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Parallel Improvement of HbA1c and Arteriosclerosis during Clinical Progress for Diabetic Patient

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Abstract

Current case is 68-year-old male with Type 2 diabetes (T2D), hypertension and arteriosclerosis of peripheral artery disease (PAD) and coronary heart disease (CHD). HbA1c was stable for 5.5-6.6% in 2021-2022, unstable afterwards, and it peaked to 7.5% in April 2023. By imeglimin (Twymeeg) administration, HbA1c decreased to 6.2% for 5 months. Pulse wave velocity (PWV) exam was continued from 2016, with rather higher results of cardio-ankle vascular index (CAVI). However, CAVI was lower in 2021-2022, which was consistent with lower HbA1c period. This parallel phenomenon may be partly from average blood glucose and mean amplitude of glucose excursions (MAGE).

Keywords: Imeglimin (Twymeeg); Pulse wave velocity (PWV); Cardio-ankle vascular index (CAVI); Japan LCD promotion Association (JLCDPA); Mean amplitude of glucose excursions (MAGE)

Introduction

From bio-psycho-social points of view, diabetes has become crucial problem worldwide [1]. Each country in several regions has managed diabetic matters for long, such as European and North American [2,3]. American Diabetes Association (ADA) has announced the latest guideline for managing type 2 diabetes (T2D) in Jan 2024 [3]. Recent topics include some types of novel oral hypoglycemic agents (OHAs) beneficial for actual practice. Among them, imeglimin (Twymeeg) has been introduced with pharmacological function mechanism through mitochondria pathway [4]. Authors' et al have presented some reports of T2D patients with clinical efficacy by imeglimin [5].

For T2D, basic principle for treatment includes nutritional therapy, exercise continuation and medicine of OHA or insulin. As diet method, calorie restriction (CR) was formerly usual measure, but low carbohydrate diet (LCD) has been recently known with clinical efficacy for T2D [5]. LCD was started in medical care and health care regions, where two doctors of Atkins and Bernstein have contributed much through educational books [6,7]. Successively, LCD was also initiated in Japan, in which author's collaborators have developed social movement of LCD via Japan LCD promotion Association (JLCDPA) [8,9]. Our team has continued actual LCD prevalence more by seminars, books and various presentations [10]. We have recommended three types of useful LCD meals. They are petite LCD, standard LCD and super LCD that include carbo amount ratio by calorie calculation as 40%, 26% and 12%, respectively [11].

As we have continued diabetic practice and research for various types of patients, a meaningful T2D male case was present. He has suffered from T2D and diabetic macroangiopathy for long, and showed remarkable clinical effect by imeglimin (Twymeeg) associated with HbA1c decrease. Furthermore, he showed parallel improvement of HbA1c decrease and improved arteriosclerosis in his clinical progress. His general outlines and related clinical perspectives would be described in this article.

Presentation of Cases

Medical history

The patient is 68-year-old male with T2D. He has past history of several clinical problems. He was diagnosed as T2D in early 50s, dyslipidemia of elevated LDL and benign prostate hyperplasia (BPH) in later 50s, and peripheral artery disease (PAD) and coronary heart disease (CHD) in early 60s. Furthermore, he was pointed out to have nephropathy in late 60s.

Clinical changes in HbA1c were shown in Figure 1. He has been treated by T2D and glucose variability has been unstable for years. Authors and collaborators have managed his total therapeutic measures, including adequate nutritional therapy of low carbohydrate diet (LCD), stable exercise daily habit, and administration of oral hypoglycemic agents (OHAs). In response to these combined therapy, HbA1c value in 2018 was gradually decreased from 8.0% to 5.7% for a year. His diabetic situation had been satisfactory stable during 2019 and 2020 as keeping low HbA1c value for 5.7%-6.6%. From spring 2021, his HbA1c was gradually elevated, and then OHA was changed from pioglitazone to empagliflozin in summer 2021. After that, HbA1c was peaked to 7.5% in April 2023. Consequently, imeglimin (Twymeeg) was started and then HbA1c was decreased to 6.2% for 5 months. His diabetic status has been now kept stable so far.

Physicals and laboratory exams

The physical examination in March 2023 revealed in the following: consciousness, speech and vital signs were in the normal ranges. No remarkable changes were observed in the lung, heart, abdomen, extremities or neurological exams. He did not complain of specific symptoms or signs. His physique showed height 162.0 cm, weight 61.3 kg and BMI 23.4 kg/m^2.

Table 1: *Changes in laboratory data.*

	2019 Oct	2020 Sept	2021 Apr	2022 Sep	2023 Mar	2024 Jan	Units
Liver							
AST	33	31	28	24	24	39	(U/L)
ALT	45	36	35	31	31	47	(U/L)
GGT	50	43	45	36	36	45	(U/L)
Renal							
UA	6.1	6.2	6.0		5.9	5.7	(mg/dL)
BUN	20	22	23		28	30	(mg/dL)
Cre	1.00	1.06	1.05		0.87	1.06	(mg/dL)
Lipids							
HDL	76	66	64	59	73	69	(mg/dL)
LDL	86	87	103	81	89	106	(mg/dL)
TG	79	80	98	96	113	83	(mg/dL)
CBC							
WBC	51	46	53			50	(x10*2/μL)
RBC	423	404	455			435	(x10*4/μL)
Hb	13.1	12.3	13.8			13.3	(g/dL)
PLT	18.7	16.1	20.4			22.4	(x10*4/μL)

The results of biochemistry exam for 6 years were summarized in (Table 1). They showed almost negative findings in the liver and complete blood count (CBC), and some subnormal data in the renal and lipids associated with several oral medicines for years.

His chest X-ray and electrocardiogram (ECG) revealed negative results. As he has received several times of pulse wave velocity (PWV, sphygmograph) exams until now (Figure 2). Among them, changes in the cardio-ankle vascular index (CAVI) were summarized in Figure 3. It showed rather stable CAVI for years, but the value was lower in 2019 and 2020 for two years. Concerning ankle brachial index (ABI), obtained data showed almost stable during 0.80 – 0.90 bilaterally for these period.

Ethical standards

This report was complied with ethical guideline for the previous Declaration of Helsinki [12]. Moreover, certain commentaries were found as the protection regulation for information. The principle has been along with the ethic regulation for the clinical practice and research for the human. Some guidelines are found as the official announcement of Japanese Ministry. The information has been from Ministry of Health, Labor and Welfare (MHLW) and Ministry of Education, Culture, Sports, Science Technology (MEXT) of Japan. The authors and co-researchers have set up the ethic committee for this case, which is present in

Sakamoto Hospital, Kagawa, Japan. It has medical staffs and legal people, where hospital director, doctors, nurse, pharmacist, dietician, and legal professional person. The members have discussed the protocol in satisfactory manner, and have agreed for the research. We have taken the informed consent by the document of the patient.

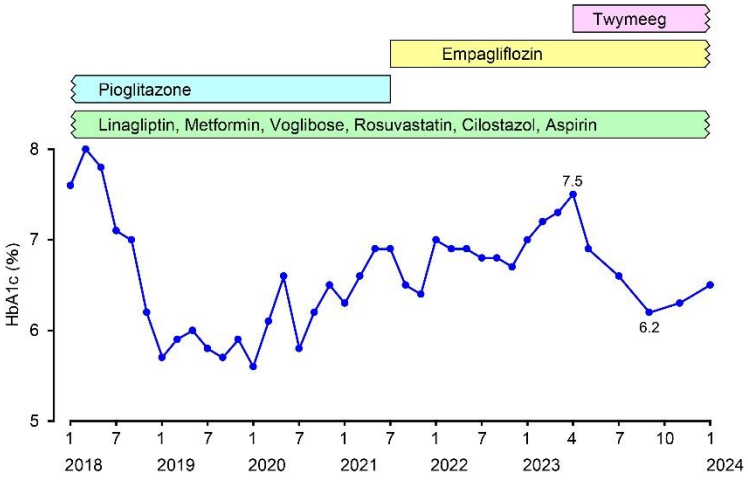

Figure 1: *Clinical progress of the case.*

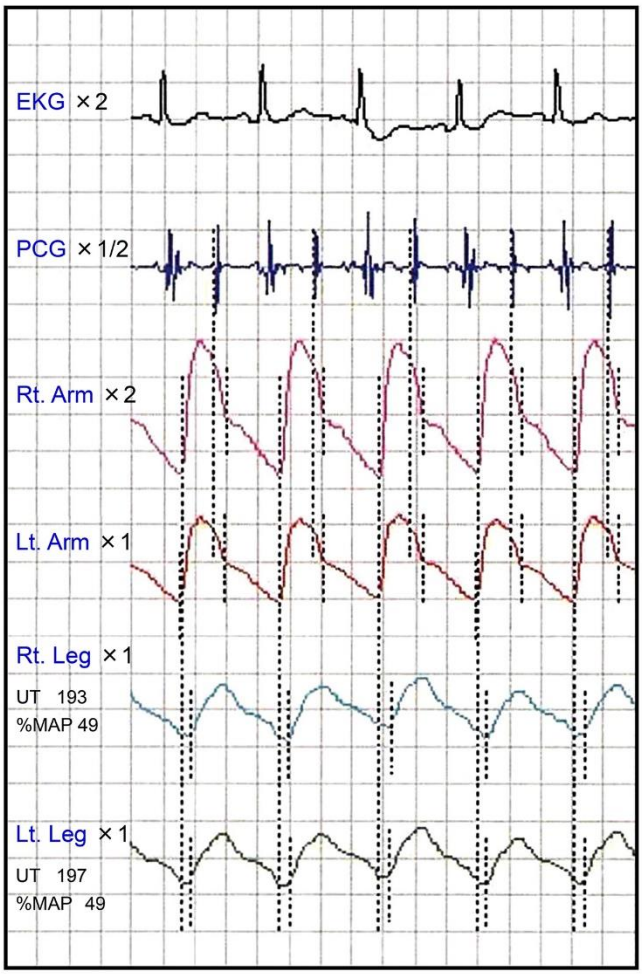

Figure 2: *Pulse wave velocity (PWV) exam.*

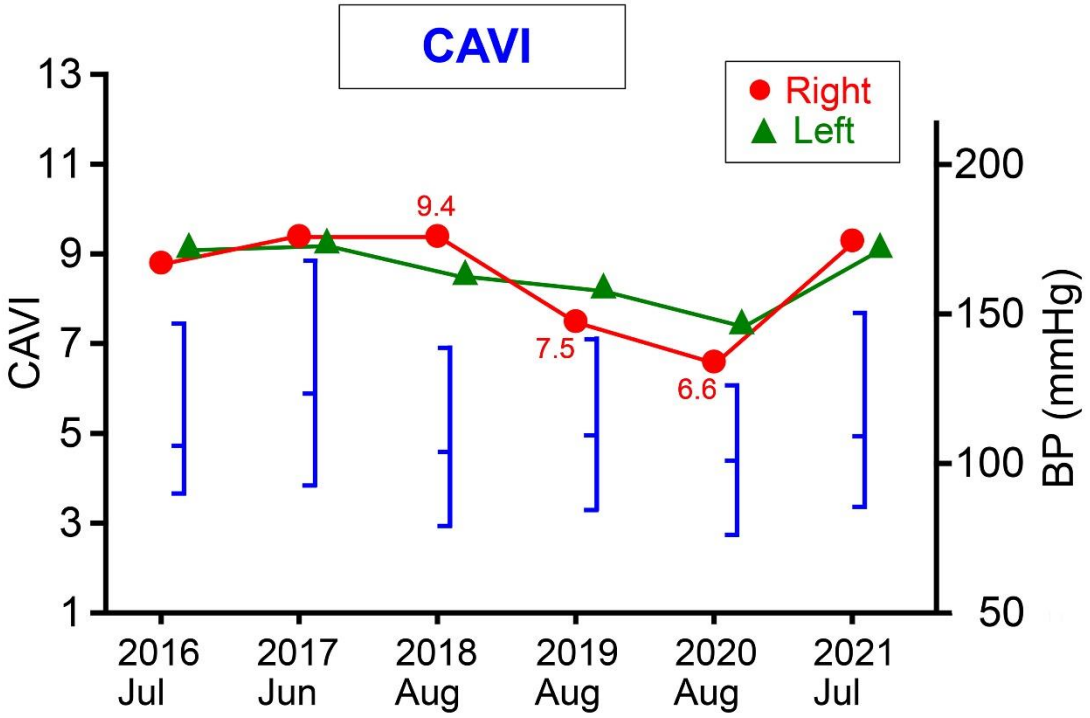

Figure 3: *Changes in cardio-ankle vascular index (CAVI).*

Discussion

Current case has been 68-year-old patient with T2D, hypertension, dyslipidemia and other diseases. He has been provided for OHAs and anti-hypertensive agents (AHAs) for years, including linagliptin, metformin, voglibose, rosuvastatin, cilostazol and aspirin. Furthermore, he has taken imeglimin (Twymeeg) which showed clinical efficacy for decreasing HbA1c. He showed the existence of diabetic macroangiopathy for CVD and PAD, as well as microangiopathy of nephropathy. He has rather long history of diabetes, and then such patient tends to have macro-and micro-angiopathy [13].

Due to the developed arteriosclerosis, pulse wave velocity (PWV, sphygmograph) showed the developed degree of arteriosclerosis [14]. When observing CAVI values of right leg, the results during 2016 to 2018 showed 8.4-9.4 [15]. After that, it showed decreased values of 7.5 and 6.6 during 2019-2020. Interestingly, HbA1c levels showed satisfactory glucose control of 5.7%- 6.6% during 2019-2020. This parallel phenomenon results may suggest the evidence of clinical importance of strict control of glucose variability, and the possibility of improving arteriosclerosis by lowering average blood glucose and mean amplitude of glucose excursions (MAGE) [16].

Consequently, current case has peripheral artery disease (PAD), in which he has been already provided anti-coagulant agents for years [17]. In the light of presence of T2D and moderate arteriosclerosis, the case will be required to be followed with close attention for several regular examination. Regarding the study of CV risk, 885 diabetic patients were studied for HbA1c, lipid profile, BP, eGFR and medication [2]. Average data were HbA1c 7.1%, BP 134/80 mmHg, BMI 32.3, hypertension 83%, obesity 64.6%, intake of metformin 87%, statin agents 67%. Average LDL values showed in the three categories of very high, high, moderate risk as 107mg/dL, 113 mg/dL, and 124 mg/dL, respectively. These factors are involved in various glucose-lowering treatment and CV risk-modifying therapies, and then LDL value is not necessarily related with risk degree of arteriosclerosis.

As to his clinical progress, HbA1c has been rather unstable until 2022. By the additional prescription of imeglimin (Twymeeg), HbA1c was rapidly decreased 1.3% for 5 months [18]. This remarkable clinical effect may be from pharmacological mechanism for decreasing insulin resistance and increasing insulin secretion [19]. As imeglimin has shown beneficial effect, it will hopefully contribute useful diabetic therapy from now [20]. This case did not feel any gastrointestinal adverse events (GI-AEs), such as nausea, constipation, diarrhea, abdominal discomfort or pain [19]. For imeglimin studies, large research of Trials of IMeglimin for Efficacy and Safety (TIMES) 1,2 and 3 were internationally conducted [21]. Clinical effects were reported in the following: only imeglimin administration 0.46%, DPP4-i 0.92%, SGLT2-i 0.57%, sulfonyl urea (SU) 0.56%, and biguanide 0.67% [22]. Current case had combined OHAs of

DPP4-i, SGLT2-I, metformin and imeglimin. Thus, safe and satisfactory effect were observed.

There may be some limitation in this article. This case presented clinical efficacy for imeglimin, but current case showed clinical effect by imeglimin, but other factors may be involved in the pharmacological response. Diabetes is always influenced by various factors, and then his clinical progress is required to be followed in the future [23,24].

In summary, 68-year-old T2D case was presented in this report. In addition, some perspectives are introduced for arteriosclerosis and novel imeglimin. We hope that it will become a beneficial reference for diabetic practice.

Conflict of Interest

The authors declare no conflict of interest.

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References

1. Rickenbach A, Acheampong MK, Bogar A, Booth G. Perspectives of the World Health Organization's physical activity guidelines among patients with musculoskeletal conditions: A mixed-methods survey. Musculoskeletal Care. 2024; 22: e1868.
2. Reurean-Pintilei D, Potcovaru CG, Salmen T, Mititelu-Tartau L, Cinteză D, Lazăr S, et al. Assessment of Cardiovascular Risk Categories and Achievement of Therapeutic Targets in European Patients with Type 2 Diabetes. J Clin Med. 2024; 13: 2196.
3. American Diabetes Association Professional Practice Committee; 1. Improving Care and Promoting Health in Populations: Standards of Care in Diabetes - 2024. Diabetes Care. 2024; 47: S11-S19.
4. Permana H, Soetedjo NNM, Yanto TA, Tendean M, Hariyanto TI, Suastika K. Different doses of imeglimin for management of type 2 diabetes mellitus: a systematic review, meta-analysis, and meta-regression of randomized clinical trials. Expert Review Endocrinol Metabolism. 2023.
5. Kobayashi T, Bando H, Okada M, Iwatsuki N, Ogawa T, Sakamoto K. Effective Imeglimin (Twymeeg) Treatment for Diabetic Patient with Various Medical Problems. SunText Rev Endocrine Care. 2024; 3: 116.
6. Feinman RD. The biochemistry of low-carbohydrate and ketogenic diets. Curr Opin Endocrinol Diabetes Obes. 2020; 27: 261-268.
7. Atkins and Robert. Dr. Atkins' New Carbohydrate Gram Counter. M. Evans and Company. 1996.
8. Bernstein RK. Dr. Bernstein's Diabetes Solution. Little, Brown and company, New York. 1997.
9. Ebe K, Wood M and Bando H. Preventing Post-Prandial Elevation of Blood Glucose by Breakfast with Less Carbohydrate. Int J Case Rep Clin Image. 2024; 6: 219.
10. Muneta T, Hayashi M, Nagai Y, Matsumoto M, Bando H, et al. Ketone Bodies in the Fetus and Newborn During Gestational Diabetes and Normal Delivery. Int J Diabetes. 2023; 5: 157-163.
11. Wood M, Ebe K, Bando H. Role of Low-Carbohydrate Diets in Diabetes Management. SunText Rev Endocrine Care. 2024; 3: 118.
12. Bando H, Ebe K. Beneficial and Convenient Method of Low Carbohydrate Diet (LCD) as Petite, Standard and Super LCD. Asp Biomed Clin Case Rep. 2023; 7: 1-4.
13. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent. 2014; 81: 14-18.
14. Yi T, Gao L, Fan F, Jiang Y, Jia J, Zhang Y, Li J, Huo Y. Association between pulse wave velocity and the 10-year risk of atherosclerotic cardiovascular disease in the Chinese population: A community-based study. J Clin Hypertens (Greenwich). 2023; 25: 278-285.
15. Park JB, Avolio A. Arteriosclerosis and Atherosclerosis Assessment in Clinical Practice: Methods and Significance. Pulse (Basel). 2023; 11: 1-8.
16. Wuttichaipradit C, Yodwut C, Sukhum P, Hengrussamee K, Treesong M, Thiangtham S, et al. CAVI (Cardio-Ankle Vascular Index) as an independent predictor of hypertensive response to exercise. BMC Cardiovasc Disord. 2024; 24: 165.
17. Fernandes NJ, Nguyen N, Chun E, Punjabi NM, Gaynanova I. Open-Source Algorithm to Calculate Mean Amplitude of Glycemic Excursions Using Short and Long Moving Averages. J Diabetes Sci Technol. 2022; 16: 576-577.
18. Association for Research into Arterial Structure and Physiology (ARTERY), the European Society of Hypertension Working Group on Large Arteries, European Cooperation in Science and Technology (COST) Action VascAgeNet, North American Artery Society, ARTERY LATAM, Pulse of Asia, and Society for Arterial Stiffness—Germany-Austria-Switzerland (DeGAG). 2024 Recommendations for Validation of Noninvasive Arterial Pulse Wave Velocity Measurement Devices. Hypertension. 2024; 81: 183-192.
19. Reilhac C, Dubourg J, Thang C, Grouin JM, Fouqueray P, Watada H. Efficacy and safety of imeglimin add-on to insulin monotherapy in Japanese patients with type 2 diabetes (TIMES 3): A randomized, double-blind, placebo-controlled phase 3 trial with a 36-week open-label extension period. Diabetes Obes Metab. 2022; 24: 838-848.
20. Vinayagam P, Senathipathi V, Shivam V, Velraju N. The role of Imeglimin in glycemic control, beta cell function and safety outcomes in patients with type 2 diabetes mellitus: A comprehensive meta-analysis. Diab Epdemiol Manag. 2023; 12: 100164.
21. American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2024. Diabetes Care. 2024; 47: S158-S178.
22. Dubourg J, Fouqueray P, Thang C, Grouin JM, Ueki K. Efficacy and Safety of Imeglimin Monotherapy Versus Placebo in Japanese Patients With Type 2 Diabetes (TIMES 1): A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Phase 3 Trial. Diabetes Care. 2021; 44: 952-959.
23. Dubourg J, Fouqueray P, Quinslot D, Grouin JM, Kaku K. Long-term safety and efficacy of imeglimin as monotherapy or in combination with existing antidiabetic agents in Japanese patients

with type 2 diabetes (TIMES 2): A 52-week, open-label, multicentre phase 3 trial. Diabetes Obes Metab. 2021.

24. Bailey CJ. Chapter 79. Future Drug Treatments for Type 2 Diabetes. (Eds) Richard IG, Holt MA, Flyvbuerg A. Textbook of Diabetes, 6th Ed, 2024. 2024.