Open Access
Volume 6 Issue 2
Case Report

International Journal of Endocrinology and Diabetes
ISSN: 2694-3875

PUBTEXTO

Beneficial efficacy for type 2 diabetes (T2D) and Metabolic syndrome (Met-S) by vildagliptin/metformin (EquMet)

Bando M[a], Takeuchi Y[a], Okumura M[a], Nagao N[a], Sakai K[a], Kimoto Y[a], Bando H[b]

[a]Bando Heart Clinic, Tokushima, Japan
[b]Tokushima University / Medical Research, Tokushima, Japan

Article Info

Article History:
Received: 16 June, 2023
Accepted: 26 June, 2023
Published: 28 June, 2023

Corresponding author: Bando H, Tokushima University/Medical Research, Nakashowa 1-61, Tokushima 770-0943 Japan;
Tel No: +81-90-3187-2485;
DOI: https://doi.org/10.36266/IJED/152

Abstract

The case is 51-year-old female with obesity, type 2 diabetes (T2D) and hypertension with BMI 31.4 kg/m^2. She has been treated by oral hypoglycemic agents (OHAs) and anti-hypertensive agents (AHAs). From January 2020, vildagliptin and metformin (EquMet) was initiated, and she showed HbA1c decrease 7.9% to 6.3%, weight reduction 74,0kg to 68.9kg, ALT 99 U/L to 19U/L and LDL 154mg/dL to 85mg/dL, suggesting clinical efficacy. Furthermore, improved findings of ECG and sleep apnea syndrome (SAS) have been found, in which general signs and symptoms of Metabolic syndrome (Met-S) were relieved. She has felt no gastro-intestinal adverse effects (GIAEs).

Keywords: Metabolic Syndrome (Met-S); oral hypoglycemic agents (OHAs); vildagliptin/metformin (EquMet); Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY); gastro-intestinal adverse effects (GIAEs).

Introduction

For some decades, Metabolic Syndrome (Met-S) has been important pathology for clinical practice across the world [1]. Among them, type 2 diabetes (T2D) would be the main position of these diseases including obesity, hypertension, dyslipidemia, fatty liver, and others [2]. For treating T2D, the purpose would be set for maintaining the same QOL and health as usual people by refraining from micro- and macro-angiopathy [3]. Recently, some novel oral hypoglycemic agents (OHAs) have been introduced to medical practice [4]. They showed beneficial effect for improving glucose variability. They include dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium–glucose cotransporter 2 inhibitor (SGLT2i), oral GLP-1 receptor agonist (GLP-1RA), imeglimin (Twymeeg) and others [5]. Furthermore, combined agents have been also in focus, such as DPP-4i and metformin. Among them, vildagliptin/metformin (EquMet) has been used, which showed medical effect by large study of Vildagliptin Efficacy in combination with metfoRmIn For early treatment of type 2 diabetes (VERIFY) [6].

Among Met-S, hypertension has been also crucial disease to be properly managed worldwide [7]. The standard guideline for hypertension was announced by harmonization of ACC/AHA/ESC. Authors and collaborators have continued clinical practice for hypertension, atherosclerotic cardiovascular disease (ASCVD), T2D, and so on [8]. Our group have developed educational activities such as workshops, books and reports for hypertension, ASCVD, lifestyle intervention, adequate daily meal with less salt. The standard guideline of hypertension in European, North American and Asian regions [9]. We have recently experienced an impressive case with T2D and ASCVD. General status and some perspectives are described in this report.

Presentation of cases

Medical History

The case is 51-year-old female with obesity, T2D and hypertension. She was pointed out to have possible cardiovascular disease (CVD) at 35 years old. As she underwent ECG, echograms of heart and carotid artery and double master exam, unremarkable positive results were found. She was diagnosed as T2D at 38 years old, and started some OHAs. After that, her body weight was increased to 85kg in maximum, associated unstable weight changes until now. On 41 years old, moderate hypertension was observed on annual health check-up, and she was provided anti-hypertensive agents (AHAs). Her clinical progress for glucose variability had been unstable, and then she was introduced to Bando Heart Clinic for further evaluation and treatment of all medical problems in January 2020. Regarding her social history, she has been working as a visiting care worker for years.

Physicals and various exams

Her physical examination showed the following status. The consciousness was alert, conversation and speech were normal. Her vitals signs were pulse 76/min, BP 154/84 mmHg, SpO2 98%. Physicals showed no adventitious sound in the lung, no murmurs in the heart, extended abdomen with fat, slight pretibial edema, palpable dorsal pedis and intact neurological exams. Her physique revealed 156.2 cm, 76.7kg, 31.4 kg/m^2 in body mass index (BMI), and 42.3% in body fat percentage.

The results of laboratory tests in April 2020 were as follows: AST

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63 U/L, ALT 99 U/L, γ-GT 46 U/L, HDL 45 mg/dL, LDL 154 mg/dL, TG 213 mg/dL, Na 154 mEq/L, K 4.5 mEq/L, Cl 106 mEq/L, Uric Acid 3.6 mg/dL, BUN 10 mg/dL, Cre 0.61 mg/dL, HbA1c 8.3%, post-prandial blood glucose 183 mg/dL, RBC 4.87 x 10^6 /μL, Hb 14.9 g/dL, Ht 43.9 %, WBC 8240/μL, Plt 25.4 x 10^4 /μL, TSH 0.84 μIU/ml, free T_3 2.7 pg/ml, free T_4 1.26 ng/dL.

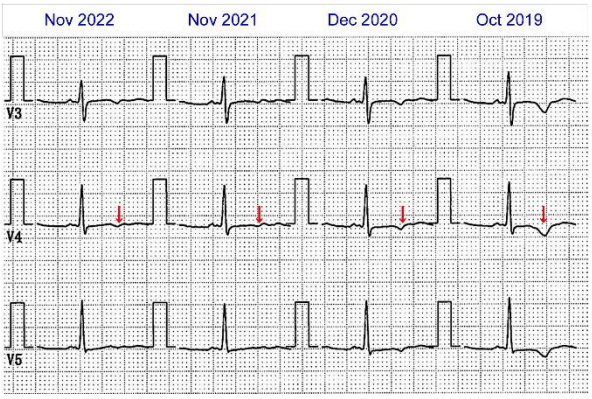

***Figure 1**: Consecutive ECG findings.*
Inverse T wave has been gradually disappeared for 3 years.

As physiological tests, chest X-ray revealed negative in the lung, and 47% in CTR. Electrocardiogram (ECG) showed ordinary sinus rhythm (OSR), left axis deviation (LAD) 14 degree, QTc 437ms, QRS 84ms, flat T wave in II, III, aVf and V6, inverse T wave in V_{1-5}. The changes in ECG were shown in Figure 1, where inverse T wave has been gradually disappeared during 3 years and pulse rate were 63-70 /min in these 4 consecutive exams.

Related to moderate obesity, she underwent the exams for sleep apnea syndrome (SAS). As a result, 3% oxygen desaturation index (ODI) was 5.1, lowest SpO_2 was 84% in June 2020. These data were normalized 2 years later as 3% ODI 2.3 and lowest SpO_2 85%.

Clinical progress

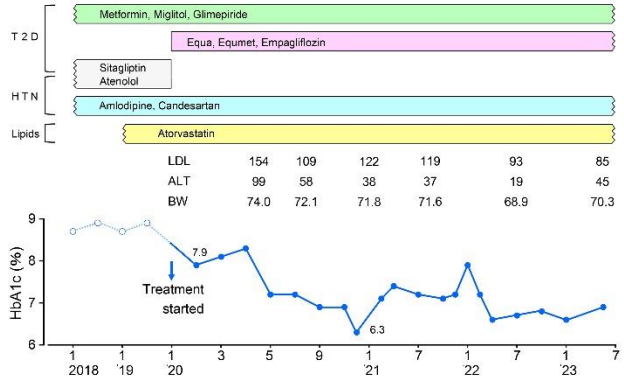

***Figure 2:** Clinical progress of the case.*

From mentioned above, her medical problems included obesity, T2D, hypertension, fatty liver, dyslipidemia. Her medication was changed from sitagliptin and atenolol to Equa, EquMet and empagliflozin, and her clinical progress was observed with close attention. Her weight was decreased from 74.0kg to 68.9kg, as well as ALT 99 to 19 and LDL 154 to 85 mg/dL (Figure 2). HbA1c value was decreased to 6.3% in December 2020. Her clinical progress showed clinical efficacy for these medical problems. She did not show any symptoms of gastro-intestinal adverse effects (GIAEs) for EquMet. In June 2022, her general status was remarkably improved without any symptoms or signs.

Ethical standards

The management of the case was complied with the ethic guideline previously presented in Helsinki Declaration. In addition, some commentaries were associated with the protection regulation of personal information. The principle was along with the ethical rules for clinical practice and research for human. Certain guidelines are presented from Japanese Ministry, which are Ministry of Health, Labor and Welfare and Ministry of Education, Culture, Sports, Science Technology. Authors et al. established ethical committee for current research, which exists in Bando Heart Clinic in Tokushima, Japan. It contains medical staffs and legal person, including the director, pharmacist, head nurse, dietitian and legal professional. Those members have discussed enough concerning this case, and agreed for current protocol. Informed consent was obtained by the written document from the patient

Discussion

The current case has been involved in several factors from metabolic syndrome. They are obesity, T2D, hypertension, dyslipidemia, and others. For the past history, she had detail check of CVD at 35 years old. At that time, apparent abnormalities were not detected for hypertension, CVD or ASCVD. However, certain underlying cardiovascular disorders may be progressed for years. As the characteristic aspect for this case, i) clinical efficacy of vildagliptin and metformin (EquMet), ii) improvement of ECG during clinical progress, and iii) improvement of SAS situation associated with weight reduction.

First, this case took Metformin before and added Equa (EquMet) from January 2020. After that, glucose variability became improvement and HbA1c was decreased from 7.9% to 6.3% for 10 months. The clinical progress suggested clinical efficacy of EquMet. As to the effect of EquMet, comparative investigation was conducted. From 11 RCTs of EquMet, 8533 cases were analyzed [10]. Compared study was between monotherapy of metformin and combined intake of EquMet. The detail measure was applied by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE). Consequently, add-on therapy showed remarkably higher efficacy of HbA1c reduction for -0.59 of mean differences (MD). Further, the incidence of adverse events (AEs) was almost similar as 0.98 of relative ratio (RR). From the results of VERIFY studies, early combination of Vil/Met shows remarkable clinical efficacy for years [11]. Further, administration twice a day would be meaningful, because it can suppress higher glucose elevation during night [12].

Regarding diabetic treatment, certain characteristic differences may

be present between Western countries and Japan. Westerners tend to show insulin resistance due to higher prevalence of increased BMI values. On the other hand, Japanese show both of increased insulin resistance and also decreased insulin secretion, in which diabetic patients in Japan include non-obese and obese for almost similar ratio [13]. Recent data were observed from larger RCT of Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3). As European and North American people are usually try to decrease insulin resistance by metformin, whereas Japanese people often try to decrease insulin resistance and to increase insulin secretion as DPP-4i [14]. Consequently, DPP4-i agents seem to be the first-line OHA in approximately 40 % of diabetic cases at hospitals and clinics in Japan.

Second, ischemic finding in ECG was relieved for during the clinical progress was found (Figure 1). By diabetic treatment of EquMet, the reduction of biochemical values was found such as HbA1c, LDL, AST and ALT. These beneficial changes may contribute the disappearance of ST depression, leading to clinical improvement of ASCVD [15]. For years, the case did not feel typical or apparent chest discomfort or pain. From the advantageous progress, the risk of CVD development will be hopefully reduced in the future [16].

Third, she showed the improvement of the exam for evaluating SAS after the treatment of EquMet [17]. Her weight has been actually decreased from 74.0 kg to 68.9 kg. This remarkable weight reduction may cause clinical improvement of probable SAS [18]. Concerning weight reduction, empagliflozin would be another factor that contributed to some extent as SGLT2i. Thus, both of EquMet and empagliflozin have been continued, and future course is required to be followed-up.

Certain limitation may exist in this article. The clinical effect of EquMet was actually observed, but additional benefit could be involved in the result, by the add-on therapy of SGLT-2i during the same period. This case has suffered from several diseases related to Metabolic syndrome. Then, future clinical progress will be followed up from several points of view.

In summary, this report showed a case of T2D treated by EquMet associated with various perspectives. We hope it will become a useful reference in the future.

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

Funding: There was no funding received for this paper.

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