



Effective SGLT2 Inhibitor for Patient with Type 2 Diabetes Mellitus (T2DM) and Depression

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Abstract

The case was a 55-year-old female patient with depression for 5 years and type 2 diabetes mellitus (T2DM) for 3 years. She has received anti-depressant and anti-hyperglycemic agents (OHAs). Approximately 1 year ago, her diabetic control became exacerbated without specific triggers. She was started to given Ipragliflozin L-Proline as Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor. After that, her glucose variability and depression had been improved. According to the previous reports, SGLT-2 inhibitors seem to have anti-depression efficacy for diabetes. The case has been followed up in detail, and this report is expected to be a useful reference for diabetes care.

Keywords

Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor; Ipragliflozin L-Proline; Depression; Oral Hypoglycemic Agents (OHA); Low-Carbohydrate Diet (LCD)

Abbreviations

T2DM: Type 2 Diabetes Mellitus; SGLT2: Sodium-Glucose Cotransporter-2; LCD: Low-Carbohydrate Diet; OHA: Oral Hyperglycemic Agents; DPP-4: Dipeptidyl Peptidase-4

Introduction

Diabetes mellitus has been one of the crucial diseases from medical and economical points of view [1]. It has been prevalent across the world including developed countries and also developing countries. For adequate glycemic control, there are some diabetic standard guidelines [2,3].

Regarding the therapy of diabetes mellitus, nutritional treatment has been the fundamental treatment including various dietary methods such as

calorie restriction (CR), Mediterranean diet, low-carbohydrate diet (LCD) and so on [4]. LCD was initiated by Bernstein and other investigators in the North American region [5,6]. Successively in Japan, LCD was started and developed by author and colleagues so far through the Japan LCD promotion association (JLCDPA) [7,8].

Regarding the pharmaceutical aspect of diabetes, there have been recently several kinds of effective oral hyperglycemic agents (OHA). They include α -

glucosidase inhibitors, glinides, dipeptidyl peptidase-4 (DPP-4) inhibitors and Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors [9]. In particular, DPP-4 inhibitors and SGLT2 inhibitors have been in focus for clinical diabetic practice and research [2].

On the other hand, a certain relationship between type 2 diabetes mellitus (T2DM) and depression has been known for various studies [10]. The prevalence of depression in T2DM is lower in East Asia and higher in the US and Europe [10]. The ratio would be 10.6% in the US, 9.3% in the UK and 6.1% in China, and female cases show higher prevalence than male in each country [11-13].

T2DM has been suggested to be one of the risk factors for depressive state or depression [14]. Furthermore, both diabetes and depression have been independent risk factors for developing dementia [15]. Thus, these three factors would be highly risky for brain atrophy with hippocampal atrophy by brain MRI [16]. Consequently, it is crucial to prevent exacerbation of diabetes and depression.

Regarding the two topics mentioned above, there was a report related to OHA and depression in diabetic patients [9]. Among them, the influence of the administration of DPP-4 and SGLT2 inhibitors for developing depression are shown. These aspects would be meaningful for diabetes practice in the actual out clinic and primary care setting.

The authors have continued diabetic research for long in several axes [17]. They include a daily profile of blood glucose, M value, continuous glucose monitoring (CGM), elevated ketone bodies, comparison of CR and LCD, elevated ketone bodies in fetus-placenta-pregnant woman-newborn, and so on [18,19]. During our diabetic practice and research, we have an impressive case associated with diabetes and depression. Then, we describe the case and some discussions in this article.

Case

Present History:

The case was a 55-year-old female patient with T2DM. She has diagnosed as a depressive state 5 years

ago and has received anti-depressant agents. About 3 years ago, she was pointed out to have diabetes in another psychosomatic clinic. At that time, her data included moderate obesity, negative anti-GAD antibody, and T2DM as a diagnosis.

After that, her general status including depression and diabetes had been stable. Then she hoped to be treated at a nearer hospital and was introduced to our hospital.

Physicals:

We have evaluated her diabetes in detail. She has slight peripheral neuropathy in the hands and feet, no apparent retinopathy and stage 1 nephropathy. Regarding physical examination, she showed normal vital signs and unremarkable physical status (pulse 76, BP 112/77, SpO₂ 96%), and no consciousness or feeling disorders from hyper- or hypoglycemia. She has moderate obesity, with the body mass index (BMI) 28.7 kg/m².

Laboratory Exam:

The data of the laboratory tests were in the following. The fundamental peripheral blood and biochemical data were: WBC 5100 / μ L, RBC 4.31 x 10⁶ / μ L, Hb 13.6 g/dL, Plt 22.1 x 10⁴ / μ L, AST 20 IU/mL, ALT 30 IU/mL, ALP 197 IU/mL (100-340), LD 158 IU/mL (100-210), T-Bil 0.5 mg/dL, BUN 14 mg/dL, Cre 0.8 mg/dL, Uric Acid 5.4 mg/dL, Na 141 mmol/L, K 4.3 mmol/L, Cl 104 mmol/L, HDL 69 mg/dL, LDL 155 mg/dL, TG 226mg/dL. Data related diabetes were HbA_{1c} 6.7%, pre-prandial glucose 184 mg/dL. Urine analysis revealed negative for protein, sugar and ketone bodies.

Detail Evaluation:

From the data mentioned above, we have pointed out her medical problems. Her problem lists showed that #1 T2DM, #2 dyslipidemia (on anti-dyslipidemia agent), #3 metabolic syndrome, #4 osteoarthritis (OA) of the bilateral knees, #5 depression (slight).

Clinical Progress:

Successively, the same treatment had been continued and her HbA_{1c} was stable at around 6.5%.

As to the medication, she had been provided metformin 1000mg, vildagliptin 100mg and Ezetimibe 10mg per day as the treatment of T2DM and dyslipidemia.

For the depressive status, she showed rather an unstable situation with depression, general malaise and sometimes suicide desire for years. She had been provided duloxetine hydrochloride (Cymbalta) 20mg in the morning as Serotonin and Noradrenaline Reuptake Inhibitor (SNRI), mirtazapine (Reflex) 15mg before sleep as Noradrenergic and Specific Serotonergic Antidepressant (NaSSA), and etizolam (Depas) 1.0 - 1.5 mg per day as Benzodiazepine anxiolytics.

Approximately 1 year ago, her HbA1c value was suddenly elevated up to 7.9% without any special causes detected. Consequently, she was started to have Ipragliflozin L-Proline (Sugar) 25 mg as an SGLT2 inhibitor. By the administration of SGLT2-I, her blood glucose and HbA1c values were decreased to a satisfactory degree. The progress of HbA1c value, urine sugar and the administration of anti-diabetic agents were shown in (Fig-1). HbA1c was reduced from 7.9% to 6.4% and urine sugar was increased after providing of Ipragliflozin.

After 1 year from the initiation of Ipragliflozin, lipid profile revealed that HDL 65 mg/dL, LDL 110 mg/dL,

TG 128 mg/dL. Although there was not a quantitative evaluation for the degree of her depressive state, unstable psychiatric symptoms such as suicide desire have gradually disappeared after the starting of the Ipragliflozin administration.

Discussion

In recent diabetic practice, the spread of LCD and beneficial effects of SGLT2 inhibitors have been attracting attention. In the light of carbohydrates, the former is to reduce the intake of carbohydrates, and the latter is to increase the excretion of carbohydrates. Then, both seem to have a common basis for the function of carbohydrates. In this article, we report a case of T2DM showing improved glycemic variability and depression by the administration of SGLT2 inhibitors.

According to the common statement of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA), LCD has been recommended for the management of diabetes [20]. LCD is defined as the diet which reduces carbohydrate intake less than 26% of total daily energy intake. LCD has been reported to have the efficacy of reducing blood glucose in diabetic patients. On the other hand, moderate restriction of carbohydrates (26-45%) showed no additional effect [20]. Also, LCD can reduce the risk for patients with metabolic syndrome, in which the values of blood

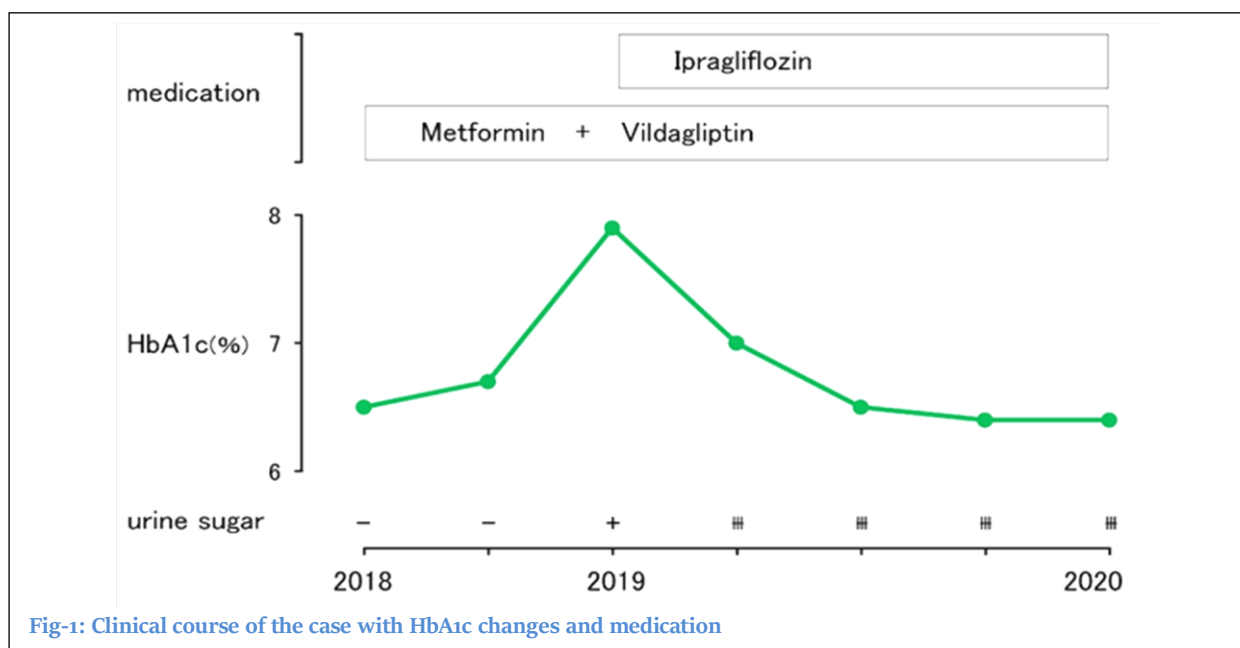


Fig-1: Clinical course of the case with HbA1c changes and medication

glucose, triglyceride and cholesterol have been reduced [21].

Recent data of the National Health and Nutrition Examination Survey (NHANES) were investigated for the effect of LCD [22]. There were some impressive and equivocal results [20]. The result was that the subjects of the lowest quartile for carbohydrate intake (39-49% of carbohydrate intake) showed the 50% elevated risk for cardio- and cerebro-vascular diseases [22]. However, despite the careful nature of their analysis [22], the cut-off for the lowest quartile of carbohydrates considered as LCD is still higher in absolute (200g/day) or relative terms (39-49% of total energy intake) compared to common LCDs. The archetypical LCD is the ketogenic diet (low carbohydrate/high fat), and ketogenic dieters consume only 10-30g/day of carbohydrates (10-20% of total energy) [21].

Other LCDs set a 50g/day carbohydrate intake per day, while moderate carbohydrate restriction allows up to 80-130g/day (26-45% of total energy) [20,21]. Therefore, the interpretation of Mazidi et al. [22] should be made with greater caution, since the study may underestimate the effect of a true LCD.

SGLT2 inhibitors have been in focus for their beneficial clinical efficacy. There have been some mega studies about them as follows: i) Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) [23], ii) Canagliflozin cardiovascular Assessment Study (CANVAS) [24], iii) Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study [25] and iv) Dapagliflozin Effect on Cardiovascular Events (DECLARE) -TIMI 58 [26].

As to the cardiovascular benefits of SGLT2 inhibitors, 38,723 patients from 4 trials for 2.9 years on average were investigated [27]. As a result, SGLT2 inhibitors could protect against CVD and death in diverse subsets of T2DM patients regardless of the CVD history [27].

One of the SGLT2 inhibitors would be Ipragliflozin

L-Proline. It has been rather prevalent and has been investigated for its efficacy in some studies. There is a STELLA-LONG TERM study, which stands for the Specified drug use results survey of Ipragliflozin treatment in type 2 diabetic patients, LONG-TERM [28]. It is a 3-year prospective post-marketing surveillance study, which is continuing on the long-term efficacy and safety of ipragliflozin [29]. Some results were reported concerning clinical effects and adverse drug reactions (ADRs) [30]. Among them, significant reductions were found in HbA1c (-0.8%), fasting plasma glucose (-31.9 mg/dL), body weight (-2.9 kg), in AST (-9.0 U/L) and ALT (-14.7 U/L) [30]. In a short period, liver function was improved in 20.5% (543/2,648) of patients after 3-month of ipragliflozin in T2DM patients with abnormal liver function [31]. As for the adverse effect of ipragliflozin, there was 0.04-0.18% of depression as psychiatric disorders, which would be very rare [28].

There was also a ASSIGN-K Study for Ipragliflozin [32]. ASSIGN-K stands for a study of the safety and efficacy of ipragliflozin in the treatment of diabetes in Kanagawa. For 301 patients with T2DM followed 104 weeks, there was the significant reduction of A1c (8.07% to 7.24%), fasting blood glucose (-19.8 mg/dL) and postprandial blood glucose (-29.6 mg/dL). In addition, both of body fat (-1.87kg) and fat-free mass (-1.02kg) were significantly reduced.

An experiment of ipragliflozin was found for giving a sugar solution to mice [33]. Experiment mice with T2DM was classified into 3 groups, in which they were fed i) ordinary drinking water, ii) water + glucose solution, or iii) water + sucrose solution. As a result, effective dose and response to ipragliflozin did not significantly differ in 3 groups. Then, anti-diabetic and anti-obesity effects of ipragliflozin were not greatly affected by sugar solution intake. Consequently, these results suggest that ipragliflozin would be an effective agent for T2DM patients, who take excessive intake of carbohydrates [33].

Depression has been one of the important complications of diabetes. In order to investigate the relationship between LCD and mental status, T2DM cases were assessed by a questionnaire for taking food

and by the depression, anxiety, and stress scale [34]. As a result, cases in the highest quartile of LCD score showed a 69% lower risk of poor sleep, and a 73% lower risk of anxiety compared with those in the lowest quartile. Consequently, T2DM patients with LCD meals seem to have better sleep conditions and less mental disorders [34].

There was a study of the association between depression in diabetes and treatment types (insulin and/or OHA) [36]. For diabetic patients of 50,774/48,978 (M/F), male subjects showed more depression of significantly higher odds ratio (OR) 1.27 in insulin, OR 1.41 in insulin and OHA, compared to those in only OHA treatment. Female showed a similar tendency, but there were no significant differences with OR 1.17 and 1.35, respectively. Thus, the influence of treatment type to depression seemed to be more in male than in female diabetic patients [35].

The risk of depression in diabetes was studied depending on different OHA [9]. T2DM subjects (n=40,214) were divided into 2 groups. Dep. group has depression (n=1979), and the cont. group has no depression (n=38,235). The adjusted odds ratio (AOR) of the dep. group was 1.39 for female and 1.18 for lower for HbA1c. Between two groups, there was no significant difference in α -glucosidase inhibitors, thiazolidinediones or glinides. In contrast, there was a significant difference (numbers of dep. group vs cont. group) in sulfonylureas (112 vs 3404), DPP-4 inhibitors (54 vs 3731), and SGLT-2 inhibitors (1 vs 378), respectively [9]. Thus, SGLT-2 inhibitors seem to have anti-depression efficacy for diabetic patients.

The case reported in this article has several distinctive features. They included i) depression was present formerly, ii) developed T2DM in the course, iii) worsened diabetic control without apparent triggers, iv) starting of SGLT2 inhibitor Ipragliflozin, v) improvement in glycemic response and depression. At that time, there were no other changes in the diabetic situation or medical agents. Therefore, clinical improvement seemed to be at least in part due to the effect of Ipragliflozin. As the limitation of this study,

all relevant factors have not been known or investigated.

In summary, an impressive diabetic case was described in this article. Administration of Ipragliflozin to T2DM with depression has improved glycemic control and depression. The case has been followed up at present and in the future, and various possible factors will be investigated. This report may become a useful reference for diabetes care.

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Conflicts of Interest

The authors declare no conflict of interest about this report.

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