



Development of Type 2 diabetes (T2D) with Remarkable Weight Gain Treated by Imeglimin (Twymeeg)

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Abstract

This patient is 42-year-old male with type 2 diabetes (T2D). Family history is positive for T2D, in which his younger sister is diabetic for 6 years. He had weight gain from 56kg to 90kg during 20 to 40 years old. He had HbA1c 12.9% in March 2023, and diagnosed as T2D. He started low carbohydrate diet (LCD) and was provided imeglimin (Twymeeg) as oral hypoglycemic agents (OHAs). HbA1c was decreased to 6.3% in August, 2023. He and his sister like to take rice, bread and cakes as carbohydrates. Consequently, both of Twymeeg and LCD may contribute remarkable clinical effect.

Keywords: Weight gain; Vildagliptin/metformin (EquMet); Low carbohydrate diet (LCD); Japan LCD promotion association (JLCDPA); Trials of IMeglimin for Efficacy and Safety (TIMES)

Introduction

Across the world, type 2 diabetes (T2D) has been increased, which becomes medical, cultural, socioeconomic, and psychological barriers [1]. The generation of young and middle age has been involved in higher incidence of T2D. Among them, obesity and excess body weight may be the crucial cause [2]. Regarding the link between elevated weight and T2D, cellular and physiological mechanisms have been complex and involved in adiposity-induced function alterations for insulin secretion, insulin resistance and adipose tissue biology [3]. As to the related factor for increased body weight, the consumption of sugar-sweetened beverages (SSBs) has attracted attention. A systematic review for 17 studies was performed concerning the relationship of SSB consumption, cardiometabolic outcomes such as obesity, T2D and CVD [4]. Elevated SSB showed significant association with higher weight gain and higher CVD outcomes. Higher SSB consumption showed greater T2D risk, with 1.51 of relative ratio among highest vs lowest group.

Regarding weight control for patients with T2D and obesity, the intake of carbohydrate amount has been important [5]. Formerly, standard diet therapy was calorie restriction (CR), but low carbohydrate diet (LCD) has been recognized for standard and effect nutritional treatment after that [6]. LCD was initiated by two doctors of Atkins and Bernstein in European and North American regions [7,8]. Variety of reports for LCD have been found with clinical satisfactory effect [9]. In Japan, the author et al. have developed LCD medically and socially through the activities of Japan LCD promotion association (JLCDPA) [10]. For our enlightening of LCD, three useful diet types were introduced. They are petite-, standard- and super-LCD, in which carbohydrate amount is included 40%, 26% and 12%, respectively [11].

For the management for T2D, American Diabetes Association (ADA) has announced the standard guideline for diabetes in 2023 [12]. Recent pharmacological development has brought some effective oral hypoglycemic agents (OHAs). They are dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium-glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like-peptide 1 receptor agonist

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(GLP1-RA), and so on. As novel OHA, imeglmin (Twymeeg) was introduced to clinical practice, which shows satisfactory medical efficacy. It has an impressive pharmacological mechanism via mitochondrial route [13]. In other words, it can decrease insulin resistance and also stimulate insulin secretion from beta cell in the pancreas [14]. Authors et al. have continued medical practice and clinical reports so far [15,16]. Recently, we have a male patient with T2D associated with some characteristic points. His general situation and related discussion would be described in the article.

Case Presentation

Medical History

The current patient is 42-year-old male with T2D. Family history is positive for T2D, in which his younger sister is 39 years old for T2D for 6 years. She has been treated in our diabetes department. Regarding his previous history, his weight was 56 kg at the age of 20. After that, the weight has been gradually increased up to 90 kg at the age of 40 (Figure 1). The weight was maximum level for him at 2021. After that, his weight has been almost stable, but acutely decreased for a few months. He visited our clinic in March 2023, and was diagnosed for T2D with HbA1c 12.9%.

Several examinations

Physical exams in March 2023 were revealed in the followings: Consciousness, speech and vitals were within normal limits. The head, heart, lung and abdomen showed unremarkable. His physique status showed height 166.5 cm, weight 68.2 kg, and BMI 24.6 kg/m².

The results of the biochemical examination were as follows: TP 7.4 g/dL, Alb 3.2 g/dL, AST 45 U/L, ALT 83 U/L, GGT 217 U/L, ALP 541 U/L (38-113), uric acid 6.7 mg/dL, BUN 8 mg/dL, Cre 0.43 mg/dL, HDL 44 mg/dL, LDL 156 mg/dL, TG 145 mg/dL, T-Cho 229 mg/dL, arteriosclerosis index (ASI) 4.2, glucose 316 mg/dl, HbA1c 12.9%, WBC 10900/μL, RBC 4.47 x 10⁶ /μL, Hb 12.6 g/dL, Ht 39.5 %, MCV 88.4 fL (80-98), MCH 28.3 pg (27-33), MCHC 32.0 g/dL (31-36), Plt 24.9 x 10⁴ /μL.

As to other exams, chest X-P revealed unremarkable, and electrocardiogram (ECG) was negative without remarkable ST-T changes. Blood pressure pulse wave (plethysmography) was performed. As a result, ankle brachial index (ABI) was 1.15/1.11 (right/left, 0.91-1.40), and Cardio-Ankle Vascular Index (CAVI) was 7.6/7.5 (right/left, 6.8-8.2), which were within normal limits as well as PEP 76, ET 324. R-AI 0.78 and PEP/ET 0.23 as normal range (Figure 2). The standard ranges of ABI and CAVI have been reported in the following. The value of ABI shows the standard range of 0.9 and more than 0.9. Further, CAVI shows the standard range of less than 0.8 [17].

Clinical progress

For diabetic treatment, he was advised to start low carbohydrate diet (LCD) at once. After that, he has refrained from eating rice, bread and cakes. Two weeks later, he began to take imeglimin (Twymeeg) without reverse effects. The HbA1c values were 11.7%, 8.6%, 6.8% and 6.3% in 4, 8, 12, 21 weeks, respectively. On August 2023, he showed satisfactory glucose variability associated with stable body weight (Figure 1). Thus, remarkable clinical improvement was found for the administration of Twymeeg.

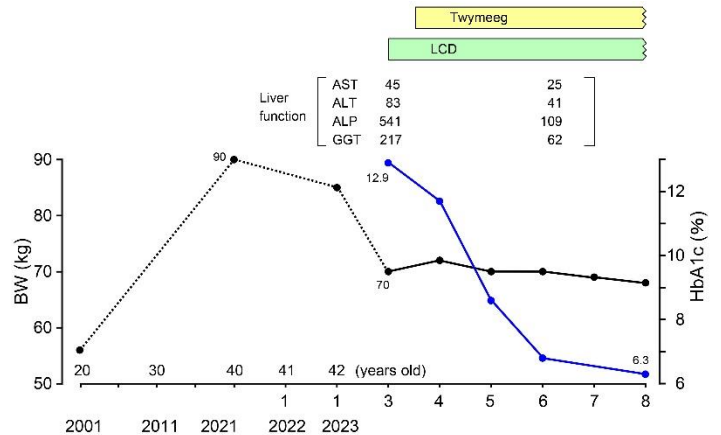


Figure 1: Clinical progress of the case.

Ethical standards

Current case complied with the standard ethical guideline for Declaration of Helsinki. Moreover, some commentary was found for the regulation of personal information. The principle was observed in ethical rule as to medical practice and also research. Medical problems for human being were present. Related guidelines were on the regulation for Japanese government, which includes Ministry of Education, Culture, Sports, Science Technology and also Ministry of Health, Labor and Welfare. The authors and collaborators have set our ethic committee concerning the case. It is present in Sakamoto hospital, Kagawa prefecture, Japan. The committee includes several staffs, which are hospital president, physician, nurse, pharmacist, nutritionist, laboratory staffs and legal professional personnel. Our committee members have discussed the research protocol in satisfactory manner. The required informed consent was taken from this case for written document.

Discussion

This report showed a middle-aged T2D patient, associated with positive family history and remarkable weight gain from 20 to 40 years old. The weight difference was 34kg, in which BMI was increased from 20.2 kg/m² to 32.5 kg/m². Furthermore, clinical

response for the administration of Twymeeg was remarkable. Some perspectives will be shown in this discussion.

As to the relationship of weight gain and incidence of T2D, previous study was observed [18]. Out of 51529 male health professionals, 272 T2D was developed. Relative risks (RR) showed 42.1 in comparison with those of BMI < 35 kg/m² vs BMI >23 kg/m² at the age of 21. A meta-analysis included 15 studies for weight gain and quantified T2D risk. The pooled relative risk (RR) for 5 kg/m² increment in BMI value showed 3.07 for early period and 2.12 for late period [19]. In the case of concurrent risk for current BMI, increased T2D risk was found for earlier weight gain as 3.38 of relative ratio. Consequently, weight gain becomes a quantifiable predictor of T2D onset. Further, weight gain would be more important in earlier period rather than middle-to-late adulthood period.

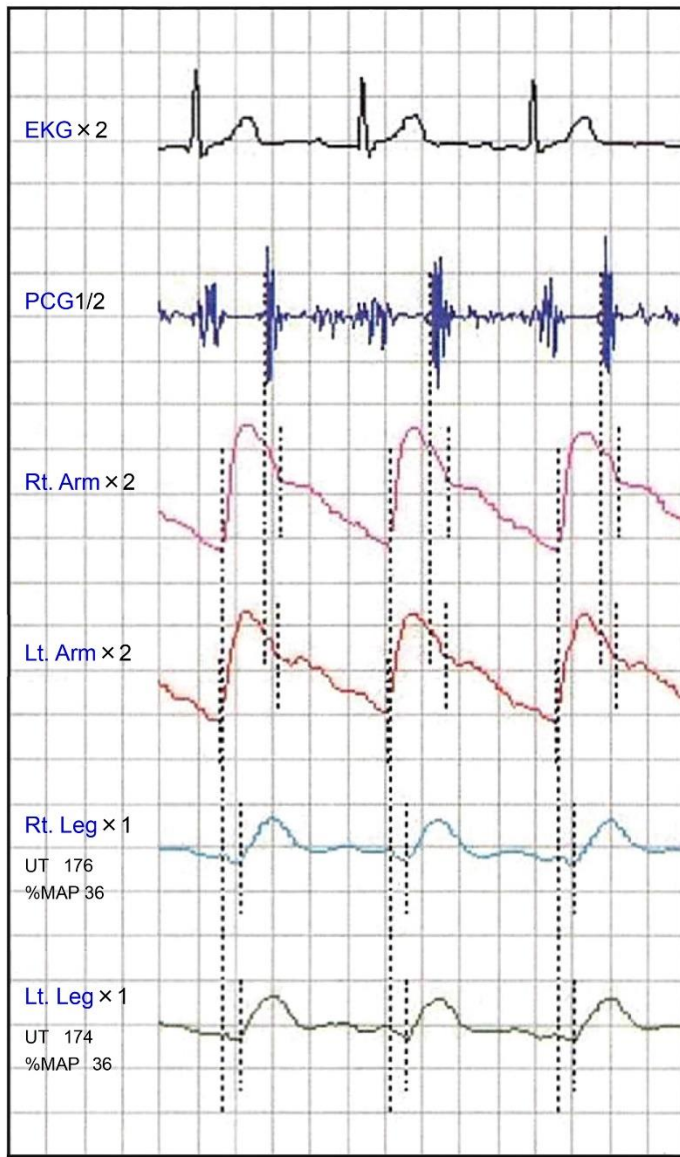


Figure 2: The exam of arterial stiffness.

Large population-based investigation was conducted for 1.47 million adolescents during 21 years. It was linked to National registry associated with the data of diabetes, weight and height. From all data of 15.8 million person-years, 2177 cases developed T2D with diagnosed at 27 years in average. Several interactions were found for BMI, male/female, and T2D incident. By adjusted sociodemographic variables, the hazard ratio in men was 1.7, 2.8, 5.8, 13.4, 25.8 for 50-74th percentile, 75-84th percentile, overweight, mild obesity, and severe obesity, respectively. Furthermore, projected fractions for adult-onset T2D were higher BMI (more than 85th percentile) was 56.9% in men [2]. Another study was observed for SSBs. Prospective cohort analyses were conducted for 9 years in Nurses' Health study II [20]. The cases were 91,249 females without diabetes, and weight data were analyzed for 51603 cases. Among them, 741 T2D incident cases were found for 716,300 person-years follow up analyses.

This patient has positive family history for T2D. His younger sister is 39 years old and treated for 6 years. They like to have carbohydrate such as rice, bread and cakes for long. Such eating habit seemed to be made during childhood [21]. His sister could not change her meal habit in short period. However, this case can start and continue LCD satisfactory. Then, he could improve glucose variability in short period. Concerning future treatment, the degree of actual LCD and pharmacological diabetic therapy is necessary to be consulted among clinical course, eating content and his lifestyle [22].

This case was provided Twymeeg, which showed remarkable clinical effect. HbA1c was decreased to normal range in short period. As the international studies, Trials of Imeglimin for Efficacy and Safety (TIMES) 1,2 and 3 were conducted for several treatment [23]. They showed that monotherapy brought 0.46% reduction of HbA1c in average. Other results included 0.92% reduction in DPP4-i and 0.57% of SGLT2-i for other add-on treatments [24]. Imeglimin has been reported to have effective mechanism through mitochondria from glucose metabolism point of view [25]. Then, further additional research would be expected for novel pathway consequently, future research will be expected for clarifying several metabolism pathway [26].

There are some limitations for the article. In this report, medical effect would be from mainly Twymeeg as well as continuation of LCD. However, other elements may be involved in the clinical progress. Consequently, further following up this case will be necessary in the future.

In summary, 42-year-old male T2D with remarkable weight gain was described with some perspectives. He revealed HbA1c reduction in short period by Twymeeg. This article is expected to become useful reference for diabetic practice in the future.

Conflict of Interest

The authors declare no conflict of interest.

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