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PUBTEXTO

Post-prandial glucose changes in mild diabetic patient with clinical effect for EquMet (vildagliptin and metformin)

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Abstract

This case is 74-year-old male with mild type 2 diabetes (T2D). HbA1c level kept 6.5-6.9% for recent several years, and took no oral hypoglycemic agents (OHAs). He likes to take delicious food of carbohydrate, and his post-prandial blood glucose levels usually increased to more than 200 mg/dL in 3 meals a day. He showed remarkable arterial stiffness, which may be from legacy effect of glucose variability. Providing vildagliptin and metformin (EquMet) has brought diabetic improvement for HbA1c 7.3% to 6.1%. Meal tolerance test (MTT) showed post-prandial hyperglycemia for 3 hours, in which prolonged glucose elevation was found after lunch.

Keywords: legacy effect, arterial stiffness, vildagliptin and metformin (EquMet), post-prandial hyperglycaemia, Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY)

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Introduction

Arteriosclerosis has been crucial problem in the world, which includes several pathophysiology of Metabolic Syndrome (Met-S), and type 2 diabetes (T2D) [1,2]. The purpose for treating T2D would be the prevention of macro-angiopathy and micro-angiopathy [3]. In order to maximize beneficial long-term protection, clinical importance of earlier and more intensive therapy has been observed for newly diagnosed T2D patient [4]. Glycemic legacy effect on clinical outcomes for T2D patient seems to be predominantly due to previous HbA1c levels that showed greater impact than recent HbA1c levels [5]. For legacy effects, several observational cohort studies and other major diabetes trials have been found. Long-term follow-up method for established diabetes cases would not be supportive. Among them, legacy effect has been found in macrovascular events as well as microvascular complications [6].

For novel treatment for diabetes, several novel oral hypoglycemic agents (OHAs) have been introduced to medical practice [7]. However, actual glycemic control in T2D has been suboptimal situation across the world. As to diabetic complications, macroangiopathy and microangiopathy have been crucial problem for long uncontrolled level of HbA1c. Consequently, early attainment of satisfactory glycemic control would be a legacy effect for T2D patient in each later life. Combination of cardio-renal-gluco-centric therapeutic strategies will develop complementary efficacy in the reduction results of trajectory for renal-cardio-related diseases [8].

Concerning the treatment for T2D, actual practice for T2D guideline has been somewhat different in United States, European countries, and Asian countries [9]. However, metformin has been the first-line agent for T2D so far [10]. From these points of view, international large studies were investigated. The Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of T2D (VERIFY) studies were performed, which included vildagliptin as dipeptidyl peptidase 4-inhibitor (DPP4-i) and metformin as biguanide [11]. The combined agents of vildagliptin/metformin would be known as EquMet, which has been widely used for medical practice [12]. Authors et al. have continued diabetic research for long on various OHAs including EquMet [13]. In addition, the relationship of Equmet and lipids were reported [14]. We recently experienced a T2D case with impressive characteristics. Its general progress and related perspective will be described in this report.

Presentation of cases

Medical History

This case has been 74-year-old male patient with T2D with mild degree for 11 years. When he was 63 years old, his HbA1c was proved to be slightly higher than the standard level. He sometimes checked blood glucose before meal and after meal. The HbA1c values are summarized (Table 1, upper), in which HbA1c was 6.3-6.5% during 2012-2016, and 6.6-6.9% until 2019, and more than 7.0% after 2020. Thus, HbA1c values are gradually increased.

Concerning his daily meal habit, he likes to eat delicious dish with carbohydrate. In 2023, he was advised to refrain from taking much carbohydrate, and to start oral hypoglycemic agents (OHAs) for better glucose control. The diabetologist and pharmacist in charge have explained the importance of lowering

daily profile of blood glucose and HbA1c levels. He has begun the intake of combination agents of vilidaglipti/metformin (EquMet LD), and after that HbA1c was acutely decreased to almost normal ranges (Table 1. lower).

Table 1: *Changes in HbA1c.*

Year	Month	HbA1c	OHAs
2012		6.3	none
2013		6.3	"
2014		6.5	"
2015		6.5	"
2016		6.5	"
2017		6.8	"
2018		6.6	"
2019		6.9	"
2020		7.0	"
2021		7.5	"
2022		7.2	"
2023	Jan	7.3	"
	Feb	7.3	"
	Mar	7.2	EquMet
	Apr	6.8	"
	May	6.5	"
	Jun	6.2	"
	Jul	6.1	"

Several exams

This case has received laboratory exam in Feb 2022 (Table 2). As a result, TG, HDL-C and LDL-C were within normal ranges. HbA1c showed 7.3% that reveals in diabetes range. Otherwise, it showed unremarkable data concerning liver, nutrition, renal and complete blood count (CBC).

Table 2: *Laboratory results for several years.*

physique	**BMI**	**23.2**	**Diabetes**	**fasting gluc**	**144**
	obesity	+5.6		HbA1c	7.3
	abd circum	85.6		urinary gluc	-
Lipids	T-Cho	179		amylase	82
	TG	95	Renal	uric acid	6.7
	HDL-C	70		creatinine	0.96
	LDL-C	80		BUN	13
liver	AST	20		eGFR	59.2
	ALT	16	CBC	RBC	438
	GGT	23		HbA1c	14.1
	ALP	107		Ht	43,7
	LDH	139		MCV	99.8
	ChE	241		MCH	32.2
	T-Bil	1.4		MCHC	32.3
nutrition	T-Protein	7.4		WBC	44
	Albumin	4.1		Plts	18.5
	A/G ratio	1.24	Others	CRP	0.05

His electrocardiogram (ECG) showed negative with no remarkable ST-T changes. He received the exam of arteriosclerosis for brachial-ankle pulse wave velocity (baPWV). The result of baPWV was more than 2100 cm/sec bilaterally. It was more than +2SD above the standard level [15]. Consequently, it is situated at the higher risk category.

This case has sometimes tried to check his pre-prandial and post-prandial blood glucose during 2013 to 2021. It was meal tolerance test (MTT). His data included from 0, 1, 2, 3 hours for breakfast, lunch and supper. Several obtained data for three meals are shown in Figure 1. Pre-prandial blood glucose ranges from 93 to 148 mg/dL. The peak level of post-prandial blood glucose ranges from 200 to 240 mg/dL. The characteristic point includes that 3-hr post-prandial level after breakfast tends to be rather lower, whereas it tends to be increased in lunch and supper.

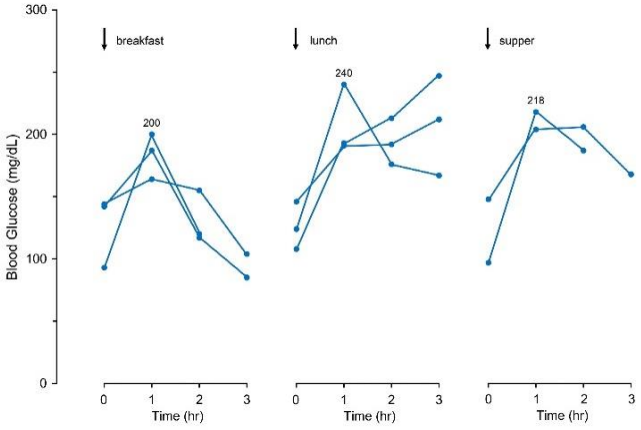

Figure 1: *Pre-prandial and post-prandial blood glucose for 3 meals.*

The actual meals for these are not the same content but different. Among them, three typical meals can be presented in Figure 2a, 2b and 2c. Total carbohydrate amount can be calculated as 0.5g, 0.9g and 27.8g, respectively.

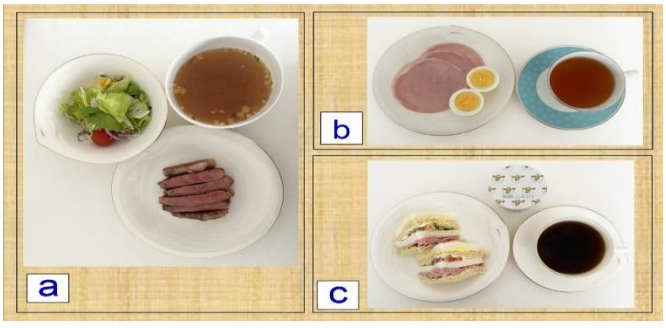

Figure 2: *Examples of meals including carbohydrate amount*
Fig 2a *includes meat steak, vegetable salad, and consomme soup, in which carbohydrate amount is 0.1g, 0.1g and 0.3g for 130mL, respectively. It has only 0.5g of carbohydrate in total.*
Fig 2b *has 2 pieces of meat ham, and one egg, that has 0.8g and 0.1g, respectively with totally 0.9g of carbohydrate.*
Fig 2c *is sandwich of own making. It includes plain bread 22g, half egg 0.05g, tomato 0.55g, meat ham 0.8g, vegetable 0.1g and yogurt (100mL) 4.3g with totally 27.8g of carbohydrate.*

Ethical consideration

This case complies with the ethical guidelines of the Declaration of Helsinki. Moreover, some commentaries are

presented for the standard regulation for personal information. Current principle has been for ethical rule about medical practice and research. Certain medical problem of human is present. Its guideline has been on the regulation of Japanese government, which are Ministry of Health, Labor and Welfare and Ministry of Education, Culture, Sports, Science Technology. The authors and co-researchers have our ethical committee about this case. It is present in Yoshinogawa hospital, Tokushima, Japan. The committee has some professional members, including the director of the hospital, physician, pharmacist, head nurse, nutritionist, medical laboratory staff and legal professional. Our team have discussed for satisfactory situation concerning current case, and agreed with general protocol. The required informed consent was given from the case for document paper.

Discussion

The characteristics of this case can be found in some points, which are i) certain amount of carbohydrates have been usually taken, ii) mild diabetes has kept for years and arterial stiffness was remarkable, iii) EquMet showed diabetic improvement for short period. Concerning these aspects, some perspectives are discussed in this order.

Firstly, the basic concept of nutritional therapy would be crucial. The recommendation has been changed and prevalent from calorie restriction (CR) to low carbohydrate diet (LCD) [16]. Accumulated evidence showed the useful and predominance of LCD for actual clinical practice [17]. When carbohydrate is taken per os for T2D, blood glucose elevates 3 mg per 1g of carbo 1g [18].

Secondly, WHO and ADA announced that the response for 75gOGTT shows four categories, which are normal, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes patterns [19]. IGT means the case who has post-prandial hyperglycemia. Such patients tend to develop macroangiopathy rather than microangiopathy [20]. This case has kept higher HbA1c for years, and seemed to have post-prandial hyperglycemia during his daily meal habit. He showed normal value of ankle brachial index (ABI), but remarkably increased baPWV. Its normal range is less than 1400 cm/sec, and cut-off level of developing arteriosclerotic cardiovascular accident (ASCVD) is less than 1800 cm/sec. He has currently showed no apparent macroangiopathy or microangiopathy, but post-prandial hyperglycemia may develop aggravation of angiopathy in the future.

Legacy effect has been known for early glycemic control to diabetic angiopathy. Cohort study for diabetic complication was conducted (n=34,737) [21]. Compared with the group 1 (HbA1c <6.5%), hazard ratio (HR) of diabetic complication was 1.204 for group 2 (HbA1c 6.5-6.9%), and HR of death was 1.290 for group 3 (HbA1c 7.0-7.9%). Consequently, legacy effect was observed, where keeping HbA1c ≥6.5% for the first year will cause worse outcomes. Another legacy effect was reported for all-cause mortality (ACM) and myocardial infarction (MI) for T2D (n=3802) [5]. HR for ACM with 1% higher HbA1c was 1.08, 1.18, and 1.36 for 5, 10 and 20 years, respectively. Similarly, HR for MI was 1.13 for 5 years, and 1.31 for 20 years. As to HbA1c reduction in early stage at diagnosis, ACM risk was decreased 18.8% for 10-15 years after. However, HbA1c reduction was only 2.7% (one-seventh) when HbA1c was decreased 10 years later after the diagnosis.

For legacy effect, recent report is found from DCCT/ EDIC research group. EDIC means Epidemiology of Diabetes Interventions and Complications (EDIC) study, in which intensive treatment was compared for earlier 10 years vs. later 10 years [22]. Then, impressive results were found. A hypothetical case (A) is supposed as HbA1c 7% for 1-10 years, and 9% for 11-20 years. Another case (B) is supposed as HbA1c 9% for 1-10 years, and 7% for 11-20 years. When compared both A and B, case A showed 33% reduction of CVD risk, and 52% reduction of eGFR rather than case B.

Thirdly, the beneficial aspect of early combined treatment would be found in the group of earlier and later onset of T2D, from the result of sub-analysis of the VERIFY [23]. The risk reduction was observed for macrovascular events for the combination therapy of vildagliptin/metformin, where HR was 0.71 [11]. Glycemic durability was studied for comparison with early EquMet vs. metformin monotherapy [23]. The patients have two groups of young-on set (YOD) and late-onset (LOD) after 40 years old, which is included for VERIFY trials. The detail analyses were conducted by statistical analysis plan (SAP) method in VERIFY study [24]. The protocol included the end point time until treatment failure (TF) of HbA1c 7.0 %<. As a result, early combination decreased the TF risk for 48% vs. 46%, in YOD vs. LOD, respectively ($p<0.0001$). Consequently, treatment-naïve YOD (6.5-7.5%) showed improvement of glycemic target with early durability and also delayed aggravation of glycemic variability.

From economic point of view, T2D brings higher risk of developing ASCVD that is accompanied by mortality, morbidity, and health care involvement. Lots of T2D cases (n=80,305) were studied for economic expenses, including ASCVD, PAD, MI and CVD [25]. Annual expenses were compared with cases with T2D/ASCVD vs. cases with T2D without ASCVD (control). As a result, annual costs per case showed higher in cases with ASCVD, in which 2.7x for PAD, previous CVD x2.2, ASCVD 1.9x and previous MI x1.7. These results suggested the required assessment for ASCVD risk and implementation for T2D therapy in the healthcare system.

In this article, some limitation may exist. Current case showed several factors for mild diabetes, intake of carbohydrate, remarkable arterial stiffness, clinical efficacy of EquMet, and others. Certain mutual influences would be involved in the pathophysiology of the case.

In summary, 74-year-old male showed impressive progress for diabetes, lipid and arteriosclerosis. Future follow-up with careful attention will be required for the adequate management

with protecting macroangiopathy. This report becomes hopefully useful reference for clinical research and practice.

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