

Clinical Improvement by Vildagliptin/Metformin (Equmet) For Diabetic Patient with Remarkable Arteriosclerosis from Slight HbA1c Elevation for Years

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Abstract

This case is 73-year-old male surgeon with light degree of type 2 diabetes (T2D) for 10 years. The HbA1c was under 7.0% until 2020, and became more than 7% after 2021 without oral hypoglycemic agents (OHAs). He was provided vildagliptin/metformin (EquMet) from March 2023, and HbA1c decreased from 7.2% to 6.2% for 3 months, indicating clinical effect. For the exam of arterial stiffness, brachial-ankle pulse wave velocity (baPWV) showed 2151/2154 in right/ left artery, respectively. It revealed +2SD of the standard level for 73 years old, suggesting that highly-developed arteriosclerosis would be from prolonged diabetic glycaemic variability for years.

Keywords: Vildagliptin Efficacy in combination with metformin for early treatment of type 2 diabetes (VERIFY); Vildagliptin/Metformin (EquMet); Brachial-Ankle Pulse Wave Velocity (BAPWV); Post-Prandial Hyperglycaemia (PPHG); Japan LCD promotion association (JLCDPA)

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Introduction

Across the world, type 2 diabetes (T2D) has been important medical, social and economic problem for decades [1]. From international point of view, American Diabetes Association (ADA) has presented the standard diabetic guideline in 2023 [2]. Regarding the basic concept of nutritional therapy, the recommendation has been prevalent from calorie restriction (CR) to low carbohydrate diet (LCD) [3]. Accumulated evidence showed the useful and predominance of LCD for actual clinical practice [4].

In addition, pharmacological development has brought some novel oral hypoglycemic agents (OHAs) associated with new pathway mechanism and combined agents of previous OHAs. Among them, useful combination includes biguanide and dipeptidyl-peptidase 4 inhibitors (DPP4-i) as vildagliptin/metformin (EquMet). Its clinical evaluation has been conducted by large international studies, that is vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY) [5]. Such intensified measure of prescription has provided a novel paradigm shift in the category of diabetic pharmacology. Future useful and effective diabetic measure will be recognized by ADA and also European Association for the Study of Diabetes (EASD) [6].

Authors and colleagues have so far continued diabetic research and Pubtextto Publishers | www.pubtextto.com

practice for long [7]. Among them, several reports with OHAs were presented including EquMet [8]. Further, T2D cases treated by EquMet were investigated for continuous 6 years [9]. For clinical experience of our diabetic team, an impressive patient was present who showed efficacy by EquMet. The general case presentation and some perspectives will be presented in this paper.

Case Presentation

Medical History

The case is 73-year-old male case with T2D, who has been working in the hospital as a surgeon. About 10 years ago, he was pointed out to be diabetic to slight degree. After that, he occasionally continued to measure pre- and post-prandial blood glucose and HbA1c values. He has followed the clinical course without any OHAs. The reason was that he likes to take delicious meal, and does not want to limit his diet style for long. His glucose variability has been a little elevated and stable. HbA1c was below 7% during 2013 to 2020, and more than 7.0% after 2021 (Figure 1). He happened to meet a diabetologist and a pharmacist for managing lots of T2D patients, and then was advised to take further evaluation and adequate treatment in February 2023.

Several Exams

His physical examination in February 2023 showed as follows:

Consciousness, conversation, and vitals were in the normal range. His head, lung, heart, and abdomen were negative. His physique showed 166.3cm in height, 64.2kg in weight, 23.2 kg/m² of BMI, and 85.6 cm of abdominal circumference.

Biochemical examinations in February 2023 showed in the following: TP 7.4 g/dL Alb 4.1 g/dL, A/G ratio 1.24, AST 20 U/L, ALT 168 U/L, GGT 23 U/L, ALP 107 U/L (38-113), LDH 139 U/L (110-220), ChE 241 U/L (165-470), T-Bil 1.4 mg/dL, uric acid 6.7 mg/dL, BUN 13 mg/dL, Cre 0.96 mg/dL, eGFR 59.2 mL/min/1.73m², HDL 70 mg/dL, LDL 80 mg/dL, TG 95 mg/dL, T-Chol 179 mg/dL, glucose 144 mg/dl, HbA1c 7.3%, WBC 4400/μL, RBC 4.38 x 10⁶ /μL, Hb 14.1 g/dL, Ht 43.7 %, MCV 99.8 fL (80-98), MCH 32.2 pg (27-33), MCHC 32.3 g/dL (31-36), Plt 18.5x 10⁴ /μL.

For other examinations, chest X-ray showed negative result, and electrocardiogram (ECG) was within normal limits without ST-T changes. Fundus examination showed normal findings with Scheie (H 0, S 0). Pulmonary test showed that lung capacity 3.27 L, %LC 92.9%, FEV_{1.0} 89.7%, with normal results. As the test for arterial stiffness, brachial-ankle pulse wave velocity (baPWV) showed 2151 and 2154 in right and left artery, respectively [10]. It revealed the +2SD of standard level for 73 years old. It indicates highly-developed arteriosclerosis, that is equivalent to more than 90 years old (Figure 2). As regards to the normal or standard range, the Japanese Circulation Society (JCS) has proposed that standard baPWV value would be 1800 cm/s as a threshold for high-risk category [11].

Clinical Progress

The HbA1c value was almost stable above 7% until Jan 2021- Feb 2023. This case has been a surgeon who didn't want to be on OHAs at previous HbA1c level or to restrict his diet. However, our diabetes team explained the necessity of maintaining lower HbA1c and better glucose variability. We also advised clinical effectiveness and benefit of the combination of OHAs from the beginning of the treatment. Consequently, the administration of Vildagliptin and Metformin (EquMet) was started. After that, HbA1c was decreased to 6.8%, 6.5%, and 6.2% in 3 months, respectively, demonstrating clinical efficacy (Figure 1). During his clinical progress, he did not change the contents of his diet so much, associated with almost similar carbohydrate intake. For example, there is a rice ball as a traditional staple food in Japan (Figure 3). 100g of food contains 33g of sugar, and in diabetic patients, 1g of sugar raises blood sugar by 3g/dL, and then blood glucose rises by about 100mg/dL in about 1 hour after eating. In this case, no apparent microangiopathy was found such as neuropathy, retinopathy, or nephropathy. Furthermore, apparent macroangiopathy was not observed so far including cerebral vascular accident (CVA), ischemic heart disease (IHD), and peripheral artery disease (PAD).

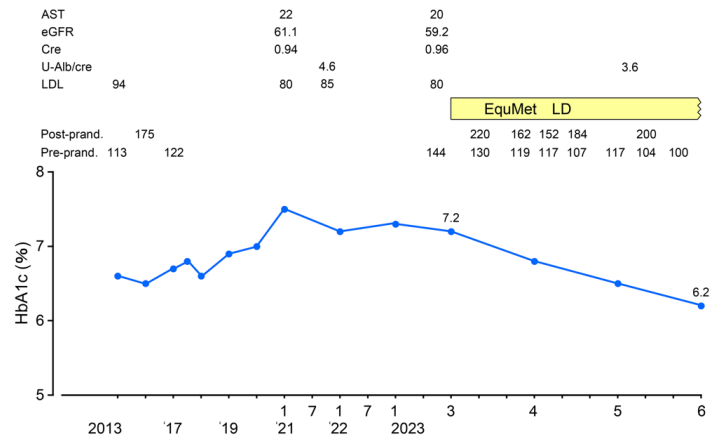


Figure 1: Clinical progress of the case.

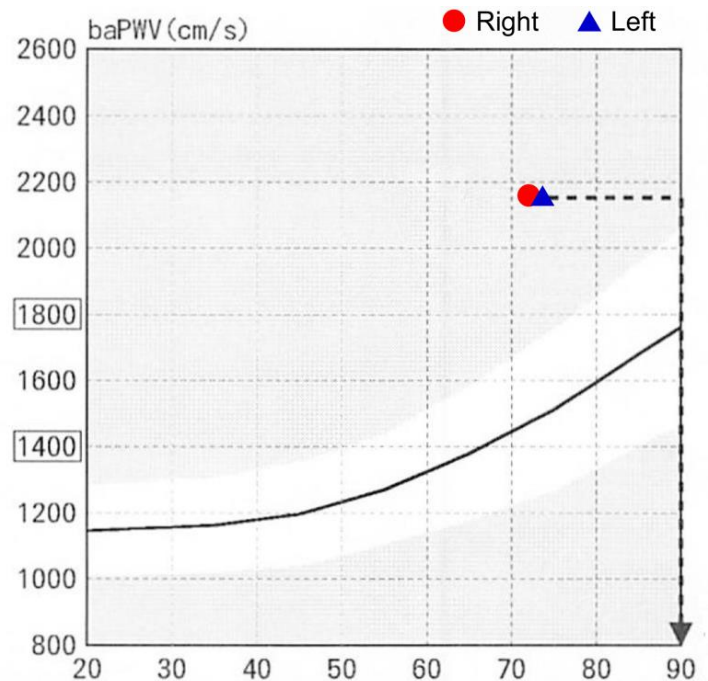


Figure 2: The exam of arterial stiffness for baPWV.



Figure 3: sample of Japanese traditional meal.

Ethical Standards

Current case is complied with the ethical guideline of Declaration of Helsinki. In addition, certain commentary is observed on the regulation from standard personal information. The principle is found in ethic rule concerning medical research and practice. Some clinical problems of human have been present. These guidelines have been on the regulation of Japanese government, that are the Ministry of Education, Culture, Sports, Science Technology and the Ministry of Health, Labor and Welfare. The authors et al. established the ethical committee as to the current case. It exists in Yoshinogawa hospital, Tokushima prefecture, Japan. This committee included several members, such as hospital director, physician, head nurse, pharmacist, dietitian, laboratory specialist and also legal professional. We have fully discussed about this the protocol and agreed with the protocol. The necessary informed consent was obtained from the current case by the written document style.

Discussion

The case is 73-year-old male case with T2D. Several characteristic points include the following: i) the case has been a surgeon who wants to eat his favorite meal and doesn't like to take OHAs previously, ii) remarkable arteriosclerosis probably due to persistence of slight elevation of HbA1c for 10 years, iii) the administration of EquMet was clinically effective as HbA1c reduction of HbA1c 1% for 3 months. Some perspectives for these will be described in this order.

First, the therapeutic principles of T2D are diet, exercise, and medicine, which are prioritized in this order [12]. On the other hand, adequate management for T2D patient includes three axes of biological, psychological, and social aspects, that are often described as bio-psycho-social points of view [13]. From mentioned above, appropriate measures for each patient would be required. Current case is a surgeon with extensive medical knowledge and fully understands the importance of glycemic control. Consequently, it would be challenging for solving the triangle matters with balance, including elevated HbA1c level for 6-7%, continuing adequate life as a doctor, and the desire to eat favorite foods in his daily life [14].

Concerning diet therapy for diabetes, calorie restriction (CR) was formerly the usual method for educating for T2D patients. It was based on the measurement of calorie intake for protein, fat and carbohydrate (PFC). However, its problem included the difficult continuation of CR because of always hungry state and rebound phenomenon. After that, low carbohydrate diet (LCD) was introduced by Bernstein and Atkins [15,16]. Successively, LCD has been prevalent across the world [17]. In Japan, authors et al. developed LCD medically and socially through the activities of Japan LCD promotion association (JLCDPA) [18]. JLCDPA has provided convenient and useful information of actual LCD

measures, which are petite-LCD, standard-LCD and super-LCD as carbohydrate involvement ratio of 40%, 26% and 12%, respectively [19].

Second, the baPWV value was remarkably high in the exam of this patient, suggesting the progression of arteriosclerosis. In this case, hyperglycemia has been pointed out for 10 years ago, and the HbA1c value was slightly high. Despite frequent self-monitoring of blood glucose, he received no specific treatment. Therefore, it is thought that post-prandial hyperglycemia has been frequently observed more than 200 mg/dL, because he likes to take carbohydrates from various food and cakes. From previous reports, post-prandial hyperglycaemia (PPHG) has been known to increase the risk twice for cardiovascular mortality [20]. Further, it also contributes much for cognitive decline, cancers and microvascular complications from diabetes.

Recent report showed the crucial relationship of hyperglycemia and major adverse cardiac events (MACE) [21]. DIAbetes and diffuse coronary Narrowing (DIANA) study was continued for 10 years with 243 cases by multi-center RCT. PPHG was investigated for comparative study using pharmacological intervention by voglibose and nateglinide. The evaluation included MACE situation of non-fatal MI, all-cause death, or unplanned coronary revascularization. As a result, voglibose or nateglinide did not decrease MACE level. However, IGT cases showed the reduction of MACE as Hazard Ratio (HR) 0.44, associated with unplanned coronary revascularization (HR = 0.46). Consequently, early improvement of PPG can decrease MACE remarkably, suggesting clinical prevention significance. As a matter of fact, preventing PPHG can be attained by mainly restricted carbohydrate food, and also by several measures using medical agents or nutritional matters [22].

Third, current case was given combined agents for vildagliptin and metformin (Equmet). It is reported to bring satisfactory glucose-lowering effect during both of day and night [23]. It is partly from its administration twice a day. Detail clinical effects were found from the large international studies, which are Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes (VERIFY) [5]. As recent report of VERIFY, 8533 applicants were analyzed from 11 RCTs [24]. The protocol was comparison of combined agents and metformin monotherapy. The method was according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE). Consequently, better effect was observed for combined treatment associated with HbA1c decrease of -0.59 for mean differences (MD). In addition, the incidence ratio of adverse events (AEs) was not elevated as relative ratio of 0.98. From various studies of VERIFY, providing EquMet from early period will bring beneficial clinical effect for long [25].

There may be some limitation for this article. This case revealed HbA1c decrease by EquMet, which suggests clinical effect for short period. Further, the case may have post-prandial

hyperglycemia (PPHG) for years, which suggests the development of arteriosclerosis. However, other factors may be involved in various his pathophysiology.

In summary, this case report is concerning 74-year-old surgeon associated with T2D and arteriosclerosis. His HbA1c showed improvement with satisfactory degree, and future clinical progress will be required to follow up. Current description will be expected to show certain reference for diabetic research development.

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