



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

Hiroshi BANDO^{1,2,3*}, Hiroko OGAWA², Hirohisa URASAKI^{3,4}, Shinji NAGAIRO^{2,5}, Hiroko URASAKI³, Miwako NAKANISHI², Osami WATANABE²

¹Medical Research / Tokushima University, Tokushima, Japan

²Yoshinogawa Hospital, Tokushima, Japan

³Japan Low Carbohydrate Diet Promotion Association (JLCDPA), Tokushima, Japan

⁴Nankai Hospital, Naruto city, Tokushima, Japan

⁵Emeritus Professor, Former Director of Tokushima University Hospital, Tokushima, Japan

Corresponding Author: **Hiroshi BANDO, MD, PhD, FACP** [ORCID ID](#)

Address: Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan;

Email: pianomed@bronze.ocn.ne.jp

Received date: 05 July 2022; **Accepted date:** 13 August 2022; **Published date:** 19 August 2022

Citation: Bando H, Ogawa H, Urasaki H, Nagahiro S, Urasaki H, Nakanishi W, Watanabe O. Investigation of Insulin Secretion in Glucose Tolerance Test by the Intake of Novel Imeglimin (Twymeeg). *Asp Biomed Clin Case Rep.* 2022 Aug 19;5(3):113-19.

Copyright © 2022 Bando H, Ogawa H, Urasaki H, Nagahiro S, Urasaki H, Nakanishi W, Watanabe O. This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

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 HbA_{1c} 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).

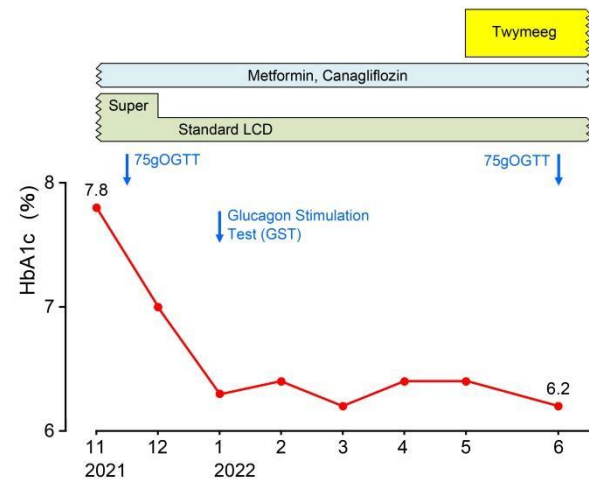


Fig-1: Clinical Progress of the current patient with T2D

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/m², 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-β was 1.6 and 38.1, respectively (Table-1).

Clinical Progress

He has continued standard LCD during Dec 2021-

Case Report

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-β was 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)	ΔGlu	ΔIRI	IGI (0-30)	ΔGlu	ΔIRI	IGI (30-60)	Glu	IRI	ΔGlu	ΔIRI	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							

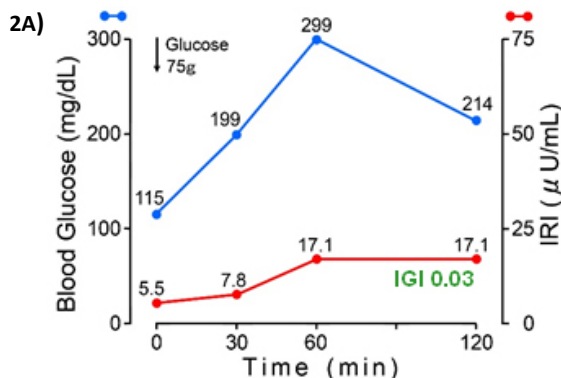


Fig-2A: T2DM: 61 M (2021 Dec)

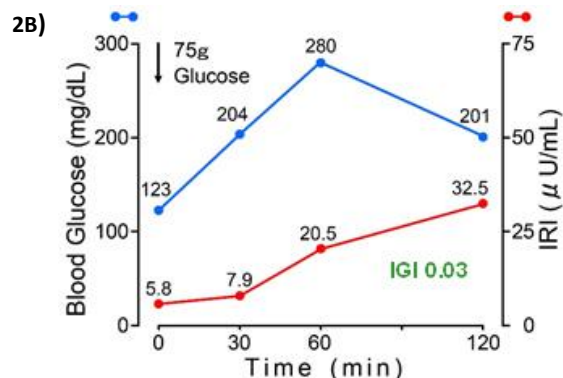


Fig-2B: T2DM: 62 M (2022 Jun)

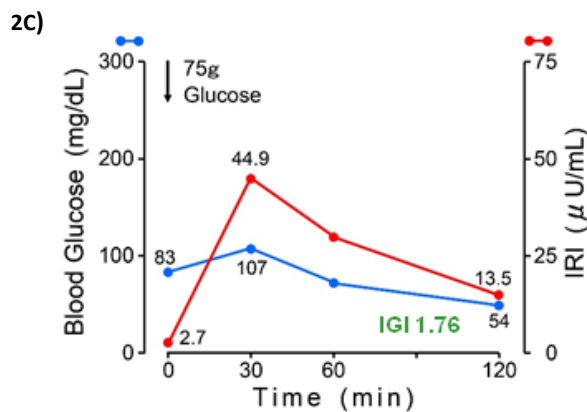


Fig-2C: Normal: 66 M (2022 Feb)

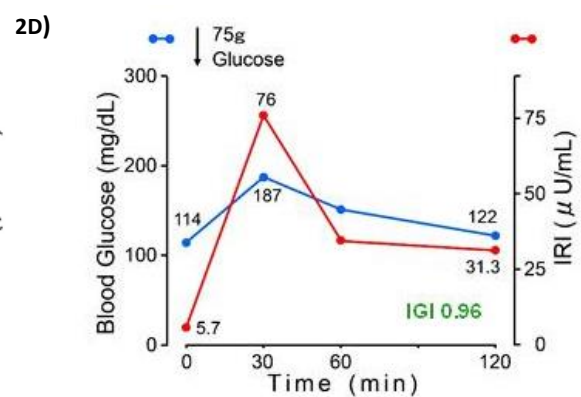


Fig-2D: 56 F (2022 Mar)

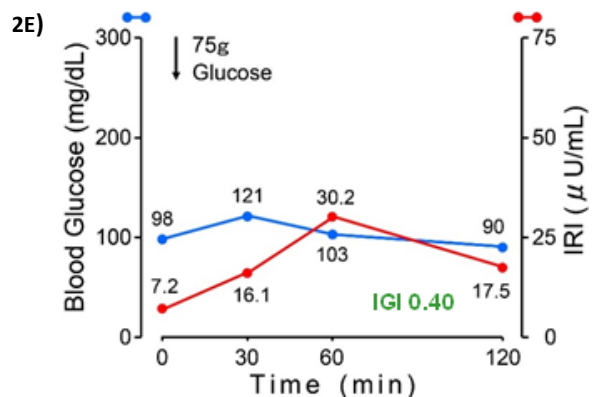


Fig-2E: Normal: 44M (2022 Apr)

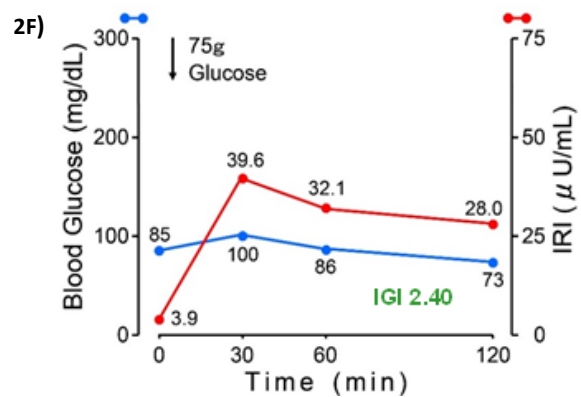


Fig-2F: Normal: 27 M (2022 Apr)

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, dietitians, 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 do 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 clamp test for imeglimin administration for 7 days. The AUC (0-45min) of insulin secretion was 14957 vs 8227 min \cdot pmol/L in imeglimin group vs control group ($+82\%$, $p<0.05$). Further, insulin secretion rate (ISR) was raised by $+112\%$ (iAUC_{0-45min}) 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.

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.

References

- [1] Gram-Kampmann EM, Hansen CD, Hugger MB, Jensen JM, Brønd JC, Hermann AP, Krag A, Olsen MH, Beck-Nielsen H, Højlund K. Effects of a 6-month, low-carbohydrate diet on glycaemic control, body composition, and cardiovascular risk factors in patients with type 2 diabetes: An open-label randomized controlled trial. *Diabetes Obes Metab.* 2022 Apr;24(4):693-703. [PMID: 34984805]
- [2] American Diabetes Association Professional Practice Committee; American Diabetes Association Professional Practice Committee; Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, Green J, Huang E, Isaacs D, Kahan S, Leon J, Lyons SK, Peters AL, Prahalad P, Reusch JEB, Young-Hyman D. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022 Jan 1;45(Suppl 1):S60-82. [PMID: 34964866]
- [3] Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, Accurso A, Frassetto L, Gower BA, McFarlane SI, Nielsen JV, Krarup T, Saslow L, Roth KS, Vernon MC, Volek JS, Wilshire GB,

- Dahlqvist A, Sundberg R, Childers A, Morrison K, Manninen AH, Dashti HM, Wood RJ, Wortman J, Worm N. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition.* 2015 Jan;31(1):1-13. Erratum in: *Nutrition.* 2019 Jun;62:213. [PMID: 25287761]
- [4] Muneta T, Hayashi M, Nagai Y, Matsumoto M, Bando H, Ebe K, Watanabe H, Watanabe S. Ketone Bodies in the Fetus and Newborn During Gestational Diabetes and Normal Delivery. *Int J Diabetes.* 2022;3(1):142-48.
- [5] Bando H. Useful tips for actual low carbohydrate diet (LCD) with super-, standard- and petite-LCD methods. *EC Nutrition.* 2020;15(5):01-04
- [6] Nakamura T, Kawashima T, Dobashi M, Narita A, Bando H. Effective Nutritional Guidance for Obesity by Low Carbohydrate Diet (LCD). *Asp Biomed Clin Case Rep.* 2019;2(s1):16-21.
- [7] American Diabetes Association. Introduction: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022 Jan 1;45(Suppl 1):S1-S2. [PMID: 34964812]
- [8] American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, Green J, Huang E, Isaacs D, Kahan S, Leon J, Lyons SK, Peters AL, Prahalad P, Reusch JEB, Young-Hyman D. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022 Jan 1;45(Suppl 1):S125-43. [PMID: 34964831]
- [9] Iwatsuki N, Bando H, Okada M. Pharmacological Characteristic of Imeglimin (Twymeeg) For Dual Mechanism to Insulin Secretion and Resistance. *SunText Rev Pharm Sci.* 2022;3(1):113.
- [10] Mima A. Mitochondria-targeted drugs for diabetic kidney disease. *Heliyon.* 2022 Feb 3;8(2):e08878. [PMID: 35265754]
- [11] Giruzzi M. Imeglimin. *Clin Diabetes.* 2021 Oct;39(4):439-40. [PMID: 34866787]
- [12] Yendapally R, Sikazwe D, Kim SS, Ramsinghani S, Fraser-Spears R, Witte AP, La-Viola B. A review of phenformin, metformin, and imeglimin. *Drug Dev Res.* 2020 Jun;81(4):390-401. [PMID: 31916629]
- [13] Shah N, Abdalla MA, Deshmukh H, Sathyapalan T. Therapeutics for type-2 diabetes mellitus: a glance at the recent inclusions and novel agents under development for use in clinical practice. *Ther Adv Endocrinol Metab.* 2021 Sep 23;12:20420188211042145. [PMID: 34589201]
- [14] Dubourg J, Ueki K, Grouin JM, Fouquieray P. Efficacy and safety of imeglimin in Japanese patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled, dose-ranging phase 2b trial. *Diabetes Obes Metab.* 2021 Mar;23(3):800-10. [PMID: 33275318]
- [15] Bando H, Okada M, Iwatsuki N, Sakamoto K, Ogawa T. Improved HbA1c value by combined treatment of Dulaglutide and Imeglimin for patient with type 2 diabetes mellitus (T2DM). *Int J Endocrinol Diabetes.* 2022;5(1):132.
- [16] Okada M, Bando H, Iwatsuki N, Ogawa T, Sakamoto K. Clinical Efficacy of Imeglimin (Twymeeg) for Elderly Patient with Type 2 Diabetes Mellitus (T2DM). *Asp Biomed Clin Case Rep.* 2022 Feb 21;5(1):33-37.
- [17] Bender DA, Mayes PA. Carbohydrates of Physiological Significance. In: Rodwell VW, Bender DA, Botham KM, Kennelly PJ, Weil P. eds. *Harper's Illustrated Biochemistry*, 30e. McGraw Hill; 2016. Accessed August 14, 2022. Available from: <https://accesspharmacy.mhmedical.com/Content.aspx?bookid=1366§ionid=73243509>
- [18] Ebe K, Hashimoto M, Bando H, Bando M, Muneta T. Proposal of Meal Tolerance Test (MTT) For Investigating Ability of Insulin Secretion for Small Carbohydrate Load. *Diab Res Open Access.* 2020 Jun 12;2(2):31-37.
- [19] Park SY, Gautier JF, Chon S. Assessment of Insulin Secretion and Insulin Resistance in Human. *Diabetes Metab J.* 2021 Sep;45(5):641-54. [PMID: 34610719]
- [20] Yasuhara D, Naruo T, Nagai N, Tanaka M, Muranaga T, Nozoe S. Insulinogenic index at 15 min as a marker of nutritional rehabilitation in anorexia nervosa. *Am J Clin Nutr.* 2003 Feb;77(2):292-99. [PMID: 12540385]
- [21] Faber OK, Binder C. C-peptide response to glucagon. A test for the residual beta-cell function in diabetes mellitus. *Diabetes.* 1977 Jul;26(7):605-10. [PMID: 326604]
- [22] Rijkkelijkhuizen JM, Girman CJ, Mari A, Alsema M, Rhodes T, Nijpels G, Kostense PJ, Stein PP, Eekhoff EM, Heine RJ, Dekker JM. Classical and model-based estimates of beta-cell function during a mixed meal vs. an OGTT in a population-based cohort. *Diabetes Res*

- Clin Pract. 2009 Feb;83(2):280-88. [PMID: 19097663]
- [23] Bando H, Iwatsuki N, Sakamoto K, Ogawa T. Satisfactory Rapid Response to Xultophy Associated with Meal Tolerance Test (MTT) by Carbohydrate Loading. *Asp Biomed Clin Case Rep.* 2021 Aug 12;4(2):145-52.
- [24] Hijikata M, Higa M, Ichijo T, Hirose T. A comparison of meal tolerance test and oral glucose tolerance test for predicting insulin therapy in patients with gestational diabetes. *Food Nutr Res.* 2021 Feb 26;65. [PMID: 33776619]
- [25] Hashimoto M, Ebe K, Bando H, Bando M, Muneta T. Response of insulin secretion to small amount of meal on low carbohydrate diet (LCD). *Biomed Sci J.* 2020;1:03.
- [26] Hallakou-Bozec S, Kergoat M, Moller DE, Bolze S. Imeglimin preserves islet β -cell mass in Type 2 diabetic ZDF rats. *Endocrinol Diabetes Metab.* 2020 Nov 7;4(2):e00193. [PMID: 33855202]
- [27] Pacini G, Mari A, Fouqueray P, Bolze S, Roden M. Imeglimin increases glucose-dependent insulin secretion and improves β -cell function in patients with type 2 diabetes. *Diabetes Obes Metab.* 2015 Jun;17(6):541-45. [PMID: 25694060]

