



Actual Meal of Low Carbohydrate Diet (LCD) for Diabetic Patient Treated by Effective Imeglimin (Twymeeg)

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Received date: 12 July 2023; **Accepted date:** 24 July 2023; **Published date:** 31 July 2023

Citation: Kusumoto T, Bando H, Hayashi K, Yasuoka E, Shibata M, Takagishi H. Actual Meal of Low Carbohydrate Diet (LCD) for Diabetic Patient Treated by Effective Imeglimin (Twymeeg). *Asp Biomed Clin Case Rep.* 2023 Jul 31;6(3):178-85.

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Abstract

The case is a 51-year-old male with obesity, type 2 diabetes (T2D), dyslipidemia, and hypertension. His HbA1c value increased to 8.0%, accompanied by oral semaglutide administration. Glucose variability was exacerbated after that, and then novel imeglimin (Twymeeg) was initiated. HbA1c decreased from 7.4% to 6.7% over 4 months with a 3 kg weight reduction. The case also had low back pain (LBP) and lumbar spinal stenosis (LSS), probably resulting from Metabolic syndrome (Met-S), and had actual experience with a low carbohydrate diet (LCD) in the hospital meals. Four patterns of LCD meals had carbohydrates ranging from 17.8g to 28.0g, with 501-690kcal.

Keywords

Low Back Pain, Lumbar Spinal Stenosis, Low Carbohydrate Diet, Imeglimin (Twymeeg), Trials of IMeglimin for Efficacy and Safety

Abbreviations

LBP: Low Back Pain; LSS: Lumbar Spinal Stenosis; LCD: Low Carbohydrate Diet; TIMES: Trials of IMeglimin for Efficacy and Safety

Introduction

For decades, low back pain (LBP) has been an important problem and a major symptom of lumbar spinal stenosis (LSS). These issues affect a large number of individuals, including patients with various diseases [1]. LBP and LSS have often been linked to locomotive syndrome, obesity, Metabolic syndrome (Met-S), and related diseases [2]. Furthermore, these

medical problems show a close relationship with type 2 diabetes (T2D) [3]. According to a recent report by the International Diabetes Federation (IDF), there are 537 million people worldwide with diabetes [4]. Diabetes is associated with complications such as microangiopathic and macroangiopathic problems, which include peripheral artery disease (PAD), cardiovascular disease (CVD), and cerebral vascular

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accidents (CVA) [5]. Additionally, orthopedic problems such as LBP and LSS are prevalent among individuals with obesity and Met-S.

In January 2023, the American Diabetes Association (ADA) presented the "Standards of Care in Diabetes," which outlined the standard management measures for Type 2 diabetes (T2D) [6]. The guidelines emphasized crucial points like adequate nutrition, exercise, and various treatments. Among these, oral hypoglycemic agents (OHAs) were introduced, including dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like-peptide 1 receptor agonists (GLP1-RA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i). Additionally, imeglimin (Twymeeg) was introduced as a novel treatment option with a unique mechanism involving mitochondrial function [7,8].

The authors and their colleagues have been actively engaged in diabetic research and practice, covering areas related to T2D, obesity, Met-S, CVD, chronic kidney disease (CKD), meal tolerance tests (MTT), low carbohydrate diets (LCD), and more [9,10]. Moreover, they have reported on cases involving OHAs, such as Twymeeg, and other effective agents [11]. Recently, they encountered a diabetic patient with remarkable characteristics. This report aims to present the general situation and provide some perspectives on this case.

Case Presentation

Medical History:

This case involves a 51-year-old male who has been dealing with obesity, type 2 diabetes (T2D), dyslipidemia, and hypertension for approximately 6-8 years. He first visited our clinic about 5 years ago and has been receiving treatment for various medical issues. The clinical progress of his HbA1c levels and body weight from January 2021 is depicted in Fig-1.

Over the course of about 1 year, the HbA1c value gradually increased up to 8.0%. To address this, the patient's treatment was modified, and he started taking semaglutide, an oral glucagon-like-peptide 1 receptor agonist (GLP-1RA), in place of linagliptin, which is a dipeptidyl peptidase-4 inhibitor (DPP4-i). Subsequently, there was a gradual improvement in HbA1c levels and weight for about 10 months. However, by December 2022, the HbA1c value had worsened again, reaching 7.4%. As a result, further evaluation and assessment were conducted.

Physical Examination:

His consciousness and speech have been normal. His vitals are stable: BP 132/78 mmHg, pulse 68 /min, and SpO₂ 99%. Unremarkable findings are observed for the head, face, neck, heart, and lungs. The abdomen

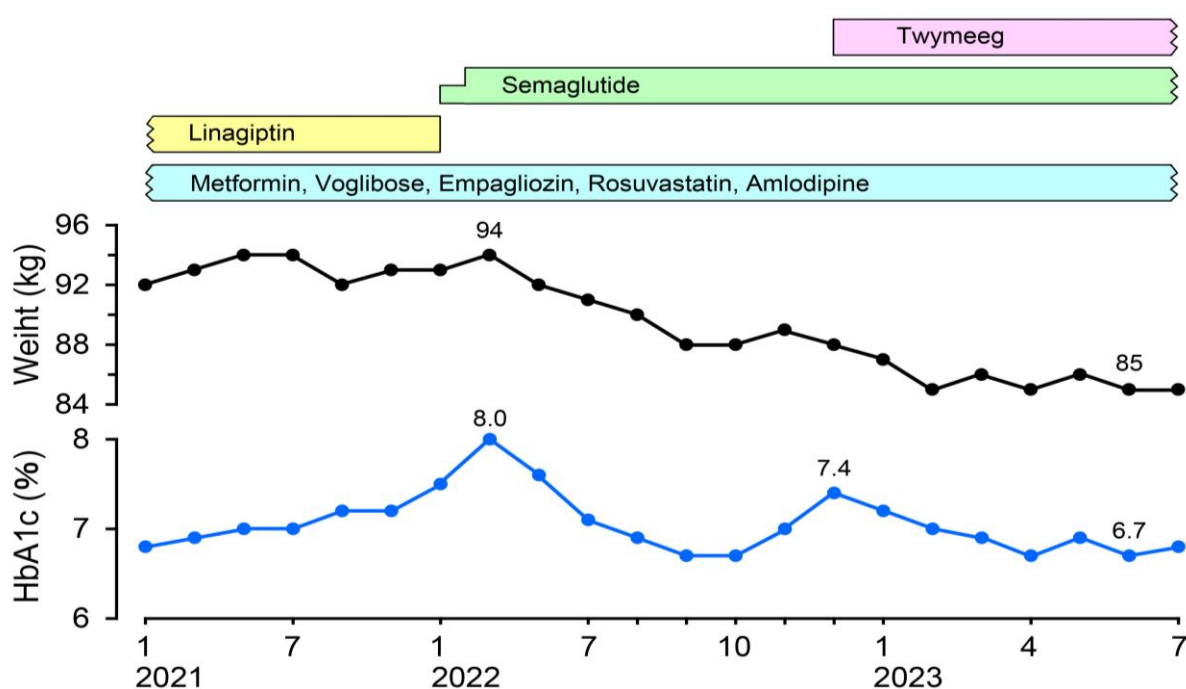


Fig-1: Clinical Progress of the Case

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showed distension but is soft with usual bowel sounds. However, he has been complaining of long-term low back pain (LBP). For orthopedic diagnosis of lumbago, Lasègue's test (straight leg raise, SLR) was positive at 40 degrees on the right side and 50 degrees on the left side. Patellar tendon reflex (PTR) and Achilles tendon reflex (ATR) were slightly weakened bilaterally. He experiences sensory disturbance in his right foot and its right 1st thumb. His physique showed degree 1 obesity, associated with a stature of 165 cm, weight of 88.4 kg, and BMI of 32.5 kg/m².

Several Exams:

The results of laboratory exam in December 2022 were in the following: HbA1c 7.4 %, pre-prandial blood glucose 132 mg/dL, RBC 4.91 x 10⁶ /μL, Hb 16.1 g/dL, Ht 47.6 %, MCV 97.0 fL (80-98), MCH 32.8 pg (27-33), MCHC 33.8 g/dL (31-36), WBC 9200/μL, Plt 31.7 x 10⁴ /μL, TP 7.2 g/dL, T-Bil 0.7 mg/dL, GOT 19 U/L, GPT 22 U/L, γ-GTP 20 U/L, ALP 71 U/L (83-113), LD 181 U/L (124-222), ChE 363 U/L (213-501), amylase 96 U/L (35-125), Uric acid 4.9 mg/dL, BUN 13 mg/dL, Cre

0.86 mg/dL, Na 142 mEq/L, Cl 103 mEq/L, K 4.0 mEq/L, HDL 53 mg/dL, LDL 74 mg/dL, TG 157 mg/dL, T-Cho 158 mg/dL, LDL/HDL ratio 1.6, CRP 0.07 mg/dL, Urinalysis: glucose (+++), protein (-), urobilinogen (+/-), pH 5.5, occult blood (-), ketone bodies (-).

Chest X-ray test revealed negative finding. Electrocardiogram (ECG) showed pulse 70/min, normal axis, ordinary sinus rhythm without remarkable ST-T changes.

The MRI exam for the lower vertebrae showed some positive results. The lumbar spine maintains a physiological lordosis. In the L1 vertebrae, T1W1 shows a low signal, while T2W1/STIR shows a high signal. In the horizontal section, a dotted low signal area, suggestive of trabecular bone, is observed in the signal. Based on these findings, a T1W1 low signal vertebral hemangioma has been suspected (**Fig-2a** and **Fig-2b**).

The intervertebral discs in each part of the lumbar



Fig-2: Actual Hospital Meals for LCD

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vertebrae are mildly bulging, and the vertebral canal appears to be irregular in diameter. Particularly, L4/5 shows moderate central spinal canal stenosis as LSS, combined with hyperplasia of the ligamentum flavum and facet joint hyperplasia (**Fig-2c**). Stenosis of the intervertebral foramina on both sides is found to be of mild degree.

Clinical Progress:

Based on the results of laboratory and physiological exams, it was decided to provide the patient with imeglimin (Twymeeg) as a novel oral hypoglycemic agent (OHA). He started taking Twymeeg in December 2022, and over a period of 4 months, his HbA1c decreased from 7.4% to 6.7%. Concurrently, his body weight reduced from 88kg to 85kg, with a 3kg reduction.

Subsequently, we offered him an educational opportunity to learn and understand how to follow a low carbohydrate diet (LCD) as part of the treatment for his T2D. We provided actual LCD meals, detailing the carbohydrate content (**Fig-3**, and **Table-1**). These meals were available in four patterns, with carbohydrates ranging from 17.8g to 28.0g and calorie content varying from 501 to 690 kcal.

Ethical Consideration

The current case complied with the ethical

guidelines of the human Declaration of Helsinki. Moreover, some related commentary was presented from the basic regulation. The recent principle included the ethic rule as to clinical practice and research. Several medical problems concerning human being are present. Its guideline has been regulated by two Ministries of Japanese government. They are Ministry of Education, Culture, Sports, Science Technology, and Ministry of Health, Labor and Welfare. The authors and collaborators established our ethical committee for the case. It is present in Hayashi hospital, Tokushima, Japan. The committee has several related members, including hospital director, physician in charge, pharmacist, nurse, nutritionist and legal professional person. Current committed staffs have discussed satisfactory concerning the case, and we have agreed with the research content. We have obtained the document of informed consent from the case.

Discussion

This case exhibits several characteristic aspects. The patient has been dealing with multiple medical problems, including obesity, type 2 diabetes (T2D), dyslipidemia, hypertension, and low back pain (LBP). In the most recent clinical progress, the administration of Twymeeg has resulted in a reduction in HbA1c levels and an improvement in the general situation.

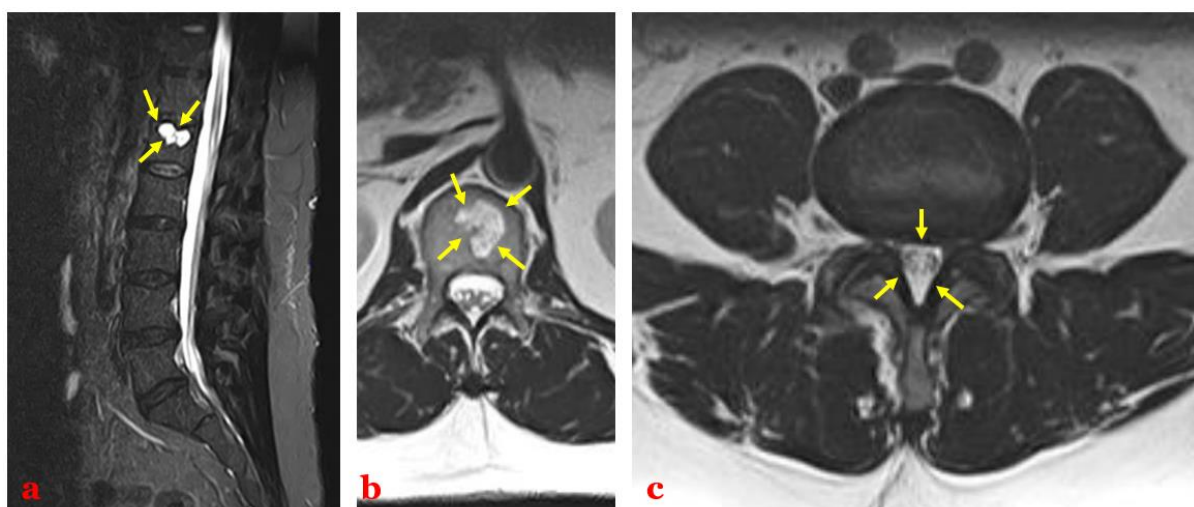


Fig-3: MRI Findings of Lower Vertebrae

- 3a: Vertebral hemangioma is suspected in L1 by axial view.
- 3b: T1W1 low signal vertebral hemangioma by horizontal view.
- 3c: L4/5 shows moderate central spinal canal stenosis.

Table-1: Calorie and Nutrients of LCD Meals

	Type of cuisine	Calorie (kcal)	Protein (g)	Fat (g)	Carbo (g)
A	Chikens saute flavor sauce	301	20.7	21.5	6.6
	Bok choy with butter soy sauce	22	0.6	1.8	1.6
	simmered deep-fried vegetable tofu	100	6.4	7.1	2.8
	salad	262	12.0	23.6	4.2
	European style soup	5	0.4	0.0	0.9
	Total		690	40.1	54.0
B	Fried horse mackerel marinated in sweet and spicy vinegar	235	24.6	9.4	15.8
	Cauliflower simmered ginger	24	1.2	0.0	4.8
	Okra tossed with mayonnaise	53	1.1	4.6	3.3
	scrambled egg	186	9.6	16.3	1.3
	miso soup	60	4.1	4.1	2.8
	Total		558	40.6	34.4
C	Beef simmered with tomatoes	263	17.7	19.3	8.4
	Asparagus and corn stir fry	129	5.0	11.5	3.6
	Chinese cabbage seasoned with soy sause	15	0.5	0.1	3.4
	Chicken piccata	164	13.9	11.3	3.6
	miso soup	62	4.2	4.1	3.5
	Total		633	41.3	46.3
D	Simmered dishes	177	15.7	8.8	9.1
	Stir-fired chinese chives	113	3.8	9.8	2.7
	Japanese mustard spinach seasoned with saltred kelp	17	1.1	0.1	3.4
	Simmered fish in sweetened soy sauce	69	10.7	2.0	2.1
	two pieces of cheeze	125	9.1	10.4	0.5
	Total		501	40.4	31.1

Regarding the LBP, the positive Lasegue sign is associated with a probable hemangioma in the L1 vertebra and lumbar spinal stenosis (LSS) at the L4/5 level. The patient's experience with actual low carbohydrate diet (LCD) meals may hopefully lead to better nutritional treatment for his T2D.

In this discussion, we will present some perspectives concerning this case and the medical problems observed.

First, this case has degree 1 obesity that has been present for several years, which may contribute to the development of type 2 diabetes (T2D) and low back pain (LBP) [1]. A close relationship has been identified between obesity and lumbar spinal stenosis (LSS). Obesity is implicated in the onset of LSS and also

affects the satisfaction ratio and outcomes after laminectomy [12].

LBP is a common symptom experienced by individuals of all ages and is one of the most common reasons for disability worldwide. In relation to LBP, LSS is characterized by age-related degeneration of intervertebral discs, facet joints, and the ligamentum flavum [2]. These changes lead to the narrowing of the space around the neurovascular spine structures. To diagnose spinal pain syndromes, various exams, such as computed tomography (CT), magnetic resonance imaging (MRI), and X-ray radiography (RTG), are conducted.

Patients with LSS have long-term impairment in their activities of daily living (ADL) and quality of life

(QOL) due to LBP and motor paralysis. However, a significant and effective preventive therapy has not been available. As our society continues to age, LSS will likely be associated with metabolic syndrome (Met-S). Exploring clinical research on LSS from the perspective of both Met-S and locomotive syndrome (Loc-S) may lead to the development of novel measures for the treatment and prevention of these problems [13].

Secondly, this case has experienced a moderate level of diabetic control over the years. The reason for this appears to be his daily dietary style, which involves a relatively higher intake of carbohydrates. The current project aimed to provide him with actual low carbohydrate diet (LCD) meals every day, aiming to offer him a comfortable experience from both physical and psychological perspectives. Indeed, he noticed a stable condition where he rarely experienced hunger or irritability during LCD meals. His blood glucose levels showed minimal fluctuations, allowing the patient to maintain a stable physical, mental, and psychological status.

LCD was initially introduced by doctors Bernstein and Atkins in European and North American countries [14,15]. Subsequently, LCD has been recognized as one of the effective nutritional methods [16]. In Japan, authors and collaborators have embraced LCD and have developed it in various medical and social contexts through the Japan LCD Promotion Association (JLCDMA) [17]. LCD can be applied in both medical and healthcare settings. For instance, three representative LCD methods are known: petite-LCD, standard-LCD, and super-LCD, with carbohydrate amount ratios of 40%, 26%, and 12%, respectively [18]. By implementing these convenient approaches, LCD is expected to become even more prevalent in the future.

Thirdly, he has been undergoing treatment for type 2 diabetes (T2D) with oral hypoglycemic agents (OHA) for several years, which has resulted in an almost satisfactory situation. One of the reasons for this includes the administration of oral semaglutide. He follows a routine of skipping breakfast, taking the medicine after waking up, and fasting for more than 2

hours. With the administration of Lybelsus 7mg, the clinical effect is equivalent to 14 mg or more. Additionally, imeglimin (Tymeeg) has been introduced as a novel OHA. The combination of these treatments led to a reduction in HbA1c by 0.7% in just 4 months, along with a 3 kg weight reduction. In this case, metformin and oral GLP-1RA had already been administered as add-on therapy before the addition of imeglimin as a new OHA.

Regarding the clinical effect of imeglimin as an add-on therapy, data from international large studies known as the Trials of IMeglimin for Efficacy and Safety (TIMES) have been reported. The detailed results of TIMES 1, 2, and 3 are as follows: metformin (biguanide) -0.67% and GLP-1RA -0.12% were related data to this case [19]. As for other OHAs, the results were as follows: DPP4-i -0.92%, monotherapy 0.46%, SGLT2-i -0.57%, alpha-glucosidase inhibitor -0.85%, SU agents -0.56% [20]. Based on this data, the add-on treatment of Twymeeg appears to be beneficial for achieving a satisfactory level of clinical practice [21]. Imeglimin may have crucial functions involving the mitochondrial mechanism for glucose and related processes [22]. Consequently, future research is expected to clarify several metabolic pathways related to imeglimin.

There are certain limitations in this article. The clinical efficacy for diabetes appears to result from the combined administration of oral hypoglycemic agents (OHAs). However, the individual efficacy of each OHA cannot be clearly determined. Additionally, the case has been consuming carbohydrates to some degree for a long time. The current experience with actual low carbohydrate diet (LCD) meals is expected to improve glucose variability. Therefore, it is necessary to continue monitoring and following up on this case.

In summary, a 51-year-old male diabetic case with low back pain (LBP) and lumbar spinal stenosis (LSS) was presented. The case showed a clinical effect from Twymeeg over a short period. This article is expected to be useful for diabetic practice in the future.

Funding Statement

There was no external funding or financial support

received for this report. The authors declare that no funding was obtained from any source, and the report was conducted without any financial assistance. All expenses related to the report were borne by the authors themselves.

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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