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Investigation of Insulin Secretion in Glucose Tolerance Test by the Intake of Novel Imeglimin (Twymeeg)

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Abstract

Background: Recent pharmacological studies reveal imeglimin (Twymeeg) including dual mechanisms for stimulating insulin secretion and reducing insulin resistance.

Case Presentation: The case is a 62-year-old male with type 2 diabetes (T2D). He showed HbA1c 6.4% and started imeglimin. After 5 weeks, a 75g oral glucose tolerance test (75gOGTT) was conducted, and the biomarkers were compared with that of 6 months ago. Insulinogenic index (IGI) 0-30min was stable, but insulin secretion was increased during 30-60min and 60-120min.

Discussion: Previous studies of imeglimin revealed improved insulin secretion for GTT. Clinical progress will be followed up with detailed investigation of glucose and insulin variability.

Keywords

Imeglimin, Twymeeg, Type 2 Diabetes, 75g Oral Glucose Tolerance Test, Insulinogenic Index, Japan LCD Promotion Association

Abbreviations

T2D: Type 2 Diabetes; 75gOGTT: 75g Oral Glucose Tolerance Test; IGI: Insulinogenic Index; JLCDPA: Japan LCD Promotion Association

Introduction

Recently, adequate nutritional therapy for diabetes has been in focus [1]. Several types of diet methods were introduced, such as calorie restriction (CR), low carbohydrate diet (LCD), Mediterranean diet, and so on. Among them, clinical significance of LCD has been accepted for health care and medical regions, and LCD is evaluated for reducing blood glucose and weight [2]. In European, North American, and East Asian countries, LCD has been widely associated with clinical

effectiveness [3]. Especially in Japan, authors and collaborators have developed the medical and social movement of LCD through the activity of Japan LCD promotion association (JLCDPA) for years [4]. We have proposed three patterns of practical LCD methods, which are super-, standard- and petite-LCD [5]. Our diabetic team has applied LCD for thousands of patients with obesity and diabetes, associated with remarkable clinical efficacy [6].

The American Diabetes Association (ADA) has announced the latest standard of diabetic care in January 2022 [7]. The ADA also proposed recent adequate pharmacological treatment [8]. Authors and collaborators have treated various diabetic patients with oral hypoglycemic agents (OHAs) and have reported so far [9]. They include GLP-1 receptor agonists (GLP-1Ras), novel imeglimin (Twymeeg), and others [10]. Imeglimin is a novel OHA that is characteristic for its tetrahydrotriazine-containing drug [11]. It was developed from the chemical moiety of metformin and it modulates the activity of mitochondrial function [12]. It has a dual mechanism for stimulating insulin secretion and reducing insulin resistance [13]. There were several clinical trials, in which clinical effects for improving glucose variability [14].

Authors et al. have reported some patients treated by imeglimin [15,16]. In our continuous diabetic practice, there was a diabetic male that has clinically meaningful case. He was provided imeglimin and showed impressive clinical progress. His general course and some perspective would be described in this report.

Case Presentation

Present History:

Current case is a 62-year-old male with type 2 diabetes (T2D). He was diagnosed with T2D approximately 6 years ago. Successively, he was advised to restrict the intake of carbohydrates. Then he continued a standard low carbohydrate diet (LCD) during his ordinary life, and his diabetic control was rather stable. His HbA1c values increased in autumn 2021, and then super-LCD and standard-LCD brought him an improved diabetic situation in winter 2021. For further evaluation of his insulin secretion ability, he received a 75g oral glucose tolerance test (75gOGTT) in Dec 2021. Furthermore, he had a glucagon stimulation test (GST) in Jan 2022 (**Fig-1**).

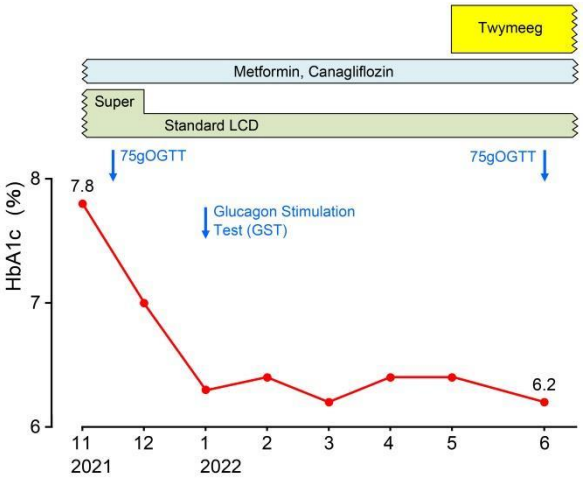

Fig-1: Clinical Progress of the current patient with T2D

Several Exams:

During autumn 2021 to spring 2022, his general condition became the improvement. Physical examination showed no remarkable changes including vital signs, consciousness, lung, heart and abdomen. His height, weight and BMI were 182cm, 87kg and 26.3 kg/m^2, respectively. Main data of biochemical exams revealed that GOT 22 IU/L, GPT 28 IU/L, GGT 25 IU/L, BUN 17 mg/dL, UA 3.9 mg/dL, Cre 0.8 mg/dL, TG 100 mg/dL, HDL-C 65 mg/dL, LDL-C 142 mg/dL. His chest X-P and ECG were negative. For the examination of pulse wave velocity (PWV), the bilateral values of ankle brachial index (ABI) were 1.19/1.19 indicating normal range.

Concerning diabetes, glucagon stimulation test (GST) was performed, where C-peptide was 2.0 ng/mL at basal level and it elevated to 4.7 ng/mL for 6 minutes after the injection of glucagon. The increased value was normal range. 75gOGTT was conducted in Dec 2021. The results showed that i) glucose and IRI (0, 30, 60min) was 115, 199, 299 mg/dL, and 5.5, 7.8, 17.1 μU/mL, respectively, ii) insulinoglycemic index (IGI) was 0.03, iii) HOMA-R and HOMA-βwas 1.6 and 38.1, respectively (**Table-1**).

Clinical Progress

He has continued standard LCD during Dec 2021-

June 2022, in which the carbohydrate content ratio is 26% in total calories. His HbA1c was stable during that period. In May 2022, he started to take imeglimin (Twymeeg) 2000mg/day (**Fig-1**). During 5 weeks taking Twymeeg, he did not feel any problems or gastrointestinal adverse effects (GIAEs). Then, his HbA1c decreased to 6.2%, and he received 75gOGTT again.

Results

The results of 75gOGTT showed that i) glucose and IRI (0, 30, 60, 120 min) was 123, 204, 280, 201 mg/dL, and 5.8, 7.9, 20.5, 32.5 μU/mL, respectively (**Fig-2A** and **Fig-2B**), ii) HOMA-R and HOMA-βwas 1.7 and 34.8, respectively that was stable with the previous result (**Table-1**), iii) IGI of 0-30 min was 0.03, which was the same as before, iv) insulin secretion was increased during 30-60min and 60-120min. Consequently, the difference between Dec 2021 and Jun 2022 showed that delayed increase of insulin was found.

Results of GTT of the current case as well as reference data of other authors are summarized (**Fig-2C, Fig-2D, Fig-2E**, and **Fig-2F**). As to clinical judgment of GTT, diabetic pattern is observed in **Fig-2A** and **Fig-2B**, and normal pattern is found in **Fig-2C** to **Fig-2F**, respectively. For **Fig-2C**, **Fig-2D**, and **Fig-2F**, general situation of insulin secretion and insulin resistance is normal. In the case of **Fig-2E**, fasting IRI was elevated and insulin response was delayed. Furthermore, several biomarkers for these cases were calculated and summarized (**Table-1**).

Ethical Considerations

The current study was performed along the Declaration of Helsinki, which was revised in 2013 for the WMA Fortaleza General Assembly. Further, some commentary was added according to the ethical guidelines for medical research. They are notified by

Table-1: Analyses of several biomarkers in 75gOGTT for some related cases

Case	Subjects	Age M/F	HOMA-R	HOMA-β	0-30 min (Delta)			30-60 min (Delta)			30-60 min (AUC)		60-120 min (Delta)		60-120 min (AUC)	
			(<2.5)	(>30)	⊿Glu	⊿IRI	IGI (0-30)	⊿Glu	⊿IRI	IGI (30-60)	Glu	IRI	⊿Glu	⊿IRI	Glu	IRI
1	Pt (2021.12) Author 3	61M	1.6	38.1	84	2.3	0.03	100	9.3	0.09	124.5	6.1	-85	0	257	17.1
2	Pt (2022. 6) Author 3	62M	1.8	34.8	81	2.1	0.03	76	12.6	0.17	121.0	7.1	-79	12	241	26.5
3	MD., PhD., Author 1	66M	0.6	48.6	24	42.2	1.76	-35	-15.0							
4	Pharm D., Author 2	56F	1.6	40.2	73	70.3	0.96	-36	-41.4							
5	Pharm D	44M	1.7	74.1	23	8.9	0.39	-18	14.1							
6	Pharm D	27F	0.8	63.8	15	35.7	2.38	-14	-7.5							

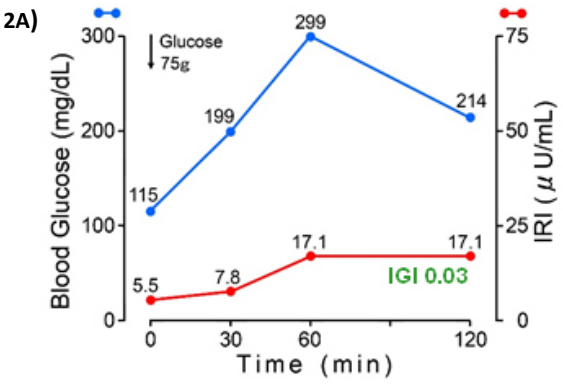

Fig-2A: T2DM: 61 M (2021 Dec)

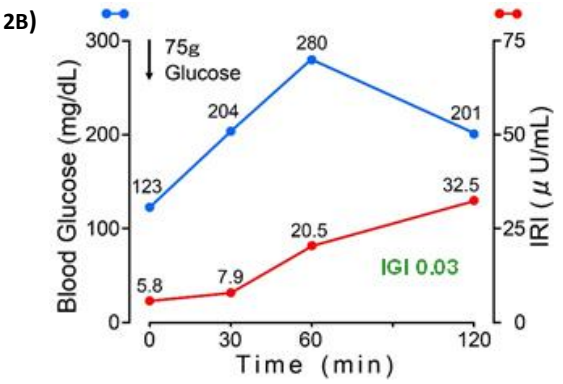

Fig-2B: T2DM: 62 M (2022 Jun)

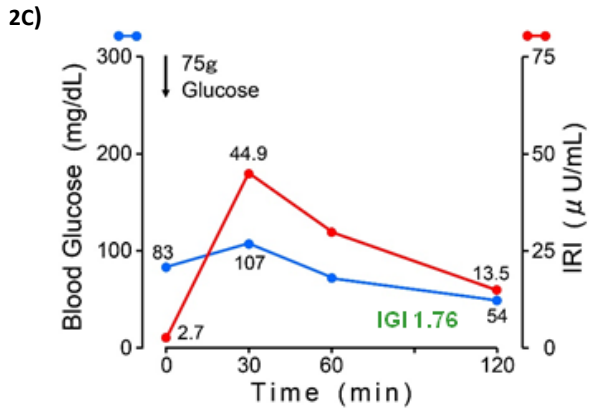

Fig-2C: Normal: 66 M (2022 Feb)

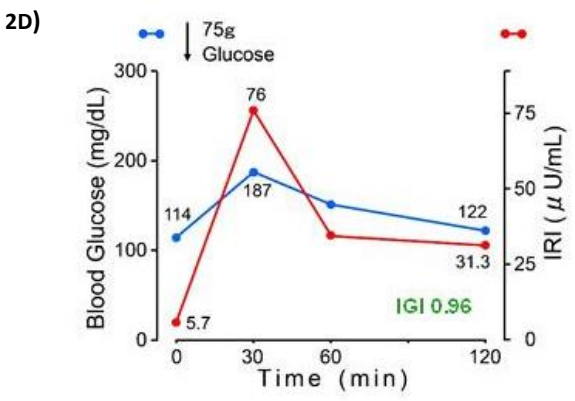

Fig-2D: 56 F (2022 Mar)

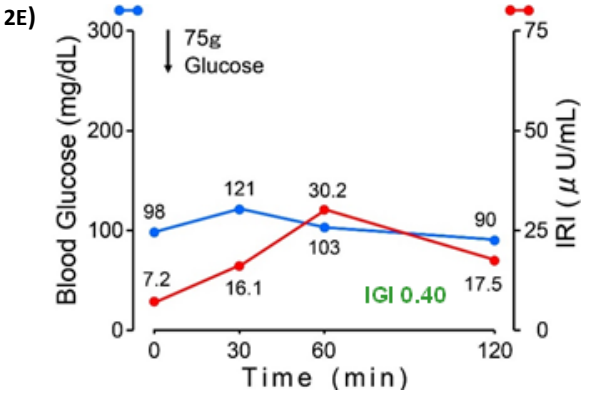

Fig-2E: Normal: 44M (2022 Apr)

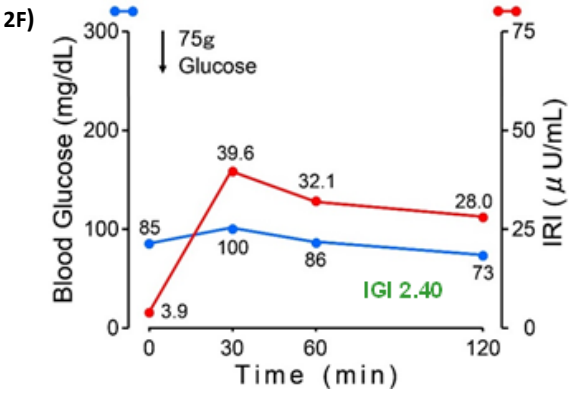

Fig-2F: Normal: 27 M (2022 Apr)

the Ministry of Education, Culture, Sports, Science and Technology [MEXT], Japan and also the Ministry of Health, Labour and Welfare [MHLW], Japan. This investigation has been explained in detail to the patient. Author and co-researchers have taken the written document agreements of the patient. This study was fully discussed in the professional ethics committee. It involved several professionals including hospital president, director, physicians, nurses, dieticians, pharmacists, and a professional legal specialty.

Discussion

From the standard information of carbohydrates, the biochemistry textbook shows that carbohydrate 1g increases blood glucose 1mg/dL for healthy person, and 3mg/dL for T2D case [17]. Then, 75gOGTT may bring 225mg/dL elevation of blood glucose for this case [18]. In fact, this showed nearly glucose elevation by 75g of carbohydrate [19]. Evaluation of beta-cell function by GTT would be similar to physiological stimulus than experimental trials such as hyperglycemic clamp method and frequently sampled intravenous glucose tolerance tests (FSIVGTT) [20].

From the result of GST, this case showed satisfactory response of C-peptide. It suggests that he would have enough ability of secreting insulin from the pancreas by pharmacological strong stimulus. GST was in itself developed for evaluating residual function of beta cell [21], where 17 cases with insulin-dependent diabetes mellitus (IDDM) were applied. Thus, difference exists between pharmacological stimulus and physiological stimulus.

Concerning 75gOGTT twice before and after intake of imeglimin, the degree of insulin resistance and insulin secretion were investigated. He showed the almost same values of fasting IRI, HOMA-R as insulin resistance [19]. As to insulin secretion, he had similar ability in IGI for 0-30min doe early period. In contrast, his insulin secretion seemed to be increased during 30-60min and 60-120min. These phenomena may be related to imeglimin 2000mg/day for 5 weeks.

However, the response of glucose and IRI includes various complex influence, and then to clarify the complete pathophysiological diabetic metabolism would be difficult. As some markers have been useful for diabetic situation, we will follow up the changes in HOMA-R, HOMA-β and IGI, where the usual normal ranges would be >0.4-0.5 of IGI, <2.5 of HOMA-R and >30% of HOMA-β [19].

IGI is applied to quantify the response of beta-cell for glucose changes. It has been calculated for the quotient of delta-IRI/ delta-glucose in 0-30min of GTT [22]. IGI is also used in the case of meal tolerance test (MTT) [23]. Comparison study with GTT and MTT was found [24]. Authors et al. investigated IRI and C-peptide responses for MTT [25,18]. Some reports indicated priority of MTT than OGTT, although components in the meal may influence the results [22].

In this case, OGTT was performed 5 weeks after imeglimin administration. As a result, insulin secretion during 30-60min and 60-120min were increased. Related to this, similar experiment is reported using Zucker diabetic fatty (ZDF) male rats and OGTT after providing imeglimin 150mg/kg for 5 weeks [26]. Compared with the control group, insulin secretion was increased and blood glucose was decreased during 0-120min. For AUC, glycemic AUC decreased by 15% and insulin AUC secretion increased by 83%. The value of IGI (0-120 min) increased by 165%. Furthermore, remarkable improvement was found histologically. ZDF control rats showed disordered islet structure with beta-cells. For imeglimin group rats, islets showed healthier with better morphology and significant increase of beta-cell mass.

The previous study showed glucose-dependent insulin secretion and improvement of beta-cell function for imeglimin [27]. The protocol included the glucose cramp test for imeglimin administration for 7 days. The AUC (0-45min) of insulin secretion was 14957 vs 8227 min·pmol/L in imeglimin group vs control group (+82%, $p<0.05$). Further, insulin secretion rate (ISR) was raised by +112% (iAUC0-45min) associated with first-phase ISR by +110% and second-phase ISR by +29% [27]. Judging from these reports, this case will show possibly improved early insulin secretion in the future.

Some limitations may be observed in this report. This is only one case with T2D, in which biomarkers of OGTT were compared after the intake of imeglimin. For 5 weeks, his early insulin secretion and IGI for 0-30min was stable, and insulin secretion for 30-60min and 60-120min was increased. A variety of factors can be related to glucose variability, and then clinical progress will be carefully followed up. In summary, this case report showed some perspectives concerning imeglimin intake, insulin secretion and blood glucose variability. It is expected that this article becomes a reference for future diabetic research and practice.

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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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Keywords: Imeglimin, Twymeeg, Type 2 Diabetes, 75g Oral Glucose Tolerance Test, Insulinogenic Index, Japan LCD Promotion Association