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Diabetic Elderly with Keeping Less Arteriosclerosis Treated by Imeglimin (Twymeeg)

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Abstract

The patient is a 73-year-old male with type 2 diabetes (T2D) and hypertension, treated for years with various oral hypoglycemic agents (OHAs) and an anti-hypertensive agent (AHA). His HbA1c levels were unstable during 2020-2022, during which time he was prescribed linagliptin, voglibose, and metformin. In 2023, his HbA1c increased to 8.4%, and imeglimin (Twymeeg) was initiated. This resulted in an acute reduction of HbA1c to 6.5% over 5 months. A pulse wave velocity (PWV) examination, using a sphygmograph, showed stable values for the cardio-ankle vascular index (CAVI) and ankle-brachial index (ABI) over 4 years. Consequently, this patient has maintained a low level of arteriosclerosis, associated with the effective treatment using imeglimin.

Keywords

Imeglimin, Twymeeg, Pulse Wave Velocity, Ankle Brachial Index, Cardio-Ankle Vascular Index, Japan LCD Promotion Association

Abbreviations

PWV: Pulse Wave Velocityl ABI: Ankle Brachial Index; CAVI: Cardio-Ankle Vascular Index; JLCDPA: Japan LCD Promotion Association

Introduction

The prevalence of overweight, obesity, and metabolic syndrome has been increasing worldwide [1,2]. Among these conditions, type 2 diabetes (T2D) has become a significant clinical challenge for diagnosis and treatment, closely related to people's lifestyle choices [3]. In January 2024, the American Diabetes Association (ADA) presented updated guidelines for the treatment of T2D [1]. Recently, several novel oral hypoglycemic agents (OHAs) have been introduced into clinical practice, including imeglimin (Twymeeg), which is known for its specific pharmacological mechanism via the mitochondrial pathway [4].

The fundamental principles for managing T2D include an adequate diet, exercise, and medication. In terms of nutritional therapy, calorie restriction (CR) was previously the standard method. However, the low carbohydrate diet (LCD) has recently been recognized

as an effective treatment for T2D [5]. LCD was initially popularized in healthcare and medical fields by Dr. Bernstein and Dr. Atkins in Western countries [6,7]. Subsequently, LCD was introduced in Asian countries by our diabetic project, the Japan LCD Promotion Association (JLCDPA) [8]. Our JLCDPA team has been developing LCD approaches both medically and socially, introducing useful and convenient measures such as super-LCD, standard-LCD, and petite-LCD, which include carbohydrate amounts of 12%, 26%, and 40%, respectively [9,10].

During our treatment of various diabetic patients, we encountered a noteworthy case involving an elderly male. This patient demonstrated remarkable efficacy with the novel OHA imeglimin (Twymeeg), maintaining reduced arteriosclerosis for years. His clinical progress and medical perspectives will be discussed in this article.

Presentation of Case

Medical History:

The patient is a 73-year-old male with type 2 diabetes (T2D). He was diagnosed with T2D in his early 50s and has since been treated with various oral hypoglycemic agents (OHAs). These included amlodipine, telmisartan, voglibose, linagliptin, and aspirin over the years. His condition has remained stable with OHAs and an anti-hypertensive agent (AHA). In the summer of 2022, his HbA1c increased to 7.6%, prompting the addition of metformin to his diabetic treatment regimen. This intervention temporarily reduced his HbA1c, but it later increased again to 8.4%. Consequently, in the summer of 2023, imeglimin (Twymeeg) was introduced, leading to an acute reduction in HbA1c to 6.5% over the next 5 months, demonstrating a remarkable clinical effect (**Fig-1**).

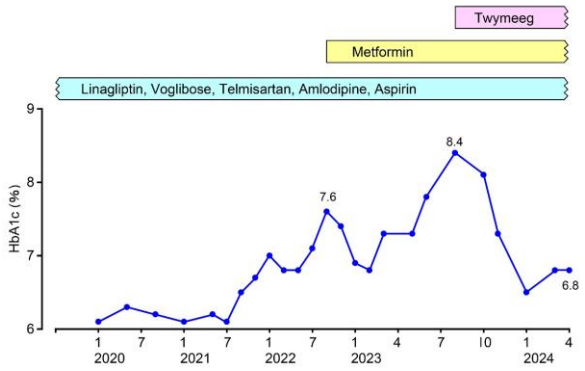

Fig-1: Clinical Progress of the Case

Physical and Laboratory Examinations:

His physical examination in March 2024 showed normal speech, consciousness, and vital signs, including pulse, blood pressure (BP), body temperature (BT), and oxygen saturation (SpO2). No significant changes were noted in his heart, lungs, abdomen, or neurological findings. He did not exhibit any symptoms or signs. His physique measurements were 156.5 cm in height and 75.0 kg in weight, resulting in a body mass index (BMI) of 30.6 kg/m^2.

His previous biochemical results, summarized in **Table-1**, showed unremarkable findings in liver function tests, lipid profiles, renal function tests, and complete blood count (CBC). A chest X-ray showed no significant changes. An electrocardiogram (ECG) revealed a normal sinus rhythm (NSR), with a pulse of 72 beats per minute, and an incomplete right bundle branch block (RBBB). He has undergone pulse wave velocity (PWV) examinations using a sphygmograph, with the results of four consecutive tests included in **Fig-2**. The cardio-ankle vascular index (CAVI) results were slightly elevated but have remained stable, indicating no significant progression of arteriosclerosis over the past four years. The ankle-brachial index (ABI) results have also been stable over this period.

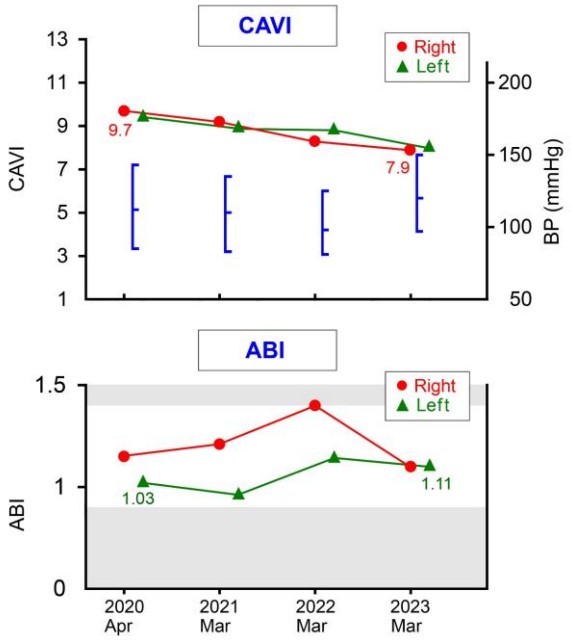

Fig-2: PWV (Plethysmography) Exam

Table-1: Changes in Laboratory Data

		2020	2021	2022		2023		
		Aug	Jul	Jan	Aug	Feb	Aug	Units
Liver	AST	23	32	25	28	26	29	(U/L)
	ALT	23	40	32	36	23	30	(U/L)
	GGT	47	60	40	54	36	80	(U/L)
Lipids	HDL	40	47	41	36	41	40	(mg/dL)
	LDL	80	99	99	66	87	75	(mg/dL)
	TG	164	124	160	195	222	148	(mg/dL)
Renal	BUN	12	15	13	13	15	13	(mg/dL)
	Cre	0.81	0.87	0.91	0.84	0.86	0.87	(mg/dL)
	UA	3.3	3.6	3.2	3.1	3.2	3.0	(mg/dL)
CBC	WBC	59	55	55	48	62	46	(x10*2/μL)
	RBC	477	494	500	482	499	480	(x10*4/μL)
	Hb	14.5	15.0	14.9	14.3	15.3	14.5	(g/dL)
	PLT	11.8	12.4	11.4	10.4	12.4	10.5	(x10*4/μL)

Ethical Standards

This case report complies with the ethical guidelines of the Declaration of Helsinki [11]. Additionally, it adheres to regulations for the protection of personal information and follows ethical standards for clinical research and practice involving human subjects as outlined by the Japanese Ministry of Health, Labor and Welfare, and the Ministry of Education, Culture, Sports, Science, and Technology. An ethical committee was established at Sakamoto Hospital in Kagawa, Japan, including medical and legal professionals such as the hospital president, physicians, head nurse, pharmacist, registered nutritionist, and a legal professional. The committee reviewed and approved the research protocol and obtained informed consent from the patient through a documented process.

Discussion

This case involves a 73-year-old male with type 2 diabetes (T2D), obesity, and hypertension, indicating metabolic syndrome. Given the probable existence of arteriosclerosis, pulse wave velocity (PWV) examinations using a sphygmograph were conducted. The results showed a low degree of arteriosclerosis, with stable cardio-ankle vascular index (CAVI) and ankle-brachial index (ABI) values over several years. Consequently, the progression of peripheral artery disease (PAD) appears unlikely [12]. This stability may be attributed to relatively controlled glucose variability over the years. The patient did not exhibit signs of macro-angiopathy or micro-angiopathy, such as cerebral vascular accident (CVA), ischemic heart disease (IHD), PAD, neuropathy, retinopathy, or nephropathy.

Regarding his clinical course, the patient maintained a relatively stable lifestyle. His medication regimen included various OHAs and anti-hypertensive agents (AHAs). The addition of imeglimin (Twymeeg) led to a satisfactory decrease in HbA1c over approximately 10 months [13]. This positive outcome is likely due to imeglimin's pharmacological mechanism, which increases insulin secretion and decreases insulin resistance [14]. Given imeglimin's beneficial effects, it is expected to make a significant contribution to diabetes treatment [15].

Following the initiation of Twymeeg, no gastrointestinal adverse events (GI-AEs) such as diarrhea, nausea, abdominal pain, vomiting, or constipation were observed [14]. The clinical efficacy of imeglimin has been supported by large international studies, including the Trials of IMeglimin for Efficacy and Safety (TIMES) 1, 2, and 3 [16]. These studies investigated imeglimin both as monotherapy and in combination with other treatments, revealing HbA1c reductions of 0.46% for imeglimin monotherapy, 0.57% for SGLT2 inhibitors, 0.92% for DPP4 inhibitors, 0.67% for biguanides, and 0.56% for sulfonylureas (SU), with treatment durations of 6-12

months [17]. In this case, the patient experienced a significant reduction in HbA1c from 8.4% to 6.5% within just 5 months. This rapid improvement may be attributed to his continued adherence to a low carbohydrate diet (LCD) and changes in appetite. After starting imeglimin, the patient reported feeling more satisfied with smaller meals [18].

The authors and co-researchers have previously published various reports on diabetes [19]. Among these, several T2D patients showed clinical efficacy with imeglimin (Twymeeg), with HbA1c reductions greater than expected. Factors contributing to these outcomes may include dietary carbohydrate intake, appetite changes, regular lifestyle habits, exercise, and consistent medication compliance [20,21].

There are some limitations to this report. While the clinical effect of imeglimin is evident, other factors may have influenced the patient's progress. Diabetes involves a variety of interrelated factors, requiring a comprehensive approach to patient management. Consequently, this case will continue to be followed with careful attention to these variables.

In conclusion, this report describes a 73-year-old male with T2D who demonstrated significant clinical improvement with the combined use of OHAs, particularly imeglimin, and discusses related perspectives on arteriosclerosis. This case may serve as a useful reference for future diabetes research.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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