

Remarkable Response of Vildagliptin/Metformin (EquMet) for Diabetic Patient with Recovered Ratio of Eicosapentaenoic Acid/ Arachidonic Acid (EPA/AA) by EPA Intake

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Abstract

The case was 70-year-old male with type 2 diabetes (T2D), dyslipidemia and bilateral internal carotid artery plaques. The eicosapentaenoic acid/ Arachidonic acid (EPA/AA) ratio was 0.21 in September 2019. By administration of ethyl icosapentate, EPA/AA was increased to 0.44 in October 2020. For echogram of carotid artery, bilateral plaque was observed, and the size of the bulbous Φ (right/left) was 2.41/2.48 mm in 2018, and 2.65/2.72 mm in 2020, respectively. For T2D, combined agents of vildagliptin/Metformin (EquMet) brought HbA1c reduction from 6.9% to 6.3% for 2 months, indicating remarkable clinical effect.

Keywords: Atherosclerotic Cardiovascular Accident (ASCVD); Vildagliptin Efficacy in combination with metformin for early treatment of type 2 diabetes (VERIFY); Polyunsaturated Fatty Acids (PUFAs); Japan EPA Lipid Intervention Study (JELIS); Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT); Carotid Artery Plaque

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Introduction

From epidemiological and evidence-based points of view, atherosclerotic cardiovascular accident (ASCVD) has been crucial medical problem across the world. Adequate lipid control has been required for patients with diabetes, dyslipidemia, hypertension, and ASCVD-related states. Polyunsaturated fatty acids (PUFAs) have been in focus for years. Among PUFAs with double bonds (2 or more) have been categorized as n-3 and n-6 PUFA. The principal n-3 PUFAs are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In contrast, principal n-6 PUFA is Arachidonic acid (AA), which is found in eggs, meat and fish. EPA has the function of anti-inflammatory and anti-hemagglutination function. In contrast, AA would be the precursor to mediators that is associated with aggregation and inflammation [1].

Concerning dyslipidemia, Japan EPA lipid intervention study (JELIS) has been conducted for 19 thousand applicants, and showed clinical effect of EPA [2]. EPA group revealed 19% reduction in major coronary events compared with control group. Thus, EPA may contribute the treatment and prevention of ASCVD. For general health situation of large population, circulating n-3 and n-6 PUFA can contribute cardiovascular problem or health [3]. In Japanese community, EPA/AA ratio was

measured for community dwellers in 2002 and 2012, respectively. The subjects included more than 3000 cases, respectively. As a result, EPA/AA value has decreased during 10 years at the population level. For CVD, the efficacy of high-purity eicosapentaenoic acid ethyl ester (hp-EPA-E) has been reported [4]. According to the JELIS, hp-EPA-E showed the clinical effect for CVD, associated with higher value of blood EPA. Concerning the risk of coronary event, the ratio of EPA/AA would be important. Consequently, the administration of EPA to human can increase the EPA/AA ratio, which may lead to the preferable status that suppresses the onset or progression of CVD.

Among various pathologies of ASCVD, type 2 diabetes (T2D) has been also important disease to be managed properly. American Diabetes Association (ADA) has presented the standard guideline for T2D in Jan 2023 [5]. Recent recommended nutritional therapy includes low carbohydrate diet (LCD) [6], and glycemic goals would be set for each patient with usual QOL [7]. Further has to be set for each patient with novel oral hypoglycemic agents (OHAs) have been developed and introduced to clinical practice. Furthermore, combined OHAs have been also produced for more convenient and effective response, in which vildagliptin/metformin (EquMet) has been widely administered. This agent was evaluated for large clinical study, which was vildagliptin and metformin

versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY) [8]. As a result, beneficial clinical efficacy was found by earlier combination of vildagliptin/metformin as DPP4-i and biguanide. This intensified may bring paradigm shift in the future treatment. These perspectives are presented by European Association for the Study of Diabetes (EASD) and ADA [9]. The combined agent of vildagliptin/metformin have been known as EquMet, and it has been useful for diabetic practice. Authors have reported seasonal glucose variability for years on EquMet, in which clinical efficacy was shown [10].

Authors and co-researchers have continued medical practice for hypertension, heart disease, ASCVD, chronic kidney disease, and so on [11]. We have covered thousands of patients in Bando Heart Clinic and always have mutually beneficial relationship with university hospital, red cross hospital, prefectural and city hospitals. For our usual clinical practice, we have lot of patients with multiple diabetic and cardiovascular problems [12]. From bio-psycho-social- points of view, we have provided holistic medicine to all patients, including lifestyle modification and medication [13]. Recently, we experienced clinically impressive case, who has plaque in the carotid artery associated with lower EPA/AA ratio [14]. In this case report, general progress and some perspectives would be presented.

Case Presentation

Medical History

Current case is 70-year-old male patient with T2D, dyslipidemia and bilateral internal carotid artery plaques. As past history, he suffered from tongue cancer, and had operation in University Hospital in April 2010, followed by oral chemotherapeutic agents for several months. In October 2010, he felt slight palpitation, and was diagnosed as premature atrial contractions (PAC) in the University hospital. For his daily work, he had been a banker for long, and his lifestyle has been stable after the operation. He has retired from the economic working in 2017.

He visited our Bando Heart Clinic, Tokushima, Japan for the first time in July 2011 for further evaluation of cardiovascular system. He underwent a treadmill exercise stress test. As a result, ST depression was found as J-shaped depression 0.05-0.07mV in II, III, aVf and V₅₋₆. It took 2 min 30 seconds until the first stage, and APC was decreased for 140 of pulse rate. SpO₂ value showed 98% and 98% for before and just after the loading. The overall diagnosis was borderline type.

After that, he has been treated for dyslipidemia for long, associated with the medication of pitavastatin, ezetimibe in our clinic (Figure 1). On the other hand, he was provided oral hypoglycemic agents (OHAs) in another clinic, including alogliptin, repaglinide, and pioglitazone. However, he often felt several episodes of hypoglycemia, and then he asked us to manage also diabetes control in our clinic from 2020.

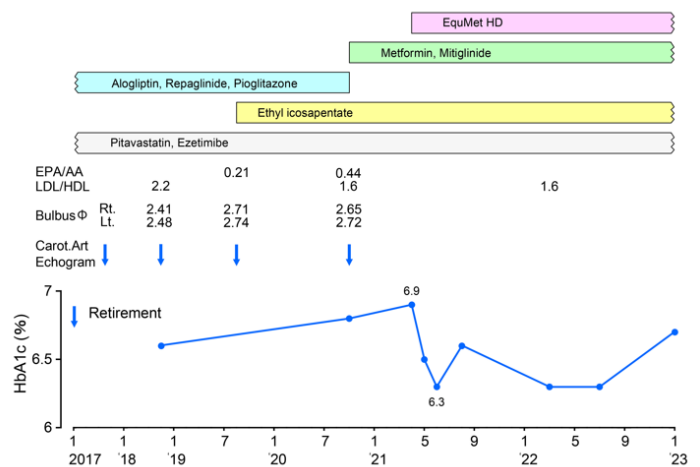


Figure 1: Clinical progress concerning HbA1c, laboratory data and treatment.

Physical Examination

His physical examination in February 2020 showed as follows: Consciousness was alert, and conversation was normal. Vitals were in the normal range as BP 114/66 mmHg, pulse 68 /min, SpO₂ 99%. His head, face, neck, heart and lung showed unremarkable. Abdomen revealed flat, soft with no abnormal bowel sound. Neurological examination showed unremarkable findings. His physique showed height 167 cm, weight 75 kg and BMI 26.9 kg/m².

Laboratory Exams

Laboratory exams in February 2020 were in the following: TP 7.1 g/dL, T-Bil 0.6 mg/dL, GOT 28 U/L, GPT 23 U/L, LDH 235 U/L, GGT 18 U/L, CPK 151 U/L, Uric acid 4.3 mg/dL, BUN 19 mg/dL, Cre 0.89 mg/dL, eGFR 65.9 mL/min/1.73m², Na 143 mEq/L, Cl 104 mEq/L, K 3.9 mEq/L, HDL 46 mg/dL, LDL 72 mg/dL, TG 146 mg/dL, T-Cho 136 mg/dL, LDL/HDL ratio 1.6, glucose 67 mg/dl, WBC 6500/μL, RBC 4.40 x 10⁶ /μL, Hb 13.8 g/dL, Ht 42.9 %, MCV 97.5 fL (80-98), MCH 31.4 pg (27-33), MCHC 32.2 g/dL (31-36), Plt 14.2x 10⁴ /μL.

Physiological Exams

As physiological exams in February 2020, chest X-P showed within normal limits. Electrocardiogram (ECG) revealed normal axis, pulse 74 /min, ordinary sinus rhythm (OSR), and unremarkable ST-T changes. Concerning the consecutive exams of ECG, the results during 2020-2023 are summarized in Figure 2. For recent 4 years, he did not show arrhythmia such as PAC that was found formerly.

The echogram of carotid artery was performed 4 times every year during 2017-2020. Among them, the results of 2018 and 2020 were shown (Figure 3, 4). Concerning the image, the plaque was present in bilateral carotid artery, and its size was rather smaller 2 years later. The size of the bulbus Φ (right/left) was 2.41/2.48 mm in

2018, and 2.65/2.72 mm in 2020, respectively.

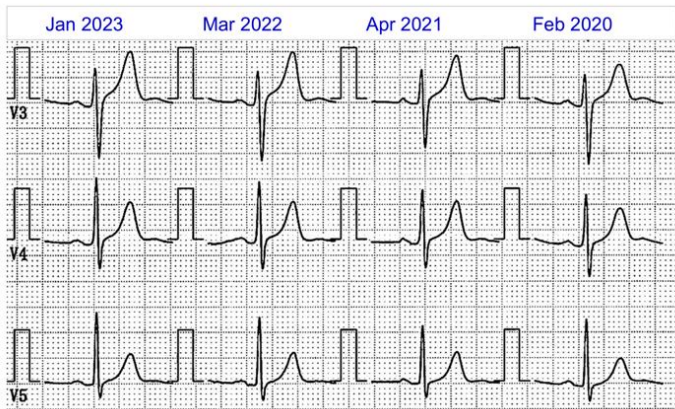


Figure 2: Consecutive ECG findings
 Remarkable ST-T changes were not apparent.

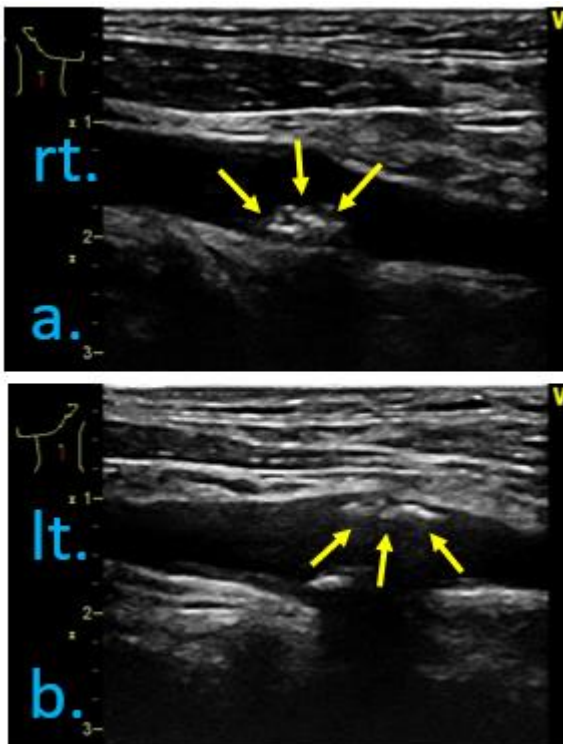


Figure 3: Echogram of carotid artery in Nov 2018
 3a. Plaque is present in right carotid artery
 Bulbus ϕ 2.41mm (rt)
 3b. Plaque is present in left carotid artery
 Bulbus ϕ 2.48mm (lt)

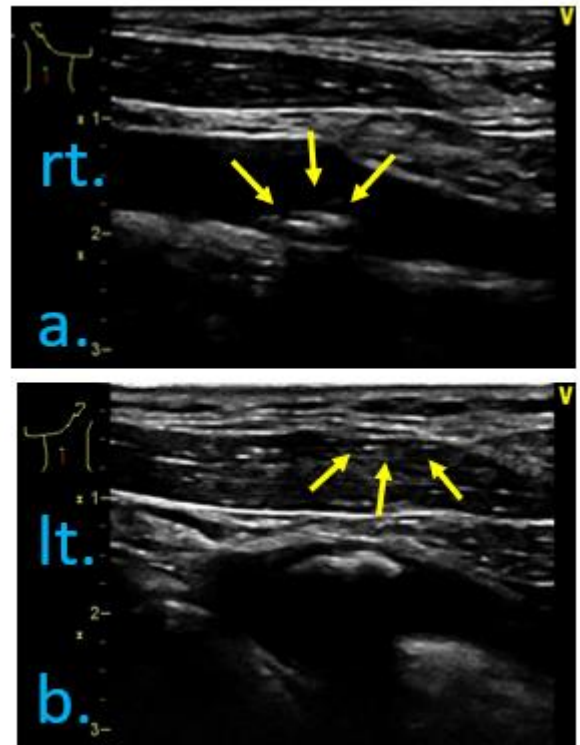


Figure 4: Echogram of carotid artery in Sept 2020
 4a. Plaque is present in right carotid artery
 Bulbus ϕ 2.65mm (rt)
 4b. Plaque is present in left carotid artery
 Bulbus ϕ 2.72mm (lt)

Clinical Progress

This case showed the presence of plaque in bilateral carotid artery. As biochemical exam, EPA/AA ratio was checked in September 2019. The result was 0.21, that was remarkably lower than standard level. Then, he started to have ethyl icosapentate 1.8g per day. In October 2020, EPA/AA ratio was proved to be 0.44, which was remarkably elevated. Recognizing the evidence of clinical efficacy, he was advised to continue ethyl icosapentate.

Concerning glucose variability, HbA1c value has been gradually increased. Then, we began the administration of Metformin and Mitiglinide. However, clinical effect was not enough and HbA1c was up to 6.9% in April 2021. Consequently, he was begun to take vildagliptin/metformin (EquMet). The HbA1c was remarkably decreased to 6.3% for only 8 weeks. After that, his diabetic control has been rather stable.

Ethical Standards

Current article is complied with the standard ethic guideline from Declaration of Helsinki. Moreover, some comment is based on the protective regulation with personal information. The principle can be found in the ethical rule concerning the clinical research and

practice. It is involved in several problems of human being. The standard guideline has been from Japanese government. They 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 concerning current patient. It was in Bando Heart Clinic, Tokushima, Japan. The committee included hospital director, physician, nurse, pharmacist, nutrition, and legal professional. We have thoroughly discussed as to the protocol and agreed for current protocol. We have taken the informed consent by written document from the patient.

Discussion

Current case was 70-year-old male patient with several medical problems. They can be summarized as follows: #1 T2D, #2 dyslipidemia, #3 hypertension, #4 plaque in bilateral carotid artery, #5 past history of tongue cancer, #5 previous premature atrial contractions (PAC), and #6 possible cardiovascular disease (CVD), #7 clinically efficacy of oral ethyl icosapentate and #8 rapid effect of EquMet for glucose variability. Among these problems, some aspects will be discussed with certain perspectives, which are i) EPA/AA and treatment of EPA, ii) clinical effect of EquMet, and iii) various relationship among these problems (mentioned above for #1-#8).

Firstly, EPA/AA ratio in this case increased from 0.21 to 0.44 by EPA administration. EPA/AA has been recently an important marker. When it is higher value, the patient would have lower risk of CVD [14]. In the community-based study on Hisayama study, Japan, higher CVD risk was found in the group of EPA/AA ratio \leq 0.29 compared with those of ratio \geq 0.59 [15]. In Hisayama study, circulating EPA/AA ratio was decreased significantly in 4251 cases (40 years \leq) with the data of 0.40 in 2002 to 0.32 in 2012. This reduction was remarkable in younger ages of 40' and 50' years. For Hisayama study, circulating AA levels may be increased by several situation [15]. They include intake of animal meat, alcohol consumption, smoking physical activity, certain drug usage and value of body mass index (BMI).

In Japan EPA lipid intervention study (JELIS) study, 1.8g of ethyl icosapentate was daily provided [2]. Concerning the usual dosage of ethyl icosapentate, 900 mg twice a day has been usually administered for the treatment of dyslipidemia [16]. When the case has also the abnormality of triglyceride, 900mg three times daily can be provided. If the patient has peripheral artery disease (PAD) associated with the diagnosis of arteriosclerosis obliterans (ASO), 600mg three times daily would be standard treatment. From the data of the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT), EPA supplementation was provided as 4.0g per day, which was proved to show preventive efficacy [17].

As to the detail of JELIS, multi-center RCT investigation for cardiovascular disease (CVD) or with diabetes was conducted for 4.9 years in median [17]. The applicants (n=8179) showed LDL

(41-100 mg/dL) and TG (135-499 mg/dL). Icosapent ethyl was provided 2g twice daily and other group for placebo. For the detail of the primary end point, the following were included as nonfatal stroke, unstable angina, nonfatal myocardial infarction, cardiovascular death or coronary revascularization. Further, secondary end point included nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death. As a result, hazard ratio (HR) for primary and secondary end point was 0.75 and 0.74, respectively, $p < 0.001$ for icosapent ethyl group/placebo group.

Secondly, current case was given EquMet, that was remarkably effective for short period. It is the combined agent of vildagliptin and metformin, and its clinical effect was proved by Vildagliptin Efficacy in combination with metfoRmIn For early treatment of type 2 diabetes (VERIFY) studies [8]. VERIFY was international multi-centered investigation for 34 countries [18]. Compared with other OHAs, EquMet shows benefit for decreasing fluctuation of blood glucose during day and night [19]. For the obtained comparative data, mean amplitude of glycemic excursion (MAGE) was significantly decreased. It would be from pharmacological characteristics of twice administration per day.

Thirdly, the general feature of this case can be summarized as #1-#8 mentioned above. The underlying factors are three main diseases of T2D, dyslipidemia and hypertension. The combined exacerbation of these factors brought the gradual or rapid onset of ASCVD. They also involve plaque in bilateral carotid artery (#4) and PAC (#5). Furthermore, T2D has been known to show elevated incidence of malignant diseases about 20 %. Taking his consuming much alcohol and cigarettes for years into consideration, general habit and diseases have caused the development of tongue cancer (#5). Concerning the treatment, medical problems of T2D and dyslipidemia (#1 and #2) have led to these two kinds of treatments (#7 and #8), respectively.

Some limitation has been found in current report. This case has shown remarkable clinical efficacy of EquMet HD as the combined agents of DPP4-i and biguanide. On the other hand, the case has improved EPA/AA ratio from 0.27 to 0.44 by administering of daily ethyl icosapentate. It seems to be necessary to follow up his clinical course in the light of diabetes, plaque of carotid artery and LDL values.

In summary, this report was the presentation of 70-year-old case with T2D, dyslipidemia and bilateral plaque of carotid artery. His general history, medical problems and various perspectives were discussed. Current description will be hopefully meaningful reference in the future diabetic research.

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