



Useful Xultophy for Older Diabetic with Various Problems

Hayashi K¹, Yasuoka T¹, Bando H^{1,2,3,*}, Miki K¹, Nakagawa M¹, Zushi T¹, Suzuki C¹, Shibata R¹, Takata T¹ and Sato M¹

¹Hayashi Hospital, Tokushima, Japan

²Tokushima University / Medical Research, Japan

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

*Corresponding author: Bando H, Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943 Japan; TEL: +81-90-3187-2485; E-mail: pianomed@bronze.ocn.ne.jp

Abstract

The case was 79-year-old female with type 2 diabetes mellitus (T2DM) and other medical problems who has been treated on insulin for Multiple Daily Injections (MDI). She has recently developed cough and was diagnosed as slight bronchopneumonia, followed by the admission to the hospital with intensive treatment. Simultaneously, she could not control her usual daily life, and then her diabetic therapy was changed to Xultophy. It is the combined agent of liraglutide and insulin degludec that can be injected once a day. In this article, the clinical progress and some discussion from various points of view would be described.

Keywords: Multiple daily insulin injection (MDI); Xultophy; Type 2 Diabetes Mellitus (T2DM); Bio-psycho-social; Glucagon like peptide-1 receptor agonist (GLP-1RA)

Introduction

The prevalence of diabetes has been increasing in the world. It is usually associated with non-communicable diseases (NCDs), such as obesity, metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and so on (Met-S) [1]. For the treatment for these diseases, adequate nutritional therapy and weight control would be required. As regard to Type 2 diabetes mellitus (T2DM), it is important to reduce several risks of macroangiopathy and microangiopathy [2]. In other words, optimal control of daily profile of blood glucose, adequate treatment for diabetes using oral hypoglycemic agents (OHAs) and/or injectable agents are important, as well as patient-oriented medical goal [3]. Concerning the therapy for T2DM, the basic principle is adequate nutritional treatment. For previous decade, the usual diet therapy was calorie restriction (CR), in which fat food was limited for reducing total calorie. After various nutritional practice and research, low carbohydrate diet (LCD) was introduced for effective way of managing T2DM [4]. Clinical efficacy of LCD has been proposed with several studies for years in European and

North American regions [5,6]. On the other hand, authors and collaborators have started LCD in Japan and developed LCD therapy in Japan until now [7]. We established Japan LCD Promotion Association (JLCDPA), and continued development of LCD medically and socially through many opportunities for workshops, seminars, medical societies and books [8]. For practical use, three recommended type of LCD have been informed broadly. They are super LCD, standard LCD and petite LCD with carbohydrate ratio as 12%, 26%, and 40%, respectively [9]. Moreover, clinical research has been continued with several medical themes, such as daily profile of blood glucose, insulinogenic index (IGI), Morbus (M) value, meal tolerance test (MTT), continuous glucose monitoring (CGM) and clinical application of Xultophy [10]. In the light of pharmacological agents, several kinds of glucagon like peptide-1 receptor agonists (GLP-1RAs) have been used in the diabetic therapy [11]. For example, there are liraglutide, dulaglutide, lixisenatide, exenatide, and others [12]. Among some research for GLP-1RAs, Network Meta-Analysis (NMA) showed the useful evaluation clinically for

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diabetic control and also some outcomes for atherosclerotic cardiovascular disease (ASCVD) [13]. As a result, the effect of cardiometabolic benefits was found by using GLP-1RA regimens. In the group of GLP-1RA agents, liraglutide has been effective and rather widely applied to diabetic patients. Related to this prevalence, Xultophy has been made and used for actual practice as the combination of liraglutide and insulin degludec [14]. When compared with either one agent each, this combined agent revealed better effect [15]. GLP-1RA brings the improved findings for reducing fasting plasma glucose and postprandial glucose [16]. Furthermore, basal insulin brings the improved result for decreasing fasting plasma glucose, and this combined agent with fixed ratio can lead improved general diabetic control by injection once per day. In addition, Xultophy has the efficacy to maintain cardioprotective activity by improving the function of beta cell in the pancreas [17]. Diabetic practice and research for years concerning CGM, MMT, Xultophy and others. Among our experience, a female elderly case receiving the treatment of Xultophy was found. She showed the effect of Xultophy, as well as the meaningful perspective from bio-psycho-social points of view. Xultophy may be useful in the light of patient-oriented medicine which is the recommended goal for medical practice. In this article, the clinical course and some discussion will be described.

Case Presentation

Past history

When she was 59 years old, she was pointed out to have type 2 diabetes mellitus (T2DM). After that, she had several diseases until 69 years old, including hypertension, atrial fibrillation (Af), hyperlipidemia, cerebral infarction in the left thalamus to slight degree and gastro esophageal reflux disease (GERD). Successively, she had developed arthralgia of large joints, and was diagnosed as rheumatoid arthritis (RA) at the age of 70 years old. When she was around 75 years old, she complained of left low back pain, associated with the diagnosis of left ureteral stone, bilateral renal stone and osteoporosis. Her arthralgia has been controlled by small doses of prednisolone 5 mg/day for the treatment of RA during 70 to 79 years old. Regarding the medical history from Feb 2017 to Nov 2020, she received a simple operation of abdominal wall scar hernia. Endoscopic examination was performed once a year for upper gastrointestinal tract, which showed reflux esophagitis (GERD grade D). The results on Feb, 2021 included i) GERD grade D (reflux esophagitis), ii) hiatal hernia slippery type, severe, iii) chronic active gastritis (atrophic gastritis) C-III, yellow tumor in the stomach, and iv) subduodenal mucosa, which are not particularly problematic.

Present history

She has been diabetic for 20 years and taking insulin for 1 year. In late Dec 2020, her lower body became weakened, which caused her to fall down a few times. This episode brought her back pain and inability to get up. She was transferred to Tokushima Red Cross Hospital (TRCH) and was proved to show low blood glucose as 55 mg/dL. On her spine XP, compression fractures were found in three locations, Th12, L4, and L5. Head CT shows periventricular hyperlucency and many small previous lacuna infarcts in the basal ganglia. Chest XP showed mild bronchopneumonia in the upper right lobe. No obvious fever was observed, SpO₂ was in the normal range, and Ceftriaxone Sodium Hydrate (CTRX) 1g was administered every 12 hours for some days. Gradually, her general condition improved, and she was transferred to Hayashi hospital. In the past few months, she has been difficult to properly manage insulin injections by MDI, because she could not inject properly predetermined units of insulin.

Current insulin treatment

She has a long history of diabetes and has recently received insulin treatment. After hospitalization in late Dec 2020, she had Multiple Daily Injections (MDI) to control blood glucose [18]. The long-acting insulin used was administered with glargine once before bedtime, and the fast-acting insulin was administered with insulin human three times daily before meals. As to insulin units, insulin human was given three times a day by the sliding scale procedure at pre-prandial time [19]. The method was as follows. i) 61-80 mg/dL: glucose 10g per os, ii) 81-200 mg/dL human 0 unit, iii) 201-250 mg/dL: 2 units, iv) 251-300 mg/dL: 4 units, v) 301-350 mg/dL: 6 units, vi) 351- mg/dL <: 8 units. In fact, the diurnal variation in blood glucose was 107-215-217-274 mg/dL, which was poorly controlled.

Physical examination

Consciousness is alert, and speech is ordinary. Vitals showed pulse rate 67/min, and blood pressure 130/67 mmHg. Her physique showed 148 cm in height, 68kg in weight, 31 kg/m² in body mass index (BMI) with ideal body weight (IBW) as 48.2kg. Physicals showed that lung vesicular, heart no significant murmurs, abdomen soft, flat, no tenderness, bowel sound audible. Neurological findings showed unremarkable.

Several examinations

The results of several examinations on admission to Hayashi Hospital were as follows. Hb 10.2 g/dL, RBC 422 x 10⁶ /μL, Ht 32.5%, MCV 77 fL (80-98), MCH 24.2 pg (27-34), MCHC 31.4 g/dL (31-36), WBC 8800 /μL, Plt 35.2 x 10⁴ /μL, BUN 27 mg/dL, Cr 1.41 mg/dL, uric acid 6.6 mg/dL, eGFR 28 mL/min/1.73m², TG 75 mg/dL, HDL-C 51 mg/dL, LDL-C 87 mg/dL, T-C 153 mg/dL, TP 5.9 g/dL, Alb 3.3 g/dL, A/G ratio 1.27, Alb 55.9%, a₁-

glb 4.0%, α_2 -glb 11.5%, β -glb 11.8%, γ -glb 16.8%, AST 13 U/L, ALT 7 U/L, γ -GT 13 U/L, ALP 199 U/L, LDH 229 U/L (100-340), LAP 41 U/L (30-70), ChE 198 U/L (213-501), T-Bil 0.5 mg/dL, CK 69 U/L (41-153), amylase 48 U/L (35-125), CRP 3.15 mg/dL, HBs Ag negative, TSH 5.9 μ IU/mL (0.35-4.94), free T₄ 1.16 ng/dL (0.7-1.48). Concerning diabetes, HbA1c 8.0%, fasting blood glucose 116 mg/dL, Urinary C-peptide 24.4 μ g/day (23-155), urinary albumin 199 mg/day (2-20). Other examinations except blood tests were as follows: Hasegawa Dementia Scale-Revised (HDS-R) 20 points (22-30). Mini-Mental State

Examination (MMSE) 20 points (20/30). Chest X-P showed mild pulmonary congestion with CTR 55%. Electrocardiogram (ECG) showed atrial fibrillation (Af). Several tests included that no retinopathy in fundus, nerve conduction velocity (NCV) within normal limits, the coefficients of variation of RR intervals (CV-RR) 1.95%, abdominal echo showed chronic liver disease and hemangioma in the segment 5 (10 x 7 x 10mm), ankle brachial index (ABI) 1.13/1.19. cardio-ankle vascular index (CAVI) 10.0/10.0.

Table 1: Changes in daily profile of blood glucose for MDI and Xultophy.

Date	Daily profile of Blood Glucose				Treatment		
	morning (mg/dL)	noon (mg/dL)	evening (mg/dL)	night (mg/dL)	Xultophy (doses)	Human (unit)	Glargine (unit)
-7	107	186	304	228		0-0-6-2	4
-6	99	217	264	202		0-2-4-2	4
-5	100	280	206	276		0-4-2-4	4
-4	96	309	119	257		0-6-0-4	4
-3	99	241	188	236		0-2-0-2	4
-2	109	256	181	236		0-4-0-2	4
-1	98	276	157	273		0-4-0-4	4
1	92		230		5		
2	96		270		5		
3	100		282		6		
4	111		232		6		
5	92		225		6		
6	87		233		7		
7	87		300		7		
8	104		241		7		
9	93		295		8		
10	88		190		8		
11	95		210		8		
12	75		174		8		
13	79		226		8		
14	86		230		8		
15	69		discharge		8		

Problems and prescription

From mentioned above, current medical problems are summarized in the following. #1 T2DM: MDI treatment, #2 bronchopneumonia: antibiotics given, #3 compression fractures of spine: (Th12, L4, L5). #4 RA: prednisolone 5mg/day administration, #5 Af, #6 GERD: grade D (reflux esophagitis). The prescriptions concerning medical problems include amlodipine besilate (Amlodine ®) 5mg 1T, prednisolone (Predonin ®) 5mg 1T, edoxaban tosilate hydrate (Lixiana ®)

30mg 1T, celecoxib (Celecox ®) 100mg 4T /day, rebamipide (Mucosta ®) 100mg 3T /day, suvorexant (Belsomra ®) 10mg 1T vds. As an evaluation of nutritional status, mild undernutrition is observed from the decreased data in TP, Alb, and A / G ratios, and anemia is observed from a low Hb value. Meals during hospitalization include 1600 kcal / day, protein 59 g / day, and water 1362 ml / day. In addition, there are moderate nutritional risks, mild undernutrition, obesity and anemia. The meal content was set to 1600 kcal, protein 59 g, water 1362 ml, and salt 6.2 g or less per day.

Clinical course

It was difficult for the patient to perform MDI completely due to the sliding scale three times a day. Several reasons were present, such as i) existing rather dementia of the patient, ii) the cooperation of the family is difficult during the daytime, and others. Consequently, the treatment for glucose variability was decided to start injection of Xultophy, which can be injected once a day. It started on January 25th at 5 doses of Xultophy. The changes of the glucose daily profile during the clinical course was summarized in **Table 1**. As a result, the application of Xultophy seemed to bring satisfactory glucose control. The successful results have encouraged the patient and also the family to continue diabetic therapy with Xultophy associated with adequate regular lifestyle. When she was discharged from the hospital, the infection was completely cured and diabetes control was good. The value of HbA1c during Dec 2020 to Feb 2021 was 8.0%, 7.1% and 7.2%, respectively. The prescription at discharge was i) ipragliflozin L-proline (Sugra ®) 50 mg / day, ii) azilsartan (Azilva ®) 20 mg 1T, iii) suvorexant (Belsomra ®) 10 mg 1T 1 x vds, iv) vonoprazan fumarate (Takecab ®) 10 mg 1T (Table 1).

Discussion

Historically, diabetic treatment has been developed including oral hypoglycemic agents (OHAs) and some kinds of injections such as insulin and GLP-1RA. For better control of glucose variability, insulin treatment was recommended as the regimen of basal-bolus injection [20]. For further natural changes in glucose and insulin, multiple daily injection (MDI) was recommended for standard method of controlling blood glucose as possible. It is indeed that it is ideal situation, but continuous 3-4 times daily injections seem to be taken too much efforts for the diabetic patient and family. Recent topic includes clinical introduction of Xultophy to patients with T2DM, which seems to be effective, convenient and useful way of regimen [14]. Some consecutive studies of clinical effect of Xultophy are observed, that is the European Xultophy Treatment Retrospective Audit (EXTRA) study. There was a real-word evidence (RWE) study (EXTRA) from the European diabetes centers [21]. As a result, significant decrease of HbA1c level (0.7%) and weight reduction (2.4 kg) for 6 months were found in the cases who have changed the treatment from MDI to Xultophy. EXTRA study has included more than 600 cases in 5 countries. The results showed that initiation treatment brought 0.9% HbA1c decrease for 6 months ($p < 0.001$) [22]. From these data, Xultophy was estimated to reveal effective and useful injectable agent, as well as convenient regular lifestyle of the patient and the family. This case was firstly admitted to the diabetes department in a large hospital and had been treated with MDI. When her clinical situation became stable, she was transferred to our hospital. The MDI method is certainly ideal for

glycemic control, but it is not easy to continue in her daily life [18]. During hospitalization, medical staffs can help management of MDI treatment with sliding scale method. However, when the patient is at home, it is not easy to continue it for the patient and family. In this case, the treatment was changed from MDI to Xultophy once a day. The first amount were 5 doses. The standard method of administration of Xultophy is to start with 16 doses in the patients with already treated on insulin [14]. When the patient is naïve for using insulin, the recommended doses would be 10 doses. However, there seem to be different situation between Western countries and Eastern countries. Authors have some clinical experiences to control glucose variability by Xultophy with small doses [23]. With reference to our former cases, this case was started to be provided Xultophy from small doses. After that, we increased the doses of Xultophy up to 8 doses, where the profile of blood glucose became rather stable. The case is elderly patient associated with several medical problems, then we did not intend to maintain the strict control of diabetes. Another factor would be present. The case has been taking prednisolone for the anti-inflammatory effect against RA. Based on her medical history, she was diagnosed as T2DM 20 years ago, and was diagnosed as RA 9 years ago. Then, she started to be taken prednisolone. From this history, it is suggested that the elevated blood glucose may be from several causes, including i) the presence of primary T2DM, ii) inflammatory influence of RA and iii) secondary influence of steroid administration [24]. Current diurnal fluctuations in blood glucose show lower in the morning and higher in the evening. If the time period of providing prednisolone changes, the daily profile of blood glucose may change [23]. When a diabetic patient is taking steroids for RA, it is difficult to evaluate detail glucose variability because hyperglycemia is influenced from both of diabetes and steroids. From Pubmed database, complete literature search was conducted for all relative reports [25]. The combined keywords included DM, insulin, hyperglycemia, glucocorticoids therapy, glucose-lowering drugs, SGLT-2i, GLP-1RA, DPP-4i. Related to these factors, further accumulation of data would be expected for future investigation and analysis. This case seemed to have characteristic glycemic variability. She was satisfactory pre-prandial glucose level in the early morning. However, post-prandial glucose level in the afternoon was rather higher. For improving this tendency, provided dose in Xultophy was increased, but rather hyperglycemia was persisted. Possible reason may be included from the medical history and laboratory data. She has chronic inflammatory situation due to RA, and decreased values of TP, albumin, A/G ratio. From these, possible existence of liver dysfunction may bring the influence of converting glucose into glycogen associated with reduced restoring function [26]. Consequently, overloaded glucose may flow into blood vessels, which causes acute glucose elevation

after meal period [27]. If the patient has impaired liver function, gluconeogenesis in the liver would be decreased. Consequently, glucose level would be lower in the early morning [28]. Regarding the background of the case, detail situation would be evaluated from three aspects which are bio-psycho-social axes [29]. The first is bio-axis. For stable control of blood glucose, a series of treatments called blood glucose measurement-sliding scale method-MDI is ideal. However, it seems to be not easy as a matter of fact. From the clinical effect of Xultophy, a satisfactory level of therapeutic efficacy is expected. The second is psycho-axis [30]. The patients themselves are elderly and managing the MDI method can be a hassle. In addition, there is a borderline condition for dementia and/or mild cognitive impairment (MCI). Based on the above, the application of Xultophy is recommended. The third is social-axis. It is preferable that the patient's family can contribute to the coverage of the treatment to some extent. For this point, it is difficult for the family to cooperate with the MDI method. On the other hand, the injection of Xultophy once a day has the advantage of possible assistance. Considering the mentioned axes above, Xultophy is considered to be preferable news for elderly diabetic patients. Regarding the course of HbA1c in this case, it was stable at 7.1-7.2% in Feb-Mar 2021. There are some limitations in this report. We report here one case with satisfactory results of Xultophy administration from various points of view. Further accumulation of cases would be required for future research. Medical staffs have to consider the background of the patient such as family situation. Xultophy is reported to have wide beneficial efficacy and further detail investigation will be expected [31]. In summary, a patient with T2DM was treated with Xultophy and several perspectives were discussed. For older diabetic patients, Xultophy would be probably recommended for better control of glucose variability and for improved daily life from bio-psycho-social points of view. This report becomes hopefully a reference for diabetic clinic and research in the future.

Conflict of Interest

The authors declare no conflict of interest.

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