic guideline in Declaration of Helsinki. Furthermore, some commentaries are based on the regulation for adequate personal information. These principles would be observed in the ethical rule as to clinical practice and research. As related, some medical problems of human are present. The certain guideline has been from Japanese government, which are Ministry of Education, Culture, Sports, Science Technology and Ministry of Health, Labor and Welfare. The authors and collaborators have established ethical committee regarding this case. It was present in Bando Heart Clinic, Tokushima city, Japan. The committee has included the hospital director, physician, nurse, pharmacist, nutritionist, laboratory specialist and legal professional. We have discussed in satisfactory manner concerning current protocol and have agreed for the protocol. The informed consent was taken from the case by the written document.

Discussion

This case is 71-year-old female patient with T2D and other problems. Some medical problems include i) relationship among renal stone, diabetes and medication of OHA and sodium glucose cotransporter 2inhibitor (SGLT2-i), ii) incomplete diet therapy and iii) inadequate exercise therapy. From these points of view, some perspectives are described in this order.

First, this case has history of renal stone, and medication of EquMet and SGLT2-i in 2017. The HbA1c decreased to 6.5% in 2018. This effect may be by both agents. During 2018-2023, several biomarkers showed almost stable. From her clinical course, the relationship of renal stone and SGLT2-i will be discussed. The close relationship exists among gout, diabetes, insulin resistance, cardiometabolic risk and kidney disease [12]. From recent study, SGLT2-i can contribute risk reduction of gout for T2D patients. SGLT2-i is known to exert favorable efficacy in decreasing uric acid (UA) level. For its mechanism, SGLT2-i increases glucose excretion in urine, associated with probably inhibiting glucose transport 9 (GLUT9)-mediated UA reabsorption in the collecting duct [13]. It will result in elevated UA excretion that is in exchange for the reabsorption of glucose. Elevated UA is associated with impaired beta cell function and insulin acts to decrease the excretion of UA [14]. Furthermore, elevated UA is observed with higher risk of hypertension, CVD, CKD and Metabolic syndrome (Met-S). Thus, clinical effect of SGLT2-i would be investigated for the relationship of CV events, glucose and UA levels.

Several reports are found for the relationship between SGLT2-i and risk of gout for T2D. When analyzing seven adequate papers, 34% reduction risk was found for developing gout for T2D patients [15]. In order to assess the relationship of SGLT2-i and gout, nationwide health registry was used for 3 years. From the data of 42 thousand person-years follow-up, SGLT2-i vs GLP1-RA users showed 4.1 vs 7.0 events per 1000 person years. It shows hazard ratio (HR) of 0.58 [16]. Using US National administrative data, association between SGLT2-i and gout incidence was studied for T2D. Totally 714 cases were analyzed for with/without SGLT2-i administration [17]. As a result, 38% reduction was observed between them. Consequently, SGLT2 inhibitors may show beneficial efficacy for T2D patients at gout risk.

Furthermore, this case was provided EquMet that is combined agent for vildagliptin and metformin. It shows beneficial glucose-lowering effect all day long [18], and international evidence was shown from Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes (VERIFY) studies [8].

Second, this patient has been advised many times by a registered dietitian in our clinic. The concept of the fundamental diet would

be on daily 1600 kcal, less than 6g/day of salt, 65g/day of protein, 30g of fat and composition (P/S ratio 1.5) [19]. One of the reasons why the long-term guidance could not produce results is that the patient liked fruits and sweets, often snacked between meals, and inevitably ate relatively large amounts of sugar. CR has historically been the standard way for guidance on diabetes. Bernstein and others, however, have been known broadly, and LCD has been recognized more. Recent data have been found from the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study, and more detailed data are expected in the future [20].

Regarding diet therapy for T2D, systematic review was performed for carbohydrate-later meal pattern (CLMP) and meal sequence [21]. It included 230 cases from 8 trials. Detail review did not show significant difference for blood glucose, HbA1c, GLP-1 and insulin levels. However, eating fast habit may lead elevated risk for diabetes and obesity. The latest study is to investigate meal sequence and eating speed for 18 healthy cases [22]. The method included three patterns, which are slow or fast eating, carbohydrate first or vegetable first, test meal or vegetables. Consequently, eating vegetable first brought suppressed post-prandial glucose elevation and insulin secretion. Third, adequate exercise therapy for diabetes has been in discussion for actual medical practice. For comparative study of aerobic and anaerobic activities, T2D patients were investigated [23]. After exercise for 30 minutes, aerobic exercise brought glucose reduction to 9.4 mmol/L after 120 minutes. In contrast, anaerobic exercise brought no changed glucose as 12.6 mmol/L. Thus, post-prandial glucose decrease can be expected by aerobic exercise.

This case states that she has daily habit of going out for walk 2-3 times a week for 20-30 minutes. However, this exercise level is not enough, and then clinical efficacy cannot be expected. On the other hand, walking for several hours in the picnic or visiting several temples for pilgrim for weeks can contribute much for aerobic exercise. Furthermore, Tokushima has world-known international Awa-dance Festival in August 12-15 every year [24]. All dancers from amateur to professional team and from elementary school children to elderly or patients with dementia can have continuous dance for some hours [25]. Such exercise can contribute much for health and fun, without giving much loading to each person.

Some limitation may be present in this report. The case showed HbA1c reduction by OHAs, which was at least in part by EquMet, SGLT2-i or other factors. She cannot continue effective nutritional treatment or exercise therapy that are related with adequate lifestyle. Further educational advice by medical staff would be expected and continuous follow-up will be required.

In summary, current article is the presentation of 71-year-old case with T2D. She presented several clinical problems, where our medical staff will manage adequately for her improving lifestyle.

General description and various perspectives will hopefully become useful reference for future diabetic practice.

Conflict of Interest

The authors declare no conflict of interest.

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