



A Case with Type 2 Diabetes (T2D) and Cardiovascular Evaluation treated by Twymeeg

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Abstract

This case is 78-year-old female patient with type 2 diabetes (T2D), cardiovascular disease (CVD), hypertension, dyslipidemia and previous treatment of percutaneous coronary intervention (PCI). She maintained stable status until autumn 2024 with HbA1c 6.8-7.0%. She developed chest oppression, and then received cardiovascular evaluation. Pulse wave velocity (PWV) showed normal cardio-ankle vascular index (CAVI), about 1.0 with following up as ankle brachial pressure index (ABI), and no acute changes of in-stent restenosis (ISR) as coronary artery angiography (CAG). Low carbohydrate diet (LCD) has showed protective effect for arteriosclerotic development. Novel concept of Cardiovascular-Kidney-Metabolic Syndrome (CKM) has been introduced for the future.

Keywords: Percutaneous Coronary Intervention (PCI); Cardiovascular-Kidney-Metabolic Syndrome (CKM); In-stent restenosis (ISR); Low carbohydrate diet (LCD); Imeglimin (Twymeeg)

Introduction

Across the world, diabetes mellitus (DM) has been increasing as 537million in 2021, in which it will rise to 783 million in 2045 [1]. Among diabetic patients, cardiovascular disease (CVD) has been the main cause of mortality and morbidity. Especially, the ratio of CVD complication is remarkably higher in 46.0% for North American and Caribbean regions, and 42.5% for Southeast Asia. In DM cases with CVD, 29.4% of them has the complication of coronary artery disease (CAD). In addition to DM, obesity has become the crucial problem. The prevalence of obese or overweight has been increased, which seems to be more than one-third across the world [2].

For years, various discussion has been observed concerning the type 2 diabetes (T2D) and the occurrence of arteriosclerotic cardiovascular disease (ASCVD) [3]. Some guideline has been valid for the control and/or prevention of ASCVD [4]. With the increasing burden of ASCVD in life style-related diseases including diabetes, hypertension, dyslipidemia, microangiopathy and macroangiopathy, various discussion has been found concerning the relationship of pre-diabetes. Almost little doubt can be recognized that pre-diabetes may develop prognostic

implications, such as ischemic stroke, myocardial infarction and peripheral artery disease (PAD) [5]. Increasing evidence has been reported about pre-diabetes status as an actionable disease entity. DM has clinical complication of microangiopathy and macroangiopathy. The latter includes cerebral vascular accident (CVA), ischemic heart disease (IHD), CVD and PAD. In order to protect the development of hyperglycemia, low carbohydrate diet (LCD) has been recognized as clinically effective method [6]. LCD was historically begun by Doctors of Atkins and Bernstein in North American and European regions [7,8]. The information of LCD was developed worldwide in health care and medical regions. In Japan, authors et al. established Japan LCD promotion association (JLCDPA) and developed social LCD movement until now [9]. We have proposed simple and useful 3 patterns of LCD meals, which are super-LCD, standard-LCD and petite-LCD that have carbohydrate ratio as 12%, 26% and 40%, respectively [10]. Various discussion has been found about the comparison of LCD vs low-fat diets (LFD) for improving glycemic variability. LCD studies include 7 RCTs with ranging from very low-carbohydrate ketogenic diet (VLKD) (<10%) to moderate carbohydrate regimens (30-45%) [11]. On the other hand, LFDs usually have 50-60% of carbohydrate with decreased fat (20-30%) and

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moderate protein involvement (15-20%). Recently, personalized dietary approaches have been reported associated with potential LCD for adequate diabetic management. Our clinical team has managed various patients with life style-related disease so far. We experienced an impressive case with T2D and CVD, and investigated the detail evaluation from cardiovascular aspect. General clinical situations and some related perspectives are described in this article.

Case Presentation

Medical history

Current case is a 78-year-old female patient with hypertension, CVD, T2D, and dyslipidemia. She developed CVD and T2D about 11 years ago, and treated by anti-hypertensive agent (AHA) and oral hypoglycemic agents (OHAs) in another hospital. For recent 6 years, she has been treated in our hospital with stable glycemic condition as HbA1c 6.8-7.0%.

She received further examination for CVD including coronary artery angiography (CAG) and percutaneous coronary intervention (PCI) in 2017 and 2018. Her last angiogram was in 2021 with no stenotic lesions, and she did not visit cardiologist after that. She visited our diabetic department in 2022 and has been treated for T2D for 4 years. Her diabetic control has been stable for years by continuing LCD and taking vildagliptin/metformin (EquMet) and imeglimin (Twymeeg). In October 2024, she felt exertional oppression sensation in the chest, and then she has received general further evaluation.

Physicals and exams

Physical examination in October, 2024 showed in the following: her vitals were BP 136/84 mmHg, pulse 72/min, SpO₂ 97%. Conversation and consciousness were normal, and no remarkable findings were found in the heart, lung, abdomen and neurological exams. Her physique showed 154cm in height, 57.1kg in body weight and BMI was 24.1 kg/m².

Blood biochemistry in November 2024 were as follows: TP 6.8 g/dL, Alb 4.1 g/dL, AST 40 U/L, ALT 44 U/L, r-GT 51 U/L, ChE 383 U/L (201-421), uric acid 3.2 mg/dL, BUN 10 mg/dL, Cre 0.61 mg/dL, eGFR 70.3 mL/ml/1.73m², Na 140 mEq/L, Cl 105 mEq/L, K 3.9 mEq/L, LDL 60 mg/dL, HDL 68 mg/dL, TG 85 mg/dL, RBC 4.93 x 10⁶ /μL, Hb 14.2 g/dL, Ht 43.5 %, MCV 88.2 fL (80-98), MCH 28.8 pg (27-33), MCHC 32.6 g/dL (31-36), WBC 4900/μL, Plt 20.7 x 10⁴ /μL, HbA1c 7.0%, Blood glucose 150 mg/dL, NT-proBNP 74.2 pg/mL (0-125), BNP (EIA) 30.5 pg/mL (0-18.4), CRP 0.08 mg/dL.

Chest X-ray revealed no remarkable acute changes. Electrocardiogram (ECG) showed pulse 76/min, normal axis, ordinary sinus rhythm (OSR). Detailed analysis included Pulse 73 /min, PR 194 ms, QRS Dur 76 ms, QT/QTc(E) Int 378/404 ms,

P/QRS/T axis 51/3/45 degree, RV5/SV1 0.940/0.995 mV, RV5+SV1 1.935 mV (Figure 1).

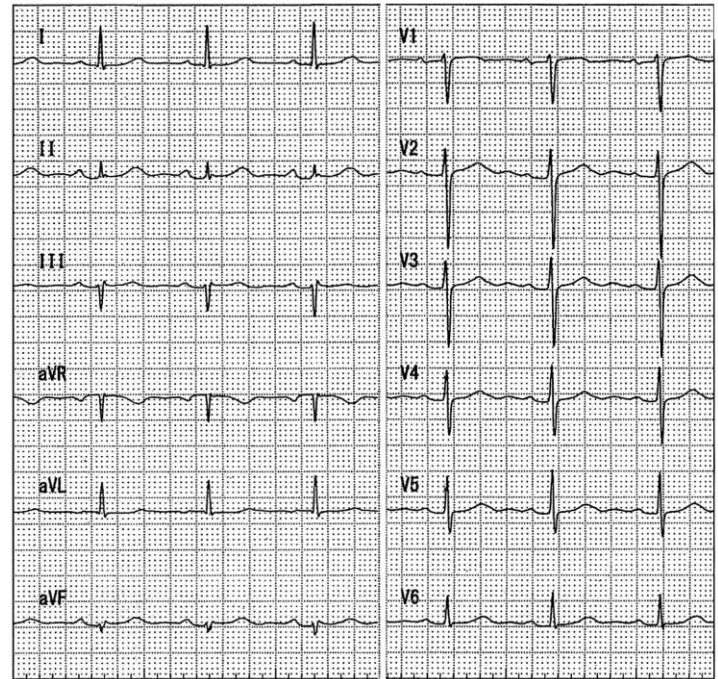


Figure 1: The result of Electrocardiogram (ECG) No remarkable ST-T changes were detected.

Cardiovascular exams

Cardiac ultrasound exam showed no abnormalities in left ventricular wall motion, a normal left ventricular ejection fraction (LVEF), and no significant valvar disease or congestion. In the left heart system, there was no left ventricular enlargement or wall thickening, LVEF = 66%, and no left atrium enlargement. In the right heart system, right ventricular contraction was maintained. No pericardial or pleural effusion was observed.

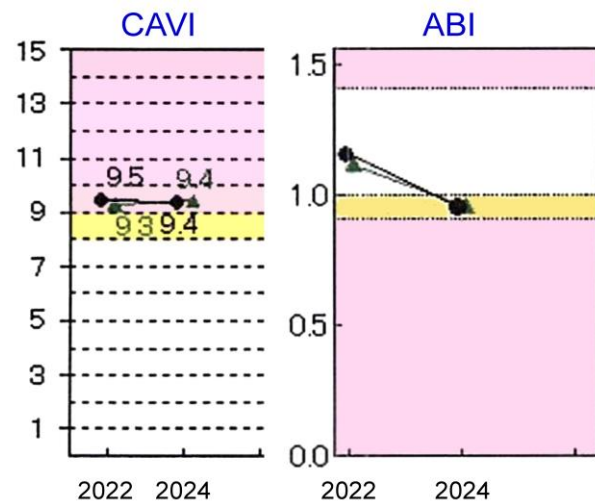


Figure 2: The result of plethysmography Slight arteriosclerosis by CAVI and decreased value of ABI.

SUNTEXT REVIEWS

Plethysmography was conducted in 2022 and 2024 [12]. As a result, ankle brachial pressure index (ABI) values were 1.16- 0.96 (right) and 1.12 -0.96 (left), and cardio-ankle vascular index (CAVI) revealed stable values around 9.3-9.5 (Figure 2). Pulse wave velocity (PWV) test showed negative findings associated with PEP 89, ET 326, R-AI 1.30, ET 312 and PEP/ET 0.27 (Figure 3). From these, unremarkable results of plethysmography were observed, where annual follow up would be required.

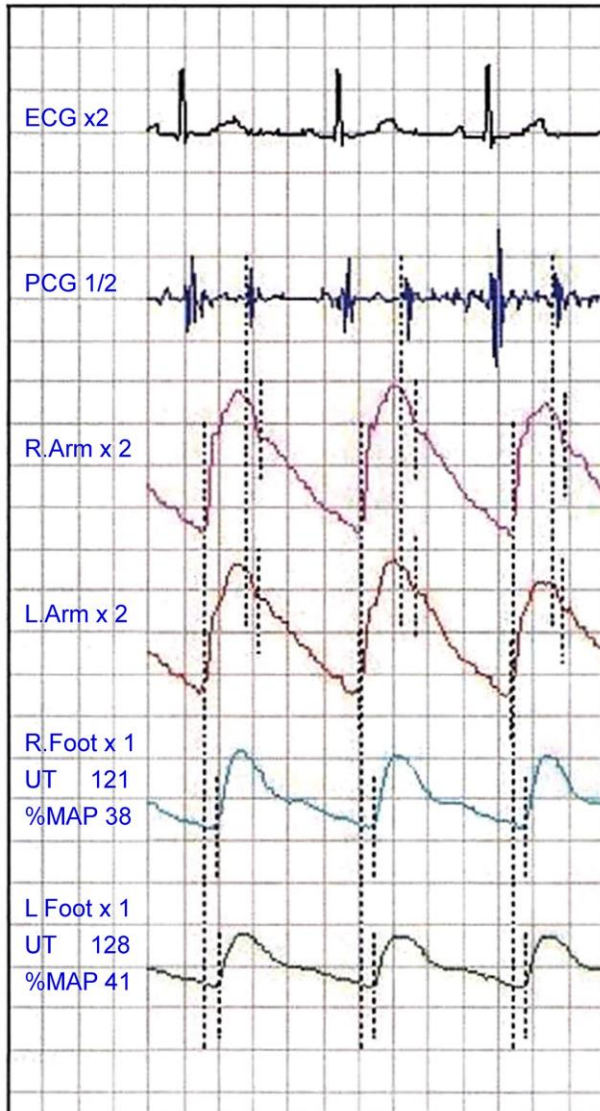


Figure 3: The result of pulse wave velocity (PWV) Unremarkable findings for stenosis or obstruction.

This patient received CAG and PCI in 2017 and 2018, associated with PCI for LAD#7 and LCX#13. She showed no in-stent restenosis (ISR) in 2021 for #7 and #13. CAG in 2025 January showed no significant stenosis of coronary arteries. The detail results were RCA#2 50%, #3 50%, LAD#7 no ISR, #9D1 50% and LCX#13 no ISR (Figure 4).

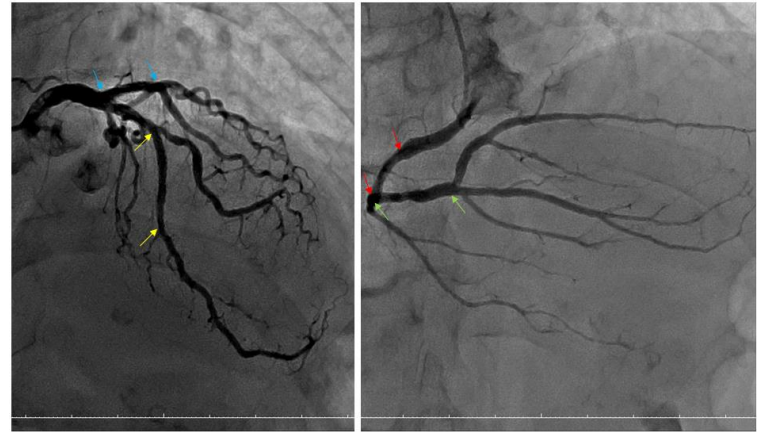


Figure 4: The results of coronary angiography in the latest exam.
 a. no ISR for LAD #7 (yellow) and no ISR for LCX #13 (blue).
 b. stenosis 50% for RCA #2 (red) and 50% for TCA #3 (green).

Clinical progress

From further clinical evaluation, she was proved to have unremarkable apparent clinical problems concerning T2D and CVD. Her medication included as follows. They are EquMet (Equa and Metformin), imeglimin (Twymeeg), pitavastatin calcium (Livalo), magnesium oxide, picosulfate, and amlodipine. From these, she has been treated for T2D, dyslipidemia, hypertension, CVD, and Gastroesophageal Reflux Disease (GERD). Regarding T2D, HbA1c value has been recently stable around 7.0%. From autumn 2024 to spring 2025, there have been no particular clinical changes since then and the condition has remained stable to the present.

Ethical consideration

The case complied with the Helsinki Declaration for ethical guideline, and some comment was announced from the regulation [13]. The principle included certain rule for medical practice and research. Clinical problems for human were present. The standard guideline was shown from Ministry of Health, Labor and Welfare and Ministry of Education, and also the Ministry of Culture, Sports, Science Technology. The author's et al. established ethical committee in Sakamoto Hospital, Kagawa, Japan. The committee included some medical members, such as hospital president, physician, pharmacist, nurse, and legal professional. These staffs discussed enough and agreed the general protocol. In addition, we were provided informed consent by the document for this case.

Discussion

Regarding this case, clinical problems and perspectives have been considered. They include i) usefulness of LCD, ii) pharmacological effect of imeglimin (Twymeeg), and iii) the

relationship of CVD risk in diabetes. Some discussion will be described in the following.

For clinical efficacy of LCD, RCT research was conducted for 1197 applicants of obesity [14]. As a result, LCD has brought the improvement reduction of HbA1c and fasting plasma glucose (FPG) as -0.36% and -10.7 mg/dL, respectively. In addition, TG and HDL improved significantly as -19.9 mg/dL and +2.49 mg/dL, respectively. Consequently, LCD can show clinically glucose control and lipid profile with patients with overweight and obesity. It emphasizes the standardization of dietary guideline. From 33 RCTs with 2821 cases, people with daily take <100g of carbohydrate did not show the reduction of fatty mass (FM) [15]. When adults with obesity or overweight limit carbohydrate <50g daily for >1 month duration of ketogenic diet (KD) and LCD, they showed the improvement of all biomarkers including FM. Then, less than 50g of carbohydrate daily would be recommended for the treatment.

The patients diagnosed as Cardiovascular-Kidney-Metabolic Syndrome (CKM) were analyzed from National Health and Nutrition Examination Survey (NHANES) database for 10 years [16]. They were divided into LCD group or non-LCD group. Totally 1,000 non-CKM individuals (stage 0) and 11,141 CKM individuals (stage 1,2,3,4) were included. The ratios of people on LCD for CKM stages 0,1,2,3,4 showed 1.16%, 2.49%, 1.94%, 1.24%, 1.68%, respectively. As a result, people on LCD showed 62%-lower risk of all-cause mortality (HR=0.38, p=0.03). By stratified analysis, no interaction of LCD and CKM stages was found. Consequently, LCD suggests to reduce the risk of all-cause mortality in the CKM individuals, which is regardless of CKM stages.

As oral hypoglycemic agent (OHA), imeglimin has been introduced to medical practice. Clinical effect of combined imeglimin and DPP-4i was investigated, where this combination has been most frequent in Japan [17]. Diabetic cases with DPP-4i alone were provided imeglimin for 16 weeks, and meal tolerance test (MTT) was studied. Furthermore, continuous glucose monitoring (CGM) was performed for evaluating glycemic variability. As a result, time in range (TIR) increased from 65.0% to 90.90% (p<0.05), and time above range (TAR) decreased from 34.0% to 9.0% (p<0.05). Thus, imeglimin + DPP-4i showed significant improvement of glycemic variability that was based on increased insulin secretion. Authors have a previous case with T2D and CVD treated by imeglimin who showed parallel improvement of HbA1c and arteriosclerosis [18].

From the latest report, diabetic patients were followed up with the changes in CVD risk [19]. The protocol included the cohort matching program with 1:1 ratio of 2 groups of life-style modifications and no intervention (n=557 each, total 1114). As a result, cases with modifications showed greater improvement in FPG (-0.84 mmol/L, diastolic blood pressure (-2.08 mmHg), BMI

(-0.29 kg/m²), LDL (-0.13 mmol/L), HDL (0.05 mmol/L), 10-year CVD risk (-0.94%), atherosclerotic CVD risk (-0.77%). Thus, enrollment of program would be beneficial for preventing CVD risk.

The risk of endothelial dysfunction (ED) has been involved in the development of ASCVD development. ED has been observed by the postprandial lipemia (PPL), which may be from Low Carbohydrate, High-Fat (LCHF) meal [20]. In the latest study, systematic review was conducted concerning ASCVD, ED, PPL and LCHF. Among them, 16 studies were chosen and postprandial triglycerides (PPTG) after LCHF meal (<26% of carbohydrate) were analyzed. As a result, consumption of LCHF meals showed negative impact on PPL on some cases. Consequently, the influence of LCHF to cardiometabolic health will be studied successively. As to atherosclerosis by diabetes, Selenoprotein S is implicated in the progression of numerous situations such as diabetes, obesity, dyslipidemia, and so on [21]. Serum selenos may function as potential biomarker and then selenos single nucleotide polymorphisms (SNPs) could become effective gene markers for developing arteriosclerosis in diabetes. Some limitation may be present in this article. The case presented some clinical problems of diabetes, CVD and previous CV treatment. Her general status has been stable, and will be followed up with careful attention.

In summary, this report described the relationship between diabetes and CVD. It will hopefully become certain reference for medical practice and research in the future.

Conflict of Interest

The authors declare no conflict of interest.

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