

Improvement By Imeglimin (Twymeeg) In Patient with Type 2 Diabetes (T2D), Cervical Spondylosis and Fatty Liver

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Abstract

Current case is 51-year-old male with type 2 diabetes (T2D). Previous problems included obesity with BMI 35.2 kg/m² and cervical spondylosis treated with baclofen (Lioresal). He was diagnosed as T2D with HbA1c 6.6%, obesity, fatty liver, hyperuricemia, dyslipidemia and chronic kidney disease (CKD). By continuing low carbohydrate diet (LCD), HbA1c was decreased to 5.2% with 6kg weight reduction. UA was 8.3 mg/dL in Jan 2021, and febuxostat was started. HbA1c increased to 6.9% in Oct 2022, and imeglimin (Twymeeg) was started. HbA1c decreased to 5.9% for 6 months. Thus, several medical problems were improved by LCD and imeglimin intake.

Keywords: Low Carbohydrate Diet (LCD); Imeglimin (Twymeeg); Cervical Spondylosis; Baclofen (Lioresal); Trials of Imeglimin for Efficacy and Safety (TIMES)

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Introduction

Across the world, non-communicable diseases (NCDs) have been crucial problems from medical and social points of view [1]. NCDs include several main diseases, such as type 2 diabetes (T2D), hypertension and dyslipidemia. The development of T2D can be restricted by usual nutritional meal content, where low carbohydrate diet (LCD) contributes lower incidence of T2D [2]. For latest clinical practice for T2D, American Diabetes Association (ADA) has announced the recommended guideline of "Standards of Care in Diabetes" in January 2023 [3]. Recent topics concerning T2D include several kinds of oral hypoglycemic agents (OHAs) that are already introduced for actual clinical practice. Their main categories exist such as dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium-glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like-peptide 1 receptor agonist (GLP1-RA) with injectable and oral types. Furthermore, recent novel OHA has been introduced into diabetic practice as imeglimin (Twymeeg) [4].

The standard first-line OHA for T2D has been metformin worldwide for long years [5]. Based on the similar molecule, imeglimin was developed for effective and novel OHA for T2D [6]. The beneficial characteristic include the application of monotherapy and also add-on treatment with almost all kinds of OHAs and insulin therapy [7]. In the light of pharmacological mechanism, it has dual effects of stimulating insulin secretion and decreasing insulin resistance. The intake method is bis in die (bid,

twice a day), which can contribute the improvement of glucose daily profile and reduction of mean amplitude of glycemic excursions (MAGE) [8].

Authors and diabetic team have continued reporting various research for long [9]. We presented actual effectiveness of low carbohydrate diet (LCD), meal tolerance test (MTT) using convenient meals, and a variety of case reports for recent OHAs [10]. We have recently experienced a diabetic patient who was involved in several impressive characteristics. The general progress and related perspectives are described in this report.

Case Presentation

History and Physicals

The case is 51-year-old male with T2D. The patient had developed several symptoms such as neck pain, stiff shoulders, and spasticity since 2015. He was diagnosed as cervical spondylosis in the orthopedic department, and was administered baclofen (Lioresal) for years. In 2019, he was pointed out to have elevated HbA1c value, and then he was referred to our diabetic department. As to previous history, his body weight was 80 kg at 20 years old.

On the first contact, his physique showed 173.4 cm in height, 105.7 kg in weight, 35.2 kg/m² in body mass index (BMI) and 112cm of abdominal circumference. His physical examination revealed in the following: consciousness alert, speech normal, vitals are within normal limits, head, face, neck, chest, abdomen were negative. Auscultation of lung and heart were normal. Neurological

examination was intact.

Several Exams

Obtained data of laboratory biochemistry in Jan 2019 were as follows: HbA1c 6.6%, fasting blood glucose 121 mg/dL, AST 126 U/L, ALT 143 U/L, GGT 101 U/L, uric acid 7.4 mg/dL, Cr 1.02 mg/dL, eGFR 63.3 mL/min/1.73m², LDL 129 mg/dL, HDL 51 mg/dL, TG 117 mg/dL. Chest X-ray showed negative result, and electrocardiogram (ECG) revealed within normal limits without specific ST-T changes. Abdominal CT scan showed severe fatty liver in Jan 2019 (Figure 2a).

Medical Problems

From mentioned above associated with various information of previous history and medication, his medical problems could be summarized in the followings.

- Obesity (weight 105.7kg and BMI 35.2)
- Type 2 diabetes (T2D) HbA1c 6.6%
- Fatty liver (elevated liver function test)
- Hypertension
- Hyperuricemia (UA 7.2 mg/dL),
- Dyslipidemia (LDL 129 mg/dL)
- CKD (cre 1.02 mg/dL, eGFR 63.3 mL/min/1.73m²)
- Cervical spondylosis with neck pain and spasticity

Clinical Progress

For several medical problems, he was advised to start LCD. The degree of LCD was mild to moderate for 6 months, and after that the degree of LCD was further restricted. It was super-LCD, that means 12% of carbohydrate content by calorie calculation. His weight was decreased to 100kg, associated with HbA1c reduction to 5.2% in April 2020 (Figure 1). Furthermore, ALT (GPT) as liver function test was decreased from 162 to 63 U/L during weight reduction period. Another biochemical change was uric acid (UA) as renal function. As LCD has been continuing for several months, UA level was also elevated. In Jan 2021, febuxostat was started for controlling UA level for chronic kidney disease (CKD).

In Oct 2022, HbA1c was increased to 6.9%, and then imeglimin (Twymeeg) as novel OHA was initiated for controlling glucose variability. Consequently, HbA1c value was successfully decreased from 6.9% to 5.9% for 6 months. His overall clinical course seemed to be rather characteristic. Regarding his daily life, his routine work has been prioritized and then regular outpatient visits were occasionally missed. In other words, the compliance with clinical treatment was somewhat problematic, where the problem #9 was likely for low compliance for continuous regular treatment. The case undergone abdominal CT in April 2023, in which fatty liver was improved compared with that in 2019 (Figure 2b). Further, CT showed fatty involvement of pancreas, increased visceral and subcutaneous fat (Figure 3a, b).

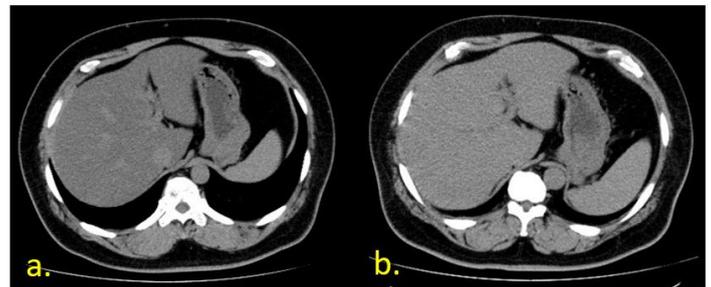


Figure 2: Changes in fatty liver for abdominal CT scan

2a. Exam in Jan 2019

2b. Exam in Apr 2023

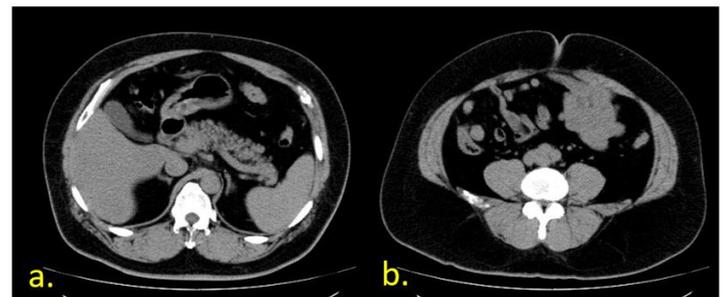


Figure 3: Abdominal CT scan in Apr 2023

3a. Pancreas showed fatty involvement.

3b. Visceral and subcutaneous fat are highly present.

Ethical Standards

This case report has been complied with the standard ethic guideline from the Declaration of Helsinki. In addition, several commentary was along with the regulation for personal information. The principle is associated with the ethical rules for medical practice and research method for human being. Some guidelines have been from official announcements of Japanese governments. The perspectives have been from Ministry of Health, Labor and Welfare (MHLW), and also Ministry of Education, Culture, Sports, Science Technology (MEXT). The authors and co-researchers have established the ethical committee concerning current research. It was present in Sakamoto Hospital, Kagawa prefecture, Japan. It includes several necessary members, such as

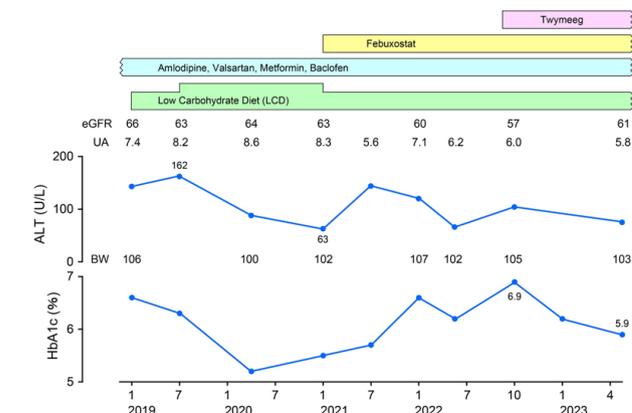


Figure 1: Clinical progress of the case.

hospital director, physicians in charge, registered nurse director, dietitian, pharmacist and legal professional personnel. These members have discussed enough for this matter, and agreed the research protocol. Consequently, informed consent was obtained from the current case by the written document.

Discussion

The characteristic of this case was that he had cervical spondylosis and received baclofen from an orthopedic department [11]. After that, he developed T2D associated with obesity and fatty liver, and his renal function has been at a borderline level. For treatment, LCD was effective and also Twymeeg improved diabetic variability for half year. For this discussion, several perspectives concerning i) baclofen, ii) LCD, iii) CKD and iv) Twymeeg would be described in this order.

Firstly, several disorders of neck and back pains have been self-limiting situation, that require judicious intake of imaging and seldom invasive therapeutic methods [12]. By previous Global Burden of Disease (GBD) study, LBP showed highest problem in 291 disorders for years lived with disability (YLDs), and higher global prevalence as 9.4% [13]. From orthopedic point of view, chronic pain has been important to manage properly [14]. The related information includes stepwise method of pharmacologic approach of non-steroidal anti-inflammatory agents before novel interventional pain reduction procedures. In the light of neurosurgical actual practice, chronic neck and back pain are also common problems for many patients [15]. These management includes some complex patterns and approaches by multidisciplinary team with well-equipped health care facility. From a recent report, baclofen and meloxicam has been formulated for combination of orally disintegrating tablet (ODT), which was investigated for using some co-processed excipients [16]. Thus, baclofen has been effective for treating osteoarthritis.

Secondly, LCD was effective for decrease of HbA1c 6.6 to 5.2%, and weight reduction 106kg to 100kg. LCD has been more prevalent by social and medical movement of authors' activity. We have proposed three simple LCD methods, which are super-LCD, standard-LCD and petite LCD where carbohydrate amount is 12%, 26% and 40%, respectively [17]. These information and related workshop were continued for many people through Japan LCD promotion association (JLCDPA). From our clinical experience, LCD was applied to about 3000 patients with obesity and T2D. Among them, weight reduction more than 10% was observed in 26%, and reduction more than 5% was observed in 60% [18]. In this case, fatty liver was relieved between 2019 and 2023 (Figure 2,3). This improvement would be from continuing LCD, weight reduction, and treatment of Twymeeg [19].

Thirdly, renal function was borderline in this case. The uric acid level was also high, but it is known that the uric acid (UA) level becomes slightly high during continuing the meal of LCD for several months [20]. Then, anti-hyperuricemic agent was not immediately administered. Since UA persisted higher, however,

febuxostat was initiated. For the current case, renal function was involved in several factors, such as diabetes mellitus [21], chronic kidney disease, baclofen intake [22], hypertension [23] and so on. Fourthly, this case showed clinical improvement of HbA1c from 6.9% to 5.9% for 6 months. Clinical efficacy of imeglimin (Twymeeg) was presented by a series of large studies, which were Trials of IMeglimin for Efficacy and Safety (TIMES) 1,2 and 3 [24]. The improvement of HbA1c decrease was shown in the following: 0.46% in monotherapy, 0.67% in the add-on treatment with biguanides such as metformin, 0.92% in add-on with DPP4-i, 0.57% in SGLT2i, 0.70% in alfa-GI [25]. Imeglimin can act through the mitochondrial pathway [26]. The impressive results were found that DPP4-i showed 0.92% decrease, whereas GLP-1RA showed only 0.12% decrease [27]. The difference may show the possible key to clarify the detail pharmacological mechanism of imeglimin for glucose variability [28].

Some limitations may exist in this report. The case was treated for cervical spondylosis, obesity, T2D, fatty liver, hypertension, hyperuricemia, CKD and showed clinical improvement by LCD and also imeglimin (Twymeeg). However, various factors have been involved in his clinical progress, and then we cannot evaluate each effect clearly. His future clinical situation will be followed up with careful attention.

In summary, this case was 51-year-old male with multiple medical problems. It suggested various possibility of mutual relationships and influences among them. In this article, several perspectives were described concerning baclofen, LCD, CKD and Twymeeg. These comments will become hopefully useful references for diabetic research in the future.

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