

HbA1c Reduction by Imeglimin (Twymeeg) In Diabetic Patient with Pancreatic Atrophy on Curved Planar Reconstruction (CPR)

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Abstract

The patient is 55-year-old male with type 2 diabetes (T2D) and pancreatic atrophy. Hyperglycemia was found in autumn 2022, and HbA1c showed 11.5% in December 2022. He has continued drinking alcohol about 3-4 bottles of beer for 35 years and pancreatic atrophy was detected by radiological method of Curved Planar Reconstruction (CPR) in the plain and enhanced abdominal CT scan. Administration of imeglimin (Twymeeg) brought improved glucose variability from 10.9% to 6.8% of HbA1c for 12 weeks, indicating remarkable clinical efficacy. Other medical problems included obesity (BMI 27.8 kg/m²), fatty liver, dyslipidemia and gall stone probable made of cholesterol.

Keywords: Curved Planar Reconstruction (CPR); Main Pancreatic Duct (MPD); Imeglimin (Twymeeg); Japan LCD Promotion Association (JLCDPA); Trials of IMeglimin for Efficacy and Safety (TIMES)

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Introduction

Recently, Metabolic Syndrome (Met-S) have given crucial impact on medical practice worldwide [1]. They include major problems of obesity, type 2 diabetes (T2D), fatty liver, dyslipidemia, hypertension and others [2]. For basic nutritional treatment, calorie restriction (CR) and low carbohydrate diet (LCD) have been known and necessary for lots of patients [3]. Among CR, LCD, Mediterranean diet, and other types have been in discussion for their clinical efficacy [4]. LCD has been evaluated for more effective type of diet [5]. Authors have also developed medical and social movement of LCD through Japan LCD promotion association (JLCDPA) by various workshops, seminars, books and English reports [6]. We have presented actually three types of LCD, in which super-, standard- and petite LCD are announced as 12%, 26% and 40% of carbohydrate involvement [7].

From recent pharmacological development, some oral hypoglycemic agents (OHAs) have been developed in medical practice [8]. Among them, imeglimin was evaluated to show beneficial effects, which has similar molecule of metformin [9]. It has characteristic mechanism of mitochondrial pathway, where it induces increased insulin secretion and decreased insulin resistance [10]. By several large clinical investigations, imeglimin (Twymeeg) has revealed satisfactory clinical efficacy for improvement of glucose variability.

Authors and our clinical team continued clinical practice and

research for long [11]. A variety of case reports have been presented concerning continuous glucose monitoring (CGM), meal tolerance test (MTT), LCD and treatment experiences with several OHAs [12]. Among them, beneficial effect of imeglimin (Twymeeg) has been found [13]. Recently, we experienced a T2D patient who was treated by Twymeeg associated with clinical efficacy. Its general clinical course and related perspectives will be described in this article.

History and Physicals

This case is 55-year-old male patient with T2D. On his health check-up in autumn 2022, he was pointed out to have hyperglycemia with recommendation of urgent evaluation in the hospital. He visited our diabetes department in December 2022, and was diagnosed as type 2 diabetes (T2D) as HbA1c 11.5%. As to his past history, he has continued drinking alcohol about 3-4 bottles of beer (350ml) for 35 years.

His physical examination in Dec 2022 revealed in the following. Consciousness and vitals were normal. He showed unremarkable findings in his head, face, lung, heart, abdomen and neurological examination. His physique was 177cm in stature, 87kg in body weight and 27.8 kg/m² in body mass index (BMI).

Clinical Progress

He was advised to start low carbohydrate diet (LCD) and to take empagliflozin as oral hypoglycemic agent (OHA). Our diabetes

clinic planned to check him in 2 weeks. However, he skipped the visit for three months because of the lack of his health insurance matter. We call him and explained the importance of diabetic treatment. He visited us again in March 2023, and his HbA1c was 10.9%. We checked his blood chemistry, which showed abnormal liver function test due to fatty liver (Figure 1). He began to have imeglimin (Twymeeg), and HbA1c was decreased to 9.3%, 7.2%, and 6.8% for 4, 8, 12 weeks. His liver function was also normalized from March to May for 8 weeks as ALT from 121 to 28 U/L.

His general biochemical exams were as follows: Cr 0.67 mg/dL, BUN 8 mg/dL, uric acid 3.5 mg/dL, LDL 145 mg/dL, HDL 32 mg/dL, post-prandial TG 395 mg/dL. WBC 9500 / μ L, RBC 4.86 x 10⁶ / μ L, Hb 15.6 g/dL, Ht 47.6 %, MCV 97.9 fL, MCH 32.1 pg, MCHC 32.8 %, Plt 28.9 x 10⁴ / μ L, AFP 2.7 ng/mL, and CEA 4.5 ng/mL.

Regarding radiological examination, he received plain abdominal CT scan in March 2023. He showed fatty liver, probable gall stone and possible atrophy of pancreas (Figure 2). For further evaluation, he received enhanced abdominal CT in May 2023 (Figure 3,4,5). Then, he was diagnosed as gall stone of probable made of cholesterol, fatty liver and atrophy of the pancreas.

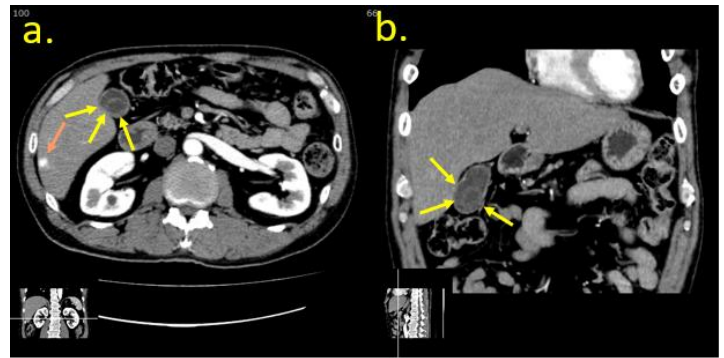


Figure 3: Enhanced abdominal CT scan (early phase)
3a. Apparent lesion in the gall bladder (transverse) Image of hemangioma is densely enhanced.
3b. Probable gall stone made from cholesterol element (coronal).

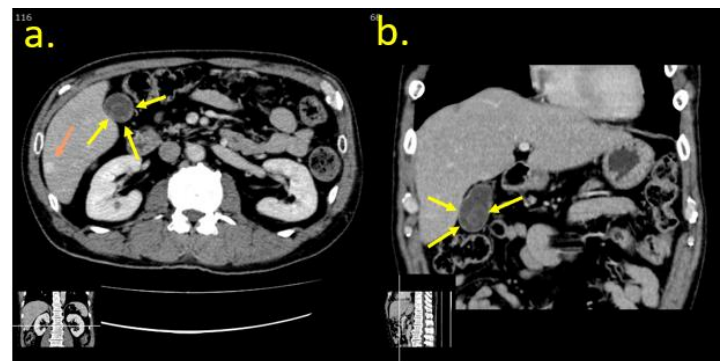


Figure 4: Enhanced abdominal CT scan (late phase)
4a. Clearer gall stone in the gall bladder (transverse) Image of hemangioma is lightly contrasted.
4b. Clearer gall stone of cholesterol element (coronal).

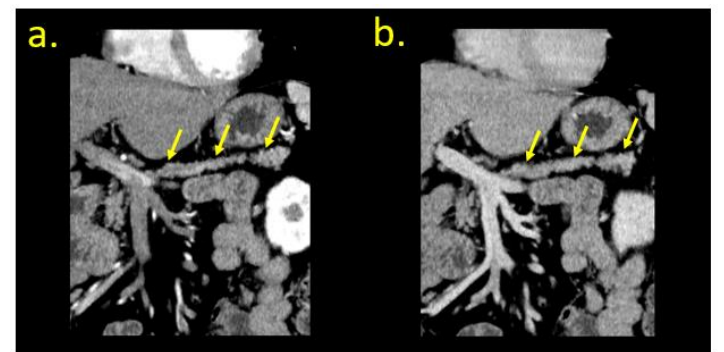


Figure 5: Image of the pancreas by Curved Planar Reconstruction (CPR)
5a. Atrophy of the pancreas is noted (early phase)
5b. Slight enhancement of the pancreas (late phase).

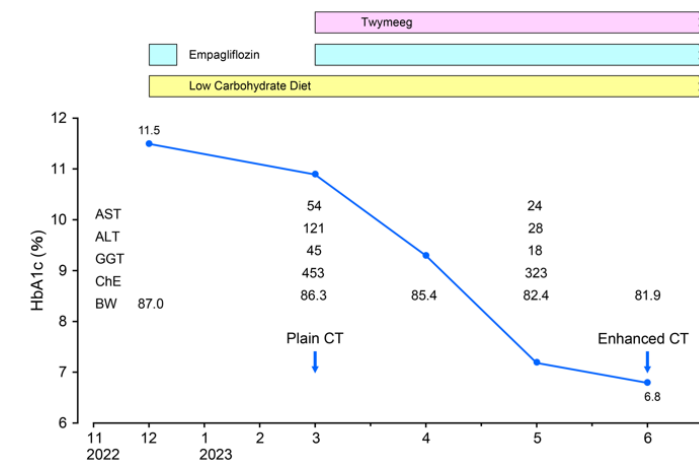


Figure 1: clinical progress of HbA1c, biochemical exam and treatment.

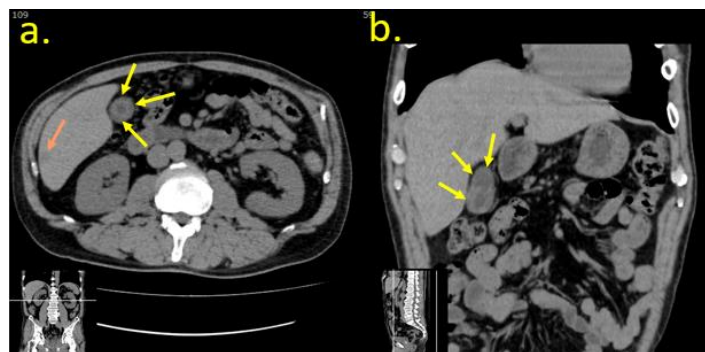


Figure 2: Plain abdominal CT scan
2a. Vague lesion in the gall bladder (transverse) Image of hemangioma is not apparent.
2b. Possible gall stone with no calcification (coronal).

Medical Problems

From mentioned his medical history, clinical progress, laboratory tests and plain and enhanced abdominal CT, his medical problems would be summarized in the following.

- 1 Obesity (BMI 27.8)
- 2 persisting alcohol drinking
- 3 fatty liver

- 4 T2D
- 5 dyslipidemia
- 6 gall stone probable made of cholesterol
- 7 atrophy of the pancreas

Ethical Standards

This reported case is complied with the ethical guideline from the Declaration of Helsinki. In addition, some commentaries are along with the regulation for personal information. The principle is associated with the ethical rules for medical practice for human rights. Some guidelines are references from Japanese government. They are the Ministry of Health, Labor and Welfare, and the Ministry of Education, Culture, Sports, Science Technology. Authors et al. has set up the ethical committee concerning the research. It is situated in Kanaiso Hospital, Tokushima, Japan. This committee includes several necessary staffs, such as hospital director, physicians in charge, radiologist, pharmacist, head nurse, dietitian and legal professional. They discussed in thorough manner about this case, and agreed the research protocol. The informed consent was taken from the case by the written style document.

Discussion

This case has been drinking alcohol for many years. There was no history of alcoholic hepatitis, acute pancreatitis, chronic pancreatitis, gout, or hyperuricemia. Hepatic dysfunction was observed in blood tests, and liver function tests normalized after 8 weeks of LCD. Abdominal CT scan showed fatty liver and pancreatic atrophy. As to this case, some medical problems may be present in the following. They are i) relationship among alcohol consumption, pancreatic atrophy, and diabetes, ii) radiological method of Curved Planar Reconstruction (CPR), and iii) effect of imeglimin (Twymeeeg). There perspectives are described for the discussion in this order.

First, this case showed pancreatic atrophy, which may be related with alcohol consumption and diabetes. Diabetes has been a crucial factor for the complication of chronic pancreatitis (CP). It is considered to develop from gradual loss of pancreatic islet cell. Pancreatic morphology was studied for 76 cases with definite CP [14]. Among them, 23 cases (30.1%) were diabetic and 23 cases were healthy age-/sex-matched healthy volunteers. When compared two groups (n=23, each), pancreatic volume was lower as 20 vs 36mL (p=0.02). Consequently, atrophy of the pancreas was observed in most CP cases with diabetes. Diabetes may arise from CP, which has been associated with increased mortality and morbidity. Cross-sectional study was conducted for 645 CP from the PROCEED study, where 276 diabetes were included [15]. The analysis was used by the area under the receiver operating characteristic curve (AUROC). As a result, independent correlations were found in CP-related factors (history, pancreatic atrophy, calcification, exocrine pancreatic dysfunction). Furthermore, T2D risk factors included before and after onset of Pubtexto Publishers | www.pubtexto.com

pancreatitis. Then, multiple factors may be involved in CP and also diabetes in CP.

Cohort study in CP were conducted for 12 years for 644 patients, where 137 cases were excluded. Of these, 64.3% were idiopathic CP, and 55.8% underwent ductal intervention [16]. Cumulative percentage of diabetes showed 57.9%. Alcohol consumption and pancreatic calculi showed independent risk factors for diabetes with odds ratio (OR) of 2.05 (p=0.01) and 2.05 (p=0.003), respectively. Large study from the Scandinavian Baltic Pancreatic Club was conducted using the diagnostic criteria of M-ANNHEIM. Detail changes in imaging-based structural pancreatic image were compared with clinical complications age, sex, disease duration, smoking and current alcohol consumption [17]. As a result, 742 cases were analyzed, where mean age 55 years, males 68%, impaired pancreatic exocrine 69%, diabetes 35%, underweight 12%, abdominal pain 68% were found. The atrophy of the pancreas and calcifications showed positive association with underweight, and severe calcification showed negative association with pain. As to histopathology of CP, consensus guidelines were announced for international working group. Among them, strong consensus included 12 statements. Three main key points showed i) the triad of fibrosis, ii) acinar tissue and iii) duct changes. For the diagnosis of CP, the integrative assessment of clinical symptom/sign, laboratory data, and imaging features were included as well as histological evaluation [18].

Second, our radiological medical team has reported several cases using high-technique computerized reconstruction methods [19]. Recently, novel PET/CT imaging methods have been developed for pancreatic diseases [20]. They include contrast-enhanced abdominal CT scan. Among them, recent curved planar reconstruction (CPR) for pancreas has been useful for pancreatic cancer, pancreatic atrophy and enlarged main pancreatic duct (MPD). Authors et al. have radiological team for high-quality analysis. They include the method of the CPR for producing adequate images along the MPD. It has been developed on the bases of three-dimensional (3-D) convolutional neural network [21]. This 3-D technique has been clinically useful for evaluating several lesions in the pancreas.

Using CPR method, a patient with Intraductal Papillary Mucinous Neoplasm (IPMN) was analyzed radiologically with detail image [22]. Recent report showed the difference of CPR achievement for accuracy and time effectiveness between manual method and automated analysis. The research included 100 consecutive cases with MPD dilatation that underwent enhancement CT scan of pancreas [21]. As a result, MPD length in the CPR images was 115.6 mm vs 110.5 mm in manual vs automated method (p<0.001). Further, average time for creating images was 174.6 sec vs 61.7 sec in each group, respectively (p<0.001). Thus, novel software for automated CPR would be useful for image quality and convenience.

Third, HbA1c value was decreased from 10.9% to 6.8% for three months by the administration of Twymeeeg. It was clinically

effective for such short period. Medical efficacy of imeglimin was analyzed through the international large studies of Trials of IMeglimin for Efficacy and Safety (TIMES) 1,2 and 3 [23]. Regarding their results, HbA1c reduction in average was reported according to several cases of monotherapy and add-on therapy. Summarized responses were in the following: 0.46% as monotherapy, 0.57% as SGLT2i, 0.92% as DPP4-i, 0.67% as biguanides, 0.70% as alfa-GI from the data in TIMES 2 [24]. Pharmacological mechanism of imeglimin would be found through mitochondrial pathway [25]. As the impressive phenomena, decreasing ability differs between DPP4-i and GLP-1RA as 0.92% and 0.12% [26]. Both medicines are known to act via common pathway. However, obtained different results suggest that other mechanism may be involved in the pharmacological function. These data will become a crucial key to detect novel mechanism of Twymeeg [27].

Concerning current report, some limitation may be present. Mutual relationships would exist among obesity, T2D, fatty liver, gall stone, persisting alcohol consumption, pancreatic atrophy and others. LCD has brought beneficial clinical progress of HbA1c, liver function tests, and body weight. Future changes will be required to observe for long clinical progress.

In summary, 55-year-old patient with several problems of life-style related diseases has shown clinical improvement by the administration of Twymeeg. Furthermore, he showed the atrophy of pancreas probably due to persistent alcohol consumption for years. Current paper will be hopefully useful reference for future research and practice for diabetes.

References

1. Wang Z, Yang B. Polypharmacology in Clinical Applications: Metabolic Disease Polypharmacology. In: Polypharmacology. 2022.
2. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. on behalf of the American Diabetes Association. 1. Improving Care and Promoting Health in Populations: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023; 46: S10-S18.
3. Yaegashi A, Kimura T, Hirata T, Iso H, Tamakoshi A. Association between low-carbohydrate diet score and incidence of type 2 diabetes among Japanese adults: the JACC Study. *J Nutr Sci*. 2023; 12: 50.
4. Tamura T, Wakai K, Kato Y, Tamada Y, Kubo Y, Okada R, et al. Japan Multi-Institutional Collaborative Cohort (J-MICC) Study. Dietary carbohydrate and fat intakes and risk of mortality in the Japanese population: the Japan Multi-Institutional Collaborative Cohort Study. *J Nutr*. 2023; 3166: 72198-72206.
5. Zhao Y, Li Y, Wang W, Song Z, Zhuang Z, Li D, et al. Low-carbohydrate diets, low-fat diets, and mortality in middle-aged and older people: A prospective cohort study. *J Intern Med*. 2023.
6. 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.
7. Bando H. Useful Tips for Actual Low Carbohydrate Diet (LCD) with Super-, Standard- and Petit-LCD Methods. *EC Nutrition*. 2020;15: 01-04.
8. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. on behalf of the American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023; 46: S140-S157.
9. Yanai H, Adachi H, Hakoshima M, Katsuyama H. Glucose-Lowering Effects of Imeglimin and Its Possible Beneficial Effects on Diabetic Complications. *Biology (Basel)*. 2023; 12: 726.
10. Yendapally R, Sikazwe D, Kim SS, Ramsinghani S, Fraser-Spears R, Witte AP, et al. A review of phenformin, metformin, and imeglimin. *Drug Dev Res*. 2020; 81: 390-401.
11. Hayashi K, Bando H, Miki K, Hamai M, Yasuoka T. Detail Measurement of Pre-Prandial and PostPrandial Blood Glucose during Imeglimin (Twymeeg) Treatment. *Asp Biomed Clin Case Rep*. 2023; 6: 40-46.
12. Bando H, Kobayashi H, Ogawa H, Nagahiro S, Nakanishi M and Watanabe O. Effect of imeglimin (Twymeeg) on pre-prandial glucose in patient with persisting post-prandial hyperglycemia. *Int J Endocrinol Diabetes*. 2023; 6: 147.
13. Okada M, Bando H, Iwatsuki N, Sakamoto K, Ogawa T. Relieved Depressive State and Glycemic Control in Type 2 Diabetes (T2D) Patient Treated by Imeglimin (Twymeeg). *Asp Biomed Clin Case Rep*. 2023; 6: 116-123.
14. Olesen SS, Hagn-Meincke R, Drewes AM, Steinkohl E, Frokjaer JB. Pancreatic atrophy and exocrine insufficiency associate with the presence of diabetes in chronic pancreatitis patients, but additional mediators are operative. *Scand J Gastroenterol*. 2021; 56: 321-328.
15. Jeon C, Hart PA, Li L, Yang Y, Chang E, Bellin MD, et al. Development of a Clinical Prediction Model for Diabetes in Chronic Pancreatitis: The PREDICT3c Study. *Diabetes Care*. 2023; 46: 46-55.
16. Talukdar R, Reddy DN, Tandan M, Gupta R, Lakhtakia S, Ramchandani M, et al. Impact of ductal interventions on diabetes in patients with chronic pancreatitis. *J Gastroenterol Hepatol*. 2021; 36: 1226-1234.
17. Nordaas IK, Tjora E, Dimcevski G, Haldorsen IS, Olesen SS, Drewes AM, et al. Scandinavian Baltic Pancreatic Club. Structural imaging findings are related to clinical complications in chronic pancreatitis. *United European Gastroenterol J*. 2022; 10: 385-395.
18. Esposito I, Hruban RH, Verbeke C, Terris B, Zamboni G, Scarpa A, Morohoshi T, et al. Working group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis. Guidelines on the histopathology of chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and the European Pancreatic Club. *Pancreatology*. 2020; 20: 586-593.
19. Ogura K, Bando H, Nishikawa S, Kato Y, Obonai T and Kato Y. Precise Investigation for Diabetic Patient with Recurrent Stroke by the Reconstruction Image of SYNAPSE VINCENT. *Int J Case Rep Clin Image*. 2022; 4: 189
20. Lv Z, Sun F, bian Y, Hao Q, Zhang Y, Xu H, Cai H. Clinical laboratory and imaging diagnosis of pancreatic diseases. Eds. Li M, Lu L, Xiao Y, u D, Zhang H. Chapter 3 Integrative Pancreatic Intervention Therapy Elsevier, 2021; 55-140.
21. Ogura K, Bando H, Kato Y, Yamashita H, Kato Y. A Case of Intraductal Papillary Mucinous Neoplasm (IPMN) Analyzed by Curved Planar Reconstruction (CPR) With Treatment of Twymeeg and Equmet for Type 2 Diabetes (T2D). *Int J Case Rep Clin Image*

- 2023; 5: 197.
22. Koretsune Y, Sone M, Sugawara S, Wakatsuki Y, Ishihara T, Hattori C, et al. Validation of a convolutional neural network for the automated creation of curved planar reconstruction images along the main pancreatic duct. *Jpn J Radiol.* 2023; 41: 228-234.
 23. 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.
 24. 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.
 25. Hozumi K, Sugawara K, Ishihara T, Ishihara N, Ogawa W. Effects of imeglimin on mitochondrial function, AMPK activity, and gene expression in hepatocytes. *Sci Rep.* 2023; 13: 746.
 26. 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.
 27. Uchida T, Ueno H, Konagata A, Taniguchi N, Kogo F, Nagatomo Y, et al. Improving the Effects of Imeglimin on Endothelial Function: A Prospective, Single-Center, Observational Study. *Diabetes Ther.* 2023; 14: 569-579.