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Case Report

Effective Xultophy administration to stable blood glucose profile by Continuous Glucose Monitoring (CGM)

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ABSTRACT
Type 2 diabetes mellitus (T2DM) need adequate diet, exercise and pharmacotherapy. Authors have continued diabetic practice and research on low carbohydrate diet (LCD), calorie restriction (CR), continuous glucose monitoring (CGM), and so on. The case is 50-year-old female patient with T2DM for 10 years. She has received insulin treatment with recent HbA1c 7.4 – 8.7%, then her glucose profile was studied on CGM by FreeStyle Libre. Treatment was changed from Glargine 15 units (until day 5) to Zultophy10-12 doses (after day 6), then her glucose variability showed remarkably improved. The average blood glucose on day 3, 5, 6, 8,10,13 was 174, 164, 125, 111, 101, 98 mg/dL, respectively. FreeStyle Libre showed estimated HbA1c as 6.2% and 44 mmol/mol.

Key words: Glucagon-like peptide-1 receptor agonist (GLP-1 RA), Japan LCD promotion association (JLCDPA), Continuous Glucose Monitoring (CGM), FreeStyle Libre, Xultophy

Abbreviations: LP-1 RA: Glucagon-like peptide-1 receptor agonist; JLCDPA: Japan LCD promotion association; CGM: Continuous Glucose Monitoring

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INTRODUCTION

Recently, diabetes mellitus is crucial disease to be managed and prevented adequately in the world [1]. When patients are in diabetic states, they will have various chronic complications, including microangiopathy and macroangiopathy [2]. In order to prevent and delay the diabetic progress, there are three kinds of principle therapies. They are nutritional therapy, exercise therapy and pharmacotherapy, which are universally common fundamental method in all countries [3].

Regarding diabetic nutritional therapy, there have been generally two kinds. They are low carbohydrate diet (LCD) and calorie restriction (CR) [4]. Recently, LCD has been evaluated to be rather effective compared with CR in lots of reports [5,6]. In western countries, LCD became well-known by Bernstein and others [7]. On the other hand, authors and co-researchers have initiated LCD in Japan [8]. We have developed LCD medically and socially through the activity of Japan LCD promotion association (JLCDPA) [9]. Further, our research team continued several reports concerning daily profile of blood glucose, M value, elevated ketone bodies in blood, meal tolerance test (MTT) and continuous glucose monitoring (CGM) [10]. As to CGM, we had reported impressive diabetic cases and clinical usefulness for detecting hyperglycemia associated with various daily activities [11].

Authors have reported some diabetic cases with efficacy for oral hypoglycemic agents (OHAs) and/or injective treatment [12,13]. Recently, there are injective vials for diabetes, which are insulin and

glucagon-like-1 receptor agonists (GLP-1 RAs). Furthermore, one of the new topics would be the combined vial of insulin and GLP-1 RA, Xultophy [14]. It shows remarkable glucose-lowering effect and its administration has been increasing [15]. We have currently an experience of a patient with type 2 diabetes mellitus (T2DM), who showed remarkable effect of Xultophy. Then, the analyzed data on CGM will be described in this article.

CASE REPORT

History of Present Illness: Current case is 50-year-old female patient with T2DM, who has medical history of 10 years of duration. As to diabetic therapy, she has been provided insulin treatment for long. Her control status has not been so satisfactory, where HbA1c persisted about 7.4 – 8.7% so far. In order to make diabetic control better, we investigated her glucose variability by using FreeStyle Libre.

Physical examination: She had no remarkable status in the physical examination, or no remarkable abnormalities of consciousness disorders from hypo- or hyperglycemia. Her vital signs were normal, and her body mass index (BMI) has been 21.5 kg/m^2. She has slight numbness in the extremities, which is supposed to be diabetic neuropathy. However, she did not have retinopathy, nephropathy or other macroangiopathic complications.

Laboratory exam: The results of laboratory exams were shown in the following. The standard biochemical data were AST 21 U/mL, ALT 24 U/mL, r-GT 25 U/mL, BUN 17 mg/dL, Cre 0.6 mg/dL, Uric Acid 5.5 mg/dL, HDL 39 mg/dL, LDL 102 mg/dL, postprandial TG 351 mg/dL, WBC 6300 /μL, RBC 4.45 x 10^6/μL, Hb 13.5 g/dL, Plt 26.2 x 10^4/μL. Data related diabetes were HbA1c 7.9%, pre-prandial glucose 157 mg/dL.

Insulin therapy: For insulin treatment, she has been provided for years by the method of multiple daily insulin injection (MDI). She was given two kinds of insulin with four times a day. The insulin agents were Novo rapid (Novo Nordisk) provided 3 times a day just before 3 regular meals, and insulin Glargine (Eli Lilly and Company) one per day at night approximately at 2100h. For last weeks, her dose amount of rapid insulin was 21, 19, 18 units of Novo rapid and 15 units of Glargine.

Application of Xultophy: For new application of Xultophy, she was given Xultophy once at 2100h, instead of previous Glargine. The protocol was as follows: Glargine 15 units on June 25-28 (day 1-4), Zultophy 8 units on June 29-30 (day 5-6), 10 units on July 1 and 2 (day 7-8), 11 units on July 3-4 (day 9-10), 12 units after July 5 (after day 11)

Methods

In this case, the detail glucose variability was measured by using by FreeStyle Libre (Abbott, USA) [16]. Her blood glucose daily profile was investigated for 2 weeks. As to continuous glucose monitoring (CGM), FreeStyle Libre (Abbott, USA) has been known which shows stable reliability for blood glucose [17]. It can show beneficial results such as point accuracy, trend accuracy, and the stability of the sensor, alarms, calibration, time lag and traceability [18]. It also revealed satisfactory results for the guideline of Clinical and Laboratory Standards Institute (CLSI) [19].

Results

The case has used CGM apparatus FreeStyle Libre satisfactory for 2 weeks. The results of blood glucose daily profiles are shown in Figure 1. It shows gradually improving glucose variability. Glucose variability showed rather unstable on day 3 and 5 giving Glargine 15 units at 2100h. Glucose variability on day 6 and 8 became more stable than before, during Xultophy 8 and 10 units. Glucose variability on 10 and 13 became more stable, during Xultophy 11 and 12 units.

The average blood glucose per day on day 3, 5, 6, 8, 10 and 13 showed 174, 164, 125, 111, 101 and 98 mg/dL, respectively. The software of FreeStyle Libre can calculate HbA1c value from the data of daily blood glucose. Estimated HbA1c value was 6.2% and/or 44 mmol/mol. On the other hand, HbA1c value in the outclinic in June 2020 was 7.9% or 60 mmol/mol. Both data has some discrepancies between them.

Discussion

In recent years, CGM has been rather prevalent in the diabetic practice [20]. Originally, it was a sensor-based device for diabetic patients. One of the most famous apparatus is FreeStyle Libre, which is produced by Abbott diabetes Care Inc., US [16]. It was evaluated to be reliable for long years, because it has simple function and good mechanism for obtaining blood glucose variability. Further, it is also useful and convenient for its small size and for giving precise data of blood glucose [17].

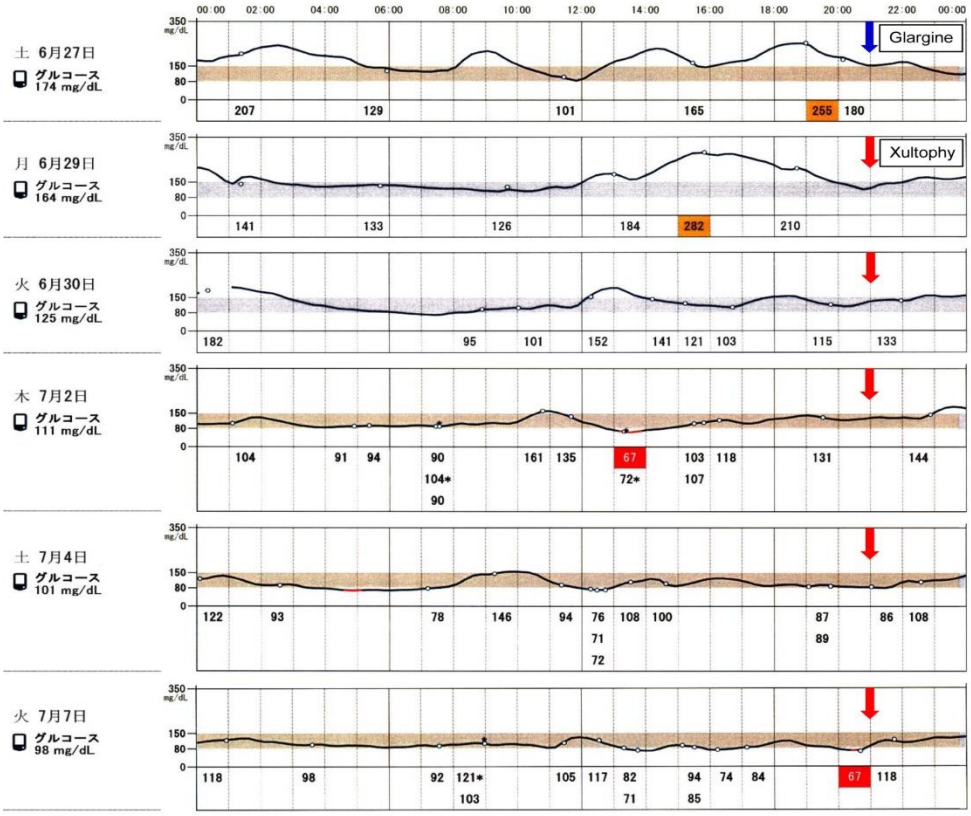

Figure 1: - The changes in the profile of blood glucose using FreeStyle Libre

In current study, some difference of HbA1c value was found between 7.9% in out clinic and 6.2% calculated by the software of FreeStyle libre. There was similar report like this situation [21]. One of the reasons for this phenomenon would be that CGM would not detect occasional acute increasing spike in blood glucose. As a matter of fact, blood glucose values are calculated in every 7.5 to 15 minutes in FreeStyle Libre and also FreeStyle Libre Pro devices [22]. These problems will be investigated from several points of view.

In this study, the case has changed the injective vial from Glargin to Xultophy. Xultophy includes combination of insulin and GLP-1 RA. As to doses of the Xultophy, 1 dose contains insulin degludec 1 unit and liraglutide 0.036 mg [14]. It is usually injected to the patients from 10 to 50 units. One Xultophy pen is prefilled by 300 doses of Xultophy 100/3.6. It means insulin degludec 300 units, and liraglutide 10.8 mg. The pen has no push-button extension or the doses button does not extend during the dialing behavior the amount [14]. The usually regimen reveals once-daily administration, and it shows less frequencies of weight gain or hypoglycemia in comparison with other intensive insulin treatment methods. In addition, it has less gastrointestinal reverse effects when compared with those of GLP-1 RA administration alone [14, 15].

In this case, Xultophy was firstly injected at 2100h on June 29. Her daily profile of blood glucose was improved after that. Average blood glucose has also gradually decreased from 164 mg/dL to 98 mg/dL. Consequently, this case showed remarkably good response for Xultophy. It suggests that pancreas function may be preserved for the stimulus of GLP-1 RA. Authors had recently a similar case treated by Xultophy with remarkable improvement of glucose variability [23]. The case was 79-year-old female with

probable secondary diabetes due to steroid administration. Clinically rapid reduction of HbA1c suggested the presence of preserved pancreas function.

There are currently two standard guidelines for diabetes mellitus. They are the American Diabetes Association (ADA) Standards of Medical Care in Diabetes—2020 [24] (American) and also the 2019 "Consensus Statement by the American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology (ACE) on the Comprehensive Type 2 Diabetes Management Algorithm" [25] (Garber-2019). Both guidelines have comments for the recommendation to physicians in charge. It is the necessity to consider the combination of injection treatment for post-prandial hyperglycemia in the diabetic cases who reveal fundamental insulin doses 0.5 units/kg/day with higher HbA1c level [24] (American-2020). Consequently, we can always consider the adequate treatment for various diabetic patients with insulin, GLP-1 RA, and other OHAs in the future practice and research.

In summary, this article described a diabetic case with clinical remarkable improvement by Xultophy. The glucose variability was investigated by CGM using FreeStyle Libre. These detail data would hopefully become some reference for future diabetic practice and research.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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REFERENCES

[1] American Diabetes Association (ADA) (2020) 3. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020 Jan; 43(Supplement 1): S32-S36. https://doi.org/10.2337/dc20-S003
[2] Mauricio D, Alonso N, Gratacòs M (2020) Chronic Diabetes Complications: The Need to Move beyond Classical Concepts. Trends in Endocrinology & Metabolism. doi:10.1016/j.tem.2020.01.007
[3] International Diabetes Federation (2019) Diabetes Atlas, 8th edition, http://www.diabetesatlas.org/
[4] Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, *et al*. (2015) Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. Nutrition, 31(1), 1–13. doi:10.1016/j.nut.2014.06.011
[5] Shai I, Schwarzfuchs D, Henkin Y, *et al*. (2008) Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. N Engl J Med. 359: 229-241.
[6] Tay J, Thompson CH, Luscombe-Marsh ND, *et al*. (2018) Effects of an energy-restricted low carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. Diabetes Obes Metab. 20:858–871. https://doi.org/10.1111/dom.13164
[7] Bernstein RK (1997) Dr. Bernstein's Diabetes Solution. Little, Brown and company, New York.
[8] Ebe K, Ebe Y, Yokota S, Matsumoto T, Hashimoto M, Sakai Y, *et al*. (2004) Low Carbohydrate diet (LCD) treated for three cases as diabetic diet therapy. Kyoto Medical Association Journal 51: 125-129.
[9] Muneta T, Kagaguchi E, Nagai Y, Matsumoto M, Ebe K, Watanabe H, Bando H (2016) Ketone body elevation in placenta, umbilical cord, newborn and mother in normal delivery. Glycat Stress Res 3 (3): 133-140. doi.org/10.24659/gsr.3.3_133.
[10] Bando H, Ebe K, Muneta T, Bando M, Yonei Y (2017) Effect of low carbohydrate diet on type 2 diabetic patients and usefulness of M-value. Diabetes Res Open J. 2017; 3(1): 9-16. doi: 10.17140/DROJ-3-130.
[11] Ebe K, Bando H, Muneta T, Bando M, Yonei Y (2019) Remarkable improvement of glucose variability by Sodium–glucose cotransporter 2 (SGLT2) inhibitors using continuous glucose monitoring (CGM). Diabetes Case Rep 2019, 4:1. DOI: 10.4172/2572-5629.1000139
[12] Kato Y, Bando H, Yamashita H, Yada S, Tokuhara S, Tokuhara H, Mutsuda (2019) Seasonal changes in HbA1c values from young to elderly diabetic patients. J Diabetes Metab Disord Control. 2019;6(3):89–92. DOI: 10.15406/jdmdc.2019.06.00187

[13] Bando H, Ebe K, Kato Y, Bando M, Yonei Y (2018) Investigation of Blood Glucose Profile by Continuous Glucose Monitoring (CGM). Endocrinol Res Metab Vol. 2 No 1:9. Homepage of Xultophy®. https://www.xultophy10036pro.com/
[14] Melzer-Cohen C, Chodick G, Naftelberg S, *et al*. (2020) Metabolic Control and Adherence to Therapy in Type 2 Diabetes Mellitus Patients Using IDegLira in a Real-World Setting. Diabetes Ther 11, 185–196. https://doi.org/10.1007/s13300-019-00725-9. Abbott Diabetes Care. https://www.myfreestyle.com/freestyle-libre-pro-cgm-system
[15] Edge J, Acerini C, Campbell F, Hamilton-Shield J, Moudiotis C, Rahman S, *et al*. (2017) An alternative sensor-based method for glucose monitoring in children and young people with diabetes. Arch Dis Child 102(6):543-549. doi: 10.1136/archdischild-2016-311530.
[16] Klonoff D, Bernhardt P, Ginsberg GH, *et al* (2008) A performance metrics for continuous interstitial glucose monitoring; approved guideline. Ed by Institute CalS, USA, CLSI, p1-57.
[17] Slattery D, Choudhary P (2017) Clinical Use of Continuous Glucose Monitoring in Adults with Type 1 Diabetes. Diabetes Technol Ther 19(S2):S55-S61. doi: 10.1089/dia.2017.0051.
[18] Taylor PJ, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Wittert G (2019) Efficacy of Real-Time Continuous Glucose Monitoring to Improve Effects of a Prescriptive Lifestyle Intervention in Type 2 Diabetes: A Pilot Study. Diabetes Ther: 10: 509. https://doi.org/10.1007/s13300-019-0572-z
[19] Abbott Diabetes Care. https://www.myfreestyle.com/freestyle-libre-pro-cgm-system
[20] Edge J, Acerini C, Campbell F, Hamilton-Shield J, Moudiotis C, Rahman S, *et al*. (2017) An alternative sensor-based method for glucose monitoring in children and young people with diabetes. Arch Dis Child 102(6):543-549. doi: 10.1136/archdischild-2016-311530.
[21] Fokkert MJ, van Dijk PR, Edens MA, Abbes S, de Jong D, Slingerland RJ, *et al*. (2017) Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. BMJ Open Diabetes Res Care 17;5(1):e000320. doi: 10.1136/bmjdrc-2016-000320. eCollection 2017.
[22] Ólafsdóttir AF, Attvall S, Sandgren U, Dahlqvist S, Pivodic A, Skrtic S, *et al*. (2017) A Clinical Trial of the Accuracy and Treatment Experience of the Flash Glucose Monitor FreeStyle Libre in Adults with Type 1 Diabetes. Diabetes Technol Ther. 19(3):164-172. doi: 10.1089/dia.2016.0392.
[23] 23) Kato Y, Bando H, Yamashita H *et al*. Impressive clinical course of diabetic patient with various medical problems and remarkable improvement by insulin degludec and liraglutide (Xultophy). MOJ Clin Med Case Rep. 2020;10(2):48–51. DOI: 10.15406/mojcr.2020.10.00341
[24] American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020;43(Suppl. 1):S98–S110
[25] Garber AJ, Abrahamson MJ, Barzilay JI, *et al*. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2019 executive summary. Endocr Pract 2019;25:69–100