Asploro Journal of Biomedical and Clinical Case Reports
(ISSN: 2582-0370)
Case Report
DOI: https://doi.org/10.36502/2023/ASJBCCR.6288

Detail Measurement of Pre-Prandial and Post-Prandial Blood Glucose during Imeglimin (Twymeeg) Treatment

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Received date: 06 February 2023; **Accepted date**: 24 February 2023; **Published date**: 02 March 2023

Citation: Hayashi K, Bando H, Miki K, Hamai M, Yasuoka T. Detail Measurement of Pre-Prandial and Post-Prandial Blood Glucose during Imeglimin (Twymeeg) Treatment. Asp Biomed Clin Case Rep. 2023 Mar 02;6(1):40-46.

Abstract

Background: Among oral hypoglycemic agents (OHAs), imeglimin (Twymeeg) would be in focus. **Case Presentation**: The patient in this case is a 58-year-old female with a history of obesity and previous operations for posterior longitudinal ligament ossification. In early September 2022, she developed dizziness and a general feeling of unwellness, leading to a diagnosis of Type 2 Diabetes (T2D) with an HbA1c level of 11.1%.

Result: The patient was treated with a low carbohydrate diet (LCD) and Twymeeg, resulting in a significant decrease in HbA1c levels from 11.1% to 9.0%, 6.7%, and 5.9% over the course of three months. Pre-prandial and post-prandial blood glucose levels were measured with great accuracy.

Discussion and Conclusion: The administration of Twymeeg was found to be effective in reducing the patient's HbA1c levels, and the relationship between HbA1c and glucose variability could be further investigated based on these results.

Keywords

Imeglimin (Twymeeg), Nathan's Equation, Low Carbohydrate Diet, Trials of Imeglimin for Efficacy and Safety, Oral Hypoglycemic Agent, Twymeeg

Abbreviations

LCD: Low Carbohydrate Diet; TIMES: Trials of Imeglimin for Efficacy and Safety; OHA: Oral Hypoglycemic Agent

Introduction

Type 2 diabetes (T2D) is one of the most critical diseases affecting both developed and developing countries. HbA1c, pre-prandial glucose, and post-prandial glucose are important factors for screening T2D [1]. Additionally, the diagnosis, treatment, and monitoring of clinical progress in T2D cases are essential for making appropriate judgments [2]. Therefore, diabetes care should be provided adequately in various situations worldwide [3]. The latest "Standards of Care in Diabetes" were proposed by the American Diabetes Association (ADA) in January 2023

[4]. Along with the standard method, adequate management should be provided for T2D patients [5].

Recently, effective oral hypoglycemic agents (OHAs) have been introduced to diabetic practice [6]. They developed better glucose variability associated with improved safety situation such as dipeptidyl peptidase-4 inhibitor (DPP-4i) and sodium–glucose cotransporter 2 inhibitor (SGLT2i). Among them, latest focus would be imeglimin (Twymeeg) as the novel OHA [7,8]. It has the similar molecule for metformin, which has been the first-line agent for T2D [9]. Imeglimin has been known for its clinical efficacy for monotherapy and also add-on therapy. Some large investigation was reported, that are **T**rials of **IM**eglimin for **E**fficacy and **S**afety (TIMES) [10]. They include TIMES 1, 2 and 3 [11]. From pharmaco-physiological point of view, imeglimin has dual effects for reducing insulin resistance and also increasing insulin secretion ability through various mechanism of mitochondria in the cell.

Authors and colleagues have developed diabetic team and continued diabetic practice and research so far [12]. Their area includes low carbohydrate diet (LCD), Carbo-70g loading test, continuous glucose monitoring (CGM) associated with several OHA reports [13]. We experienced an impressive T2D case who could check pre-prandial and post-prandial blood glucose perfectly for months. Consequently, the general progress and some perspectives are described concerning HbA1c and glucose variability in this article.

Presentation of Cases

Medical History:

The patient is a 58-year-old female who has been working as a hospital nurse for many years. She had undergone three operations for posterior longitudinal ligament ossification about 10 years ago and occasionally took analgesic medication to manage the pain, including pregabalin, mecobalamin, rebamipide, esomeprazole magnesium hydrate, and azilsartan/amlodipine combined drug. Her medical history includes hypertension and posterior longitudinal ligament ossification. In early September 2022, she began experiencing slight nausea, dizziness, and a general feeling of unwellness. On September 12, she developed dyspnea, cold sweating, dizziness, and cold sensations in her hands and fingers. A laboratory blood test was conducted, which revealed a severe diabetic condition, with HbA1c at 11.1% and post-prandial blood glucose at 395 mg/dL. She was diagnosed with type 2 diabetes (T2D).

Physicals and Various Exams:

On September 12, 2022, the patient's physical examination showed that she was alert and able to communicate clearly. Her vital signs were as follows: blood pressure was 150/96 mmHg, pulse rate was 84 beats per minute, oxygen saturation was 99%, and her respiration and body temperature were normal. There were no remarkable findings in her lung, heart, abdomen, and neurological examination. Additionally, her neurological tests were negative. Her current status showed no abnormalities in her lung, chest, and abdomen, and her neurological findings were intact. In terms of her body weight, she weighed 81kg ten years ago, and 79 kg in Sept 2022, with a gradual reduction of about 2kg. Her physique was measured as 153 cm in height and 79kg in weight, with a BMI of 33.7 kg/m^2.

The data of the laboratory examination were in the following: HbA1c 11.1 %, post-prandial blood glucose 398 mg/dL, RBC 4.80 x 10^6 /μL, Hb 14.0 g/dL, Ht 41.0 %, MCV 85.5 fL (80-98), MCH 29.1 pg (27-33), MCHC 34.1 g/dL (31-36), WBC 9200/μL, Plt 19.3 x 10^4 /μL, GOT 35 U/L, GPT 48 U/L, GGT 58 U/L, BUN 27.5 mg/dL, Cre 0.69 mg/dL, HDL 67 mg/dL, LDL 98 mg/dL, TG 119 mg/dL, T-Cho 181 mg/dL, CRP 0.4 mg/dL (0-0.3). Chest X-P showed no remarkable changes. Electrocardiogram (ECG) revealed pulse 76/min, ordinary sinus rhythm, normal axis deviation, and unremarkable ST-T changes.

Clinical Progress:

She was pointed out to have heavy level T2D on Sept 12, 2022 and then she was explained to start low carbohydrate diet (LCD) immediately and continue three months and to take Metformin 500 mg/day. Furthermore, she began to check pre-prandial and post-prandial blood glucose every day (**Table-1**). Observing the changes in blood glucose for a few days, imeglimin (Twymeeg) 2000mg/day was added to the

treatment. The combination of LCD, Metformin and Twymeeg was continued. Changes in HbA1c value showed 9.0% in 5 weeks, 6.7 % in 10 weeks and 5.9% in 15 weeks. As regards to the body weight, her weight was decreased from 79kg to 77kg for 4 months (**Fig-1**). She did not suffer from any symptoms of gastro-intestinal adverse effects (GIAEs) of Twymeeg.

Ethical Standards

The present report adheres to the ethical guidelines outlined in the Declaration of Helsinki and includes several commentaries on the protection of personal information. The principles of ethical clinical practice and research involving human subjects were followed, as outlined by guidelines proposed by the Japanese

Table 1: Clinical progress of blood glucose, HbA1c and treatment

Time		Blood Glucose							HbA1c	Treatment	
Mon	Dat	breakfast		lunch		supper		vds	(%)	Diet	Medication
		0	60	0	60	0	60	0			
Sep	12			395		270		235	11.1		
	13	222		280		244		228			
	14	298		245		191		165			
	15	201		242		172		184			
	16	184		242	272		155	193			
	17	186	240								
	18			166	190			Blood Glucose 200< 150-199 <149			
	19					176	168				
	20			191	161						
	21	183	188								
	22			152	206						
	23					127	161				
	24			145	148						
	25	166	167								
	26	189		135	175						
	27					117	144				
	28			133	113						
	29	159	182								
	30		154	121	143						
Oct	1					118	157				
	2			134	148						
	3	155	165								
	4				113						
	5	132		123	135						
	6					122	132				
	7			114	136						
	8	137	138								
	9			107	140						
	10					114	133				
	11			123	113						
	12	157	137								
	13			123	141						
	14					106	111		9.0		
	16			112	115						
	18	130	117								
	20			115	118						
	23					133	120				
	26			101	117						
	28	131	125								

Low Carbohydrate Diet

Metformin 500mg

Twymeeg 2000mg

Case Report

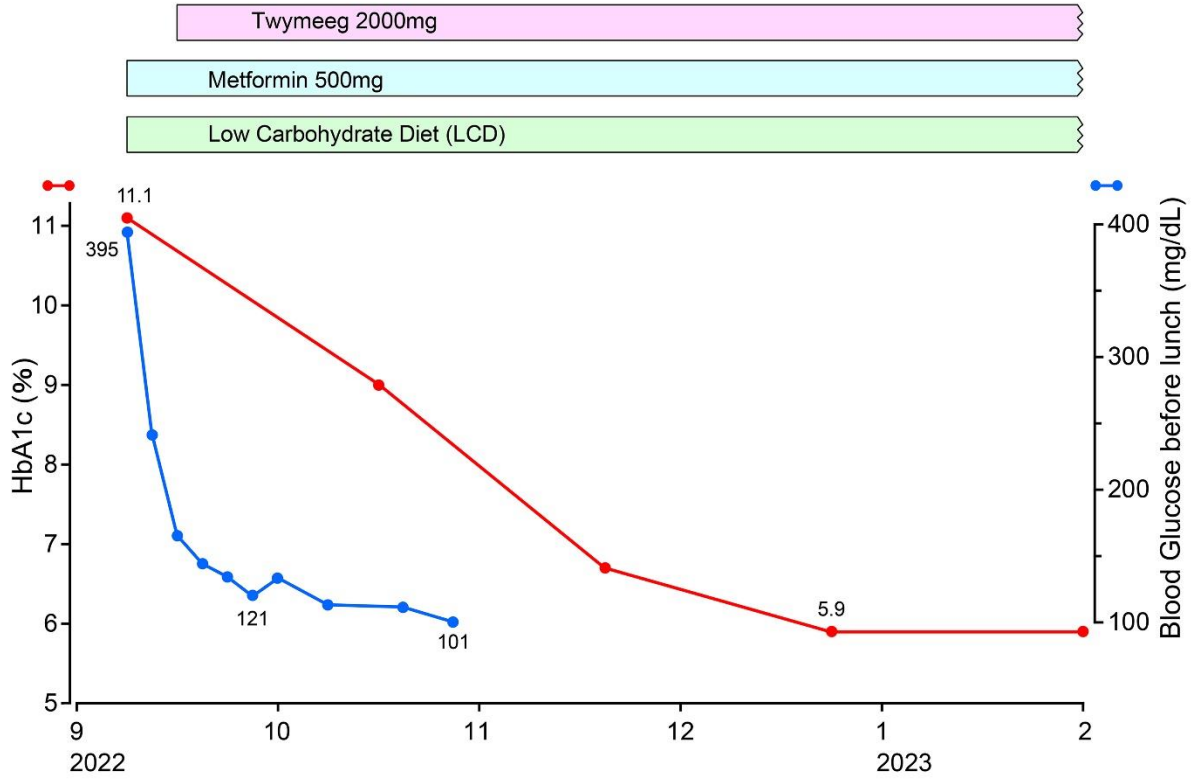

Fig-1: Clinical progress of HbA1c, blood glucose and treatment

Ministry of Health, Labor and Welfare, and the Ministry of Education, Culture, Sports, Science Technology. The authors established an ethical committee at Hayashi Hospital in Tokushima, Japan, consisting of medical staff, legal professionals, and other relevant personnel, including the director of the hospital, physicians, head nurse, pharmacist, and dietitian. The committee thoroughly discussed the protocol and determined it to be satisfactory for the current research.

Discussion

Concerning this case, three characteristic points are present in the following. They are i) Twimeeg was effective for improving glucose variability, ii) the case continued to check pre-prandial and post-prandial blood glucose vigorously, and iii) the relationship between blood sugar and HbA1c values becomes impressive matters, which are discussed in this order.

First, a 59-year-old female with underlying obesity developed T2D in September 2022. The diabetic condition was rapidly improved by LCD and administration of Twimeeg. About 10 years ago, she had multiple operations of ossification of the posterior longitudinal ligaments [14]. This past history may be related with the persistence of obesity [15,16]. Her body weight was slightly reduced due to the prescription of Twimeeg and LCD. Currently, her diabetic condition is stable, and it is expected that she will maintain her weight by continuing LCD in the future.

Second, she had been working as a hospital nurse for many years and had a thorough understanding and treatment of diabetes. Her LCD method was successfully continued at super-LCD [17]. There are three levels of LCD, which are super-, standard- and petite-, in which carbohydrate content is 12%, 26%, and 40%, respectively [18]. Furthermore, blood glucose was measured for pre-prandial and post-prandial timing in each meal. She could continue for long period. According to her complete glucose measurement, important detail data for glucose variability were obtained. Consequently, this situation contributes the following third perspective.

Third, her blood glucose has been normalized in early period. At 5 weeks, HbA1c was 9.0%, but pre-prandial and post-prandial glucose was already

normalized. During 5-15 weeks, HbA1c decreased to 9.0, 6.7 and 5.9%, while her glucose control was perfect. The same level of HbA1c 5.9% persisted for 15-20 weeks. Judging from these data, linearly decreasing HbA1c value may suggest the detail relationship of HbA1c and glucose variability [19]. Such perspectives are described in the following.

The relationship between HbA1c and blood glucose has been known as Nathan's equation [20]. That is [eAG (mg/dl) = (28.7 x HbA1c) -46.7, r^2=0.84]. Various studies have been continued for correlation of HbA1c, estimated average glucose (eAG) and fasting plasma glucose (FPG). Cases (n=1285) were analyzed for 3 groups of normal, high HbA1c and HbE, which were divided into subgroups (HbA1c ≤ 7%, or HbA1c >7%). As a result, strong correlation was found in these studies [21]. Basic understanding has been known that HbA1c indicates average blood glucose value over last 120 days [19]. For more correct data, detail glucose measurements for both of lower overnight period and postprandial peaks would be required. Some investigations showed that large ratio of HbA1c variation may be due to CGM glucose averages.

From the recent report, relationship of HbA1c and glycated albumin (GA) has been found [22]. Data set (n=2461) were analyzed from 731 cases, and lots of cases were excluded such as low Hb, Alb or eGFR and patients with hemodialysis, malignancy, pregnancy, chronic liver disease, hyperthyroidism and steroid treatment. Consequently, 284 data set were analyzed. As a result, equation became that HbA1c = 0.216 × GA + 2.978 (R^2 = 0.5882, P < 0.001).

Individual variations are present in glucose uptake and RBC turnover, and a kinetic model was reported to show the different relationship of HbA1c and glucose level [23]. As RBC turnover rate is 0.94 % per day, the standard RBC lifespan would be 106 days. For applying these data, laboratory HbA1c can be adjusted for standard RBC lifespan. It will bring more accurate biomarker of hyperglycemia associated with HbA1c [24]. For type 1 diabetes (T1D) and T2D, RBC lifespan was investigated [25]. Laboratory HbA1c and CGM data were evaluated for 6 months. The cases were 51 T1D and 80 T2D patients. As a result, mean (median) RBC lifespan was 94 (100) days in T1D, and 92 (100) days in T2D. For the detail data, mean (median) of absolute difference of adjusted HbA1c (a-HbA1c) and laboratory HbA1c (l-HbA1c) were 1.0 (0.4) % in T1D, and 1.4(0.5) % in T2D cases. Thus, T2D showed a little higher value. When RBC lifespan is less than 80 days, it showed 2% lower l-HbA1c than adjusted HbA1c. Such situation may bring miss-reading of accurate HbA1c value. On the other hand, when RBC lifespan is more than 130 days, it brings higher l-HbA1c than a-HbA1c [25].

Certain limitation may be present in this report. Current case is a nurse who could continue LCD and measurement of pre-prandial and post-prandial blood glucose perfectly. From this situation, detail relationship of HbA1c and blood glucose can be investigated. However, glucose variability is influenced by various factors, such as obesity, insulin secretion, insulin resistance, and so on. Then, further research and case accumulation would be required in the future.

In summary, this case report describes a 58-year-old female with T2D who carefully monitored her pre- and post-prandial glucose levels. Treatment with LCD and Twymeeg was successful in improving glucose variability, and the relationship between HbA1c and glucose variability was discussed. These findings provide valuable insights for future diabetic research.

Funding

There was no funding received for this paper.

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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