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Satisfactory Rapid Response to Xultophy Associated with Meal Tolerance Test (MTT) by Carbohydrate Loading

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Abstract

The case is a 69-year-old male patient with Type 2 Diabetes Mellitus （T2DM） for 21 years. His diabetic control was not so satisfactory, and his HbA1c value increased in spring 2021. Then, he started Xultophy (IDegLira), which includes a fixed ratio of two agents of basal degludec and liraglutide. Just after providing Xultophy, the daily profile of blood glucose decreased from 179-400 mg/dL to 112-171 mg/dL, with remarkable clinical efficacy. He usually takes 80g of carbohydrates in breakfast, and the meal tolerance test (MTT) was challenged. As carbohydrate loading was given 100-75-50-0%, postprandial hyperglycemia at 60-min showed 277-219-159-133 mg/dL, respectively.

Keywords

Xultophy, Insulin Degludec and Liraglutide, Type 2 Diabetes Mellitus, Meal Tolerance Test, Postprandial Hyperglycemia

Abbreviations

IDegLira: Xultophy; T2DM: Type 2 Diabetes Mellitus; MTT: Meal Tolerance Test

Introduction

Diabetes mellitus (DM) has been one of the most popular non-communicable diseases (NCDs) [1]. This is a global issue to consider and investigate the detailed situation [2]. The incidence and prevalence of DM are remarkably increasing in developed and developing countries and districts [3]. From social, economic, and medical points of view, the problems related to DM have brought enormous influences [4]. Regarding diabetic treatment, there have been several kinds of options so far, including oral hypoglycemic agents (OHAs) and some injectable diabetic agents [5].

In the light of recent treatment for DM, some agents have been evaluated to be effective in actual diabetic practice. They include long-acting insulin, sodium-glucose transporter 2 inhibitor (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP-4i), and glucagon-like peptide 1 receptor agonist (GLP-1RA) [6]. Successive to recognition of clinical efficacy of GLP-1RA, the

combination of agents of GLP-1RA and basal insulin was introduced to medical practice [7]. It showed more beneficial usefulness, and it includes a fixed ratio of basal degludec and liraglutide as IDegLira [8].

IDegLira has been known as Xultophy, which shows the combined beneficial effect from each agent of liraglutide and degludec. The former can decrease fasting blood glucose level and postprandial glucose response. Moreover, it can recover the β-cell function, maintain the post-prandial insulin response [9]. On the other hand, the latter degludec can decrease the fasting blood glucose for its long-acting suppressing the glucose value [10].

For the fixed-ratio combination of Xultophy, a study of DUAL™ (Dual Action of Liraglutide and Insulin Degludec) clinical trial program was found [11,12]. The effect and safety were analyzed in the consecutive trial of DUAL programs. The results showed that non-inferior or superior glycemic control was observed associated with some comparators, in addition to a lower risk of weight gain or hypoglycemia compared to other insulin agents [13,14].

Authors and co-researchers have continued various practices and research concerning DM. The area includes meal tolerance test (MTT), calorie restriction (CR), low carbohydrate diet (LCD), continuous glucose monitoring (CGM), Xultophy, SGLT2i, GLP-1RA, and others. [15,16]. In particular, recent reports show several cases which were applied the treatment related to Xultophy [17,18]. Xultophy seems to be clinically effective for patients with various pathology [19]. Furthermore, it may show clinical efficacy with small doses of Xultophy in the case of predisposition or constitution of the patients [20]. These situations are probably due to the benefit of combined pharmacological agents. Authors have recently experienced a diabetic patient that revealed a remarkable response to Xultophy with small doses. The outline of the case would be presented and discussed in this article.

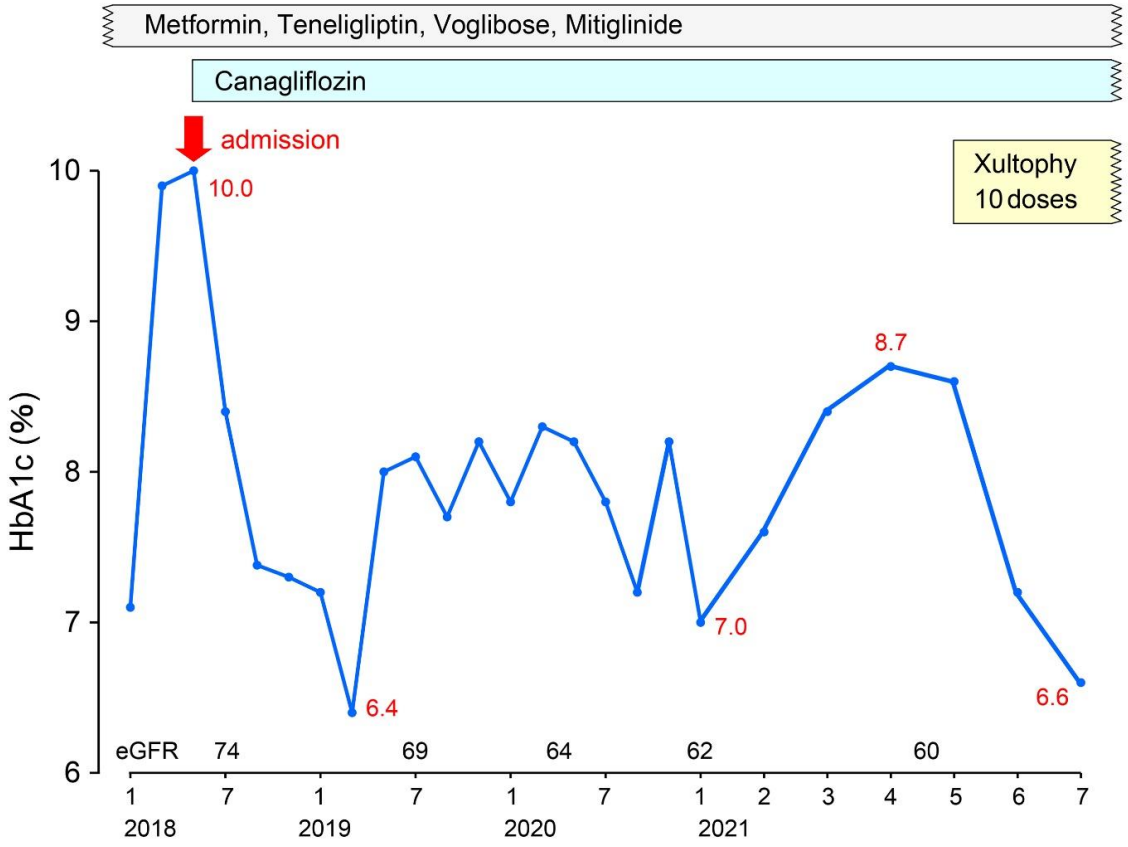

Fig-1:

Clinical progress of HbA1c changes and treatment for diabetes HbA1c showed acute reduction after Xultophy administration.

Case Presentation

History & Physical:

The case is a 69-year-old male patient with Type 2 Diabetes Mellitus (T2DM). He was pointed out to have diabetes at 48 years old. He has received DM treatment until now. As for other medical previous histories, no particular problems were found with the axes of, cardiovascular, respiratory system, digestive or neurological systems. Recent diabetic treatment included oral hypoglycemic agents (OHAs). They include metformin 1500mg/day, teneligliptin 20mg/day, voglibose 0.6mg/day, mitiglinide 30mg/day. Until winter 2017, his control was rather stable (**Fig-1**). From spring 2018, his diabetic control was exacerbated with HbA1c 9.8-10.0%. Then he was hospitalized at our hospital for further evaluation and treatment in May 2018. Regarding his physical examination, vitals and consciousness were unremarkable without any acute abnormalities. He showed negative for heart, lung, and abdomen. His neurological findings were normal without peripheral neuropathy.

Examinations:

The laboratory examination in May 2018 were revealed as follows: RBC 4.92 x 10^6 /μL, Hb 14.4 g/dL, Ht 42.5%, MCV 86.0 fL (80-98), MCH 29.3 pg (27-34), MCHC 33.9 g/dL (31-36), WBC 6600 /μL, Plt 19.5 x 10^4 /μL, AST 20 U/L, ALT 15 U/L, γ-GT 23 U/L, ALP 187 U/L (100-340), TP 7.5 g/dL, Alb 4.4 g/dL, CRP 0.1 mg/dL, BUN 16 mg/dL, Cr 0.8 mg/dL, eGFR 74 mL/min/1.73m^2, Uric acid 5.5 mg/dL, Na 140 mEq/L, K 4.2 mEq/L, Cl 102 mEq/L, T-C 185 mg/dL、HDL-C 50 mg/dL, LDL-C 123 mg/dL, TG 59 mg/dL.

Regarding examinations for diabetes mellitus, HbA1c 10.0%, fasting blood glucose 202 mg/dL. Urinalysis data were protein (-), glucose (+), urobilinogen (+/-), urine C-peptide excretion 38 μg/day (23-155) and urinary albumin 16 mg/day (2-20).

Other exams are included in the following. Chest X-P was negative for lung and heart, and ECG showed ordinary sinus rhythm with unremarkable changes. Vascular extensibility test showed ankle-brachial index (ABI) 1.11/1.10 (0.91-1.40). cardio-ankle vascular index (CAVI) 9.6/9.3 (8.3-9.9) (**Fig-2**). The detail data were that PEP 93, ET 303, R-AI 0.82, PEP/ET 0.31, and L (125) = L_1 (64) + L_2 (33) + L_3 (28). Cardiovascular changes were not apparent, and the ophthalmic test was negative for retinopathy.

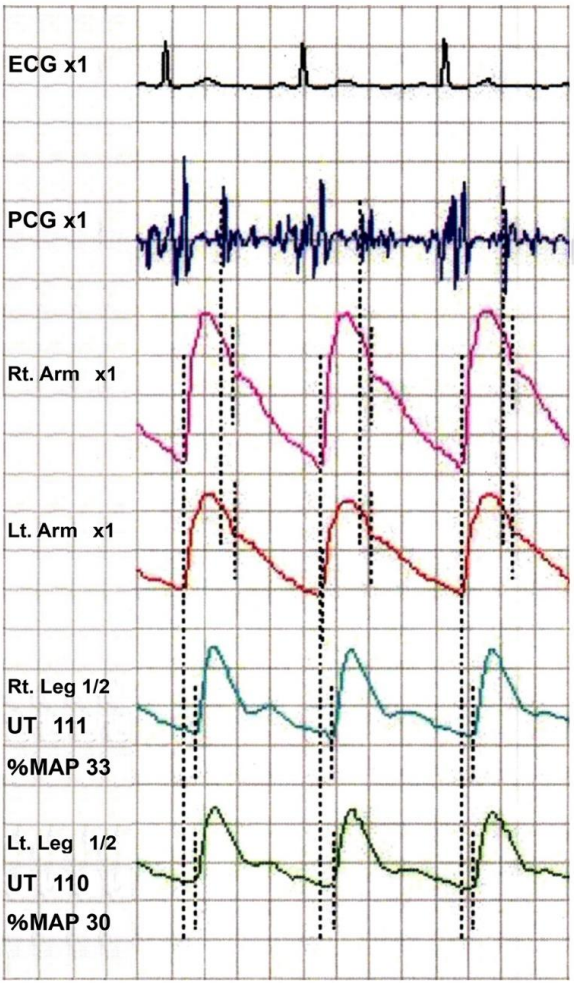

Fig-2:

Results of vascular extensibility test. Data were normal on ankle brachial index (ABI) and cardio-ankle vascular index (CAVI).

Clinical Progress

His daily profile of blood glucose was 208-285-283 mg/dL in 0700h-1100h-1700h, respectively. He was treated by nutritional therapy and also by starting Canagliflozin 100mg/day as a sodium-dependent glucose cotransporter 2 inhibitor (SGLT2i). His admission period was 10 days, in which his daily profile of glucose was improved to 145-194-183 mg/dL in 0700h-1100h-1700h, respectively. After that, his diabetic control was not so satisfactory as HbA1c around 7-8 %. From February to April 2021, his diabetic control became unstable. There, he has evaluated the situation in the light of diet, exercise, and

medication. As a result, pharmacotherapy was changed. As to his treatment, metformin, voglibose, mitiglinide, and canagliflozin are continued in the same way. For changed content, discontinuation of Teneligliptin as DPP4i and initiation of Xultophy, which is a combination of GLP-1RA and long-acting insulin, once a day from May 2021.

The results of diurnal variation in blood glucose due to Xultophy administration are shown in **Table-1**. After the first injection was given at 2100h on day 0, a decrease in blood glucose was observed on the next morning of day 1. Consequently, the dose of Xultophy was adjusted to 10-12 doses. Clinical effect was found in the early period, and the efficacy was continued thereafter. Furthermore, no adverse effect was observed due to Xultophy administration.

Mean Tolerance Test (MTT) was conducted during clinical progress. Post-prandial blood glucose levels for breakfast were evaluated in several situations. The carbohydrate amount that he usually consumes at breakfast is 80g including staple food and fruits. The mount was estimated to be 100% for his usual meal style. Then, 4 trials of MTT were conducted associated with carbohydrate amounts of 100%, 75%, 50%, and 0%. Consequently, the carbohydrate amount would be, 80g, 60g, 40g, and minimum gram, respectively. The degree of postprandial hyperglycemia was evaluated. As a result, the blood glucose levels measured 60 minutes after breakfast were 277 mg/dL, 219 mg/dL, 159 mg/dL, and 133 mg/dL. respectively. HbA1c levels in May were 8.6% but dropped to 6.6% in 8 weeks in July.

Ethical Considerations

This case study was basically performed with the ethical principles of the Declaration of Helsinki.

Table-1: Changes in blood glucose after Xultophy administration

Day	Breakfast		Lunch		Supper		Xultophy (doses)
	0	60	0	60	0	60	
	730	900	1200	1330	1800	1930	2100
0	192	324	179	400	181	364	10
1		167			112		11
2			171			138	12
3	86			128			10
4		158			222		10
5			164			162	11
6	89			186			11
7	**(100%) 277**				167		12
8	60						12
9	**(75%) 219**						10
10	95						10
11	**(50%) 159**						10
12			186				10
13				167			10
14	**(0%) 133**						10
15					99		10
16						149	10

1) For breakfast, patient tried to take carbohydrate amount as 100%, 75%, 50% and 0% at 0730h on day 7, 9, 11, and 14

2) The patient estimated usual amount of carbohydrate as 100% in his daily breakfast on an average

3) Preprandial and postprandial glucose levels show 0 and 60, and each clock time shows from 730h to 1930h

Moreover, the additional comment was conducted from the Ethical Guidelines for Research for Humans, associated with the concept of Good Clinical Practice (GCP). The authors related to this manuscript have established an ethical committee, including the president and vice-president of the hospital, physician, nurse, dietitian-nutritionist, pharmacist, and the person of legal specialty. The discussion has been continued with appropriate and valid manners, and it has decided to the agreements for this current protocol of the research. The informed consent and writing style of the document agreement have been obtained from the subject.

Discussion

For recent pharmacotherapy for diabetes, there have been some types of glucagon like peptide-1 receptor agonists (GLP-1RAs) [5]. They include dulaglutide, liraglutide, exenatide, lixisenatide and so on [21]. Among previous reports of GLP-1RAs, Network Meta-Analysis (NMA) presented clinical evaluation for glucose variability and research outcomes in cardiovascular disease [22]. The results showed the efficacy of cardiovascular benefits on GLP-1RA regimens. Among GLP-1Ras, liraglutide is effective and broadly used for diabetes. In relation to this popularity, Xultophy has been used widely in clinical practice for combined agents of liraglutide and basal insulin degludec [23]. If compared with mutually each agent, the combination reveals increased efficacy [7]. Xultophy holds the effect of cardioprotective activity by maintaining the beta-cell function in the pancreas [9].

For this report, medical efficacy and associated issues of Xultophy were discussed, that is the combined agents of basal-bolus insulin and GLP-1RA [10]. Some articles were found about the compared investigation of basal insulin and Xultophy. As per clinical studies on Xultophy, DUAL investigations have been well-known, which means Dual Action of Liraglutide and Insulin Degludec clinical trial program. Several outcomes for Xultophy were found with DUAL studies. These show a significant decrease of HbA1c level, weight reduction tendency, lower risk of hypoglycemia episodes in comparison with the previous standard regimens [24]. It is indeed that basal-bolus therapy shows the efficacy of lowering glucose levels, but it tends to find a higher incidence of hypoglycemia episodes [25].

In European countries, the European Xultophy Treatment Retrospective Audit (EXTRA) study was observed as a reliable program. Among EXTRA studies, real-world evidence (RWE) showed a significant reduction of HbA1c and weight in diabetic patients that changed treatment from MDI to Xultophy [26]. From the latest investigation of 2021, T2DM cases started 16 doses of Xultophy, when changed from bolus insulin to Xultophy [27]. Diabetic patients on Xultophy are advised to regulate the doses to hold glucose from 90 to 130 mg/dL twice per week. The method includes the adjustment of moving +/- 2 doses for titrating. For the effective result, HbA1c level for 6 months was compared which was 8.4% vs 7.4% in control vs Xultophy group, respectively.

Xultophy has clinical benefits to contribute to diabetic patients with rather difficult situations. One of the reasons presents the simple administration of once per day [10]. The benefits include social, medical, and psychological aspects. The amount of the dose can be easily regulated. In North American and European countries, diabetic cases with previous insulin history can begin at 16 doses, and those who are naïve for insulin can begin at 10 doses [8]. On the other hand, it seems to be a little different in Japanese people. Authors have already reported some cases of satisfactory control with small doses of Xultophy [28]. This background may be from higher sensitivity of insulin and/or GLP-1RA, diet habit, or smaller body physique [29].

In this case, insulin administration was not conducted, but DPP-4i agent was provided. As for Xultophy, insulin was firstly started and GLP-1RA was provided instead of DPP-4i. Clinical effect was satisfactory just after the first administration, in which it was possible to control glucose variability with a small amount of 10 doses. One of the reasons would be that the patient was naive to insulin treatment and was highly sensitive to the pharmacotherapy [30] Furthermore, this case may have minimum influences of micro- and macrovascular diabetic complications,

judging from the results of ABI and CAVI for 21 years of diabetic history.

MMT was performed in this case., where the usual carbohydrate intake is 80g in the breakfast. According to the carbohydrate amount in the breakfast as 100%, 75%, 50%, 0%, 60-min postprandial glucose was 277-219-159-133 mg/dL. The author has continued practice and research on low carbohydrate diet (LCD) for a long [31]. Among them, it has been enlightened to people that the blood glucose rise by ingestion of carbohydrate 1g would be 1 mg/dL for the normal subject, 3 mg/dL for T2DM, and 5 mg/dL for T1DM. Related to this information, we have proposed three types of LCDs for daily practical diet methods. They are super-LCD, standard-LCD, and petite-LCD, associated with a carbohydrate ratio of 40%, 26%, and 12%, respectively [32]. We have continued LCD movement medically and socially through the activity of the Japan LCD Promotion Association (JLCDPA) so far.

Some limitations are present in this report. It is one diabetic case with good sensitivity of Xultophy for controlling glucose variability, associated with the data by MMT. Currently, the case can continue stable condition with small doses of Xultophy, and follow-up would be necessary from various points of view. In summary, a patient with T2DM showed a satisfactory clinical course by applying Xultophy. Several data related to this case will be expected to become a reference for future investigation.

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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