



Improvement of HbA_{1c}, Weight and Fatty Liver by Short Treatment of Imeglimin (Twymeeg)

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Abstract

The patient is a 55-year-old male with type 2 diabetes (T2D). In his 20s, 30s, and 50s, his body weight was 80 kg, 95 kg, and 90 kg, respectively. HbA_{1c} was 10.9% in March 2023, and he was prescribed imeglimin (Twymeeg) as an oral hypoglycemic agent (OHA). HbA_{1c} decreased to 9.3%, 7.2%, and 6.8% within just 3 months. His body weight also decreased from 86 kg to 82 kg during this period. Liver function tests showed improvement between March and May 2023, with AST decreasing from 54 to 24 U/L, ALT from 121 to 28 U/L, and GGT from 45 to 18 U/L, respectively. This suggests an improvement in fatty liver.

Keywords

Type 2 Diabetes, imeglimin, Twymeeg, Low Carbohydrate Diet, Japan LCD Promotion Association, Trials of IMeglimin for Efficacy and Safety

Abbreviations

T2D: Type 2 Diabetes; LCD: Low Carbohydrate Diet; JLCDPA: Japan LCD Promotion Association; TIMES: Trials of IMeglimin for Efficacy and Safety

Introduction

For decades, the number of patients with type 2 diabetes (T2D) has been increasing worldwide. These issues encompass clinical, socioeconomic, cultural, and psychological barriers [1]. The younger and middle-aged generations have become more susceptible to T2D due to the higher risks associated with changing westernized lifestyles. Among various factors, obesity, metabolic syndrome, and lifestyle-related diseases may be crucial causes [2]. These mechanisms illustrate the relationships among T2D, excess adipose tissue, and

insulin resistance [3]. From a clinical practice standpoint, T2D has been effectively managed following guidelines announced by the American Diabetes Association (ADA) [4]. Diabetes manifests a variety of complications in microangiopathy and macroangiopathy [5], and the general purpose of diabetic therapy is to prevent or alleviate these comorbidities.

Concerning the essential measure to treat T2D, the intake of carbohydrates must be reduced since

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carbohydrate ingestion consistently increases blood glucose levels [6]. Historically, the primary nutritional treatment was calorie restriction (CR). Subsequently, the low carbohydrate diet (LCD) has gradually become the standard theory for an adequate method for T2D treatment [7]. The LCD was initiated by Bernstein and Atkins in North American and European districts [8,9]. Various LCD reports have observed medical efficacy [10]. In Japan, the author and collaborators have initiated LCD associated with educational developments for the Japan LCD Promotion Association (JLCDPA) [11]. Among our workshops, papers, and books, we have presented three simple and practical methods for LCD: super-LCD, standard-LCD, and petite-LCD, in which the carbohydrate content ratio is 12%, 26%, and 40%, respectively [12].

Regarding pharmacological therapy for T2D, several novel oral hypoglycemic agents (OHAs) have been introduced for clinical practice [13]. Out of several OHAs, imeglimin (Twymeeg) has come into focus for its impressive medical mechanism [14]. The authors and colleagues have experienced and reported effective T2D cases treated by imeglimin [15,16]. Recently, we treated a male T2D patient with some impressive aspects. His general progress and some perspectives

will be presented in this article.

Case Presentation

Medical History:

This case involves a 55-year-old male with T2D. He was diagnosed with T2D a few years ago but did not receive any treatment for it. In his 20s, his body weight was around 80 kg. Subsequently, his weight gradually increased, reaching a maximum of 95 kg. Throughout his 30s and 40s, his weight consistently ranged between 90-95 kg (Fig-1).

At the age of 54, his HbA1c was 7.8%, and he was advised to commence treatment for T2D. However, he did not follow the advice, leading to an increase in his HbA1c to 11.5% by December 2022. Although he took canagliflozin for only 14 days, he discontinued the oral hypoglycemic agent (OHA). He visited our clinic in March 2023, with an HbA1c level of 10.9%. Our diabetic team endeavored to provide him with detailed information about diabetes and the necessary treatment. Upon understanding the required therapy, he commenced canagliflozin and imeglimin (Twymeeg) in March 2023 (Fig-1). Within just 3 months, his HbA1c levels decreased to 9.3%, 7.2%, and

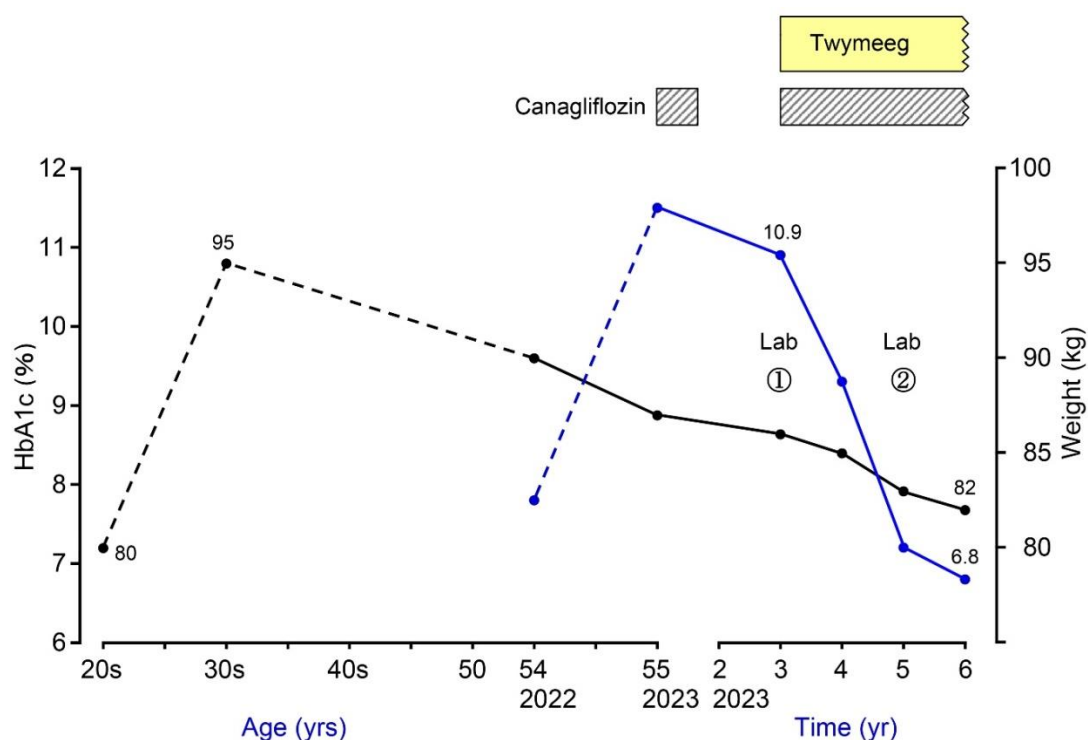


Fig-1: Clinical progress of current case

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6.8%. Additionally, his body weight decreased from 86 kg to 82 kg during this 3-month period.

Several Examinations:

Physical examinations conducted in March 2023 revealed the following: His vitals, consciousness, and speech were normal. Unremarkable findings were observed in the head, lung, heart, and abdomen. There were no abnormalities in the neurological examination. His physique measured 177 cm in height, 86 kg in weight, and a body mass index (BMI) of 27.5 kg/m².

The main results of blood biochemistry are summarized in **Table-1**, indicating the changes in liver function tests in March 2023 and May 2023. In terms of fundamental exams, the chest X-ray yielded unremarkable results, and the electrocardiogram (ECG) was within normal limits.

Ethical Standards

This patient's case adhered to the ethical guidelines outlined in the Declaration of Helsinki. Additionally, specific provisions were observed for the regulation of information, aligning with ethical rules governing medical research and practice, particularly in addressing clinical issues for humans. Corresponding

guidelines from the Japanese government, including the Ministry of Education, Culture, Sports, Science Technology (MEXT), and the Ministry of Health, Labor and Welfare (MHLW), were also followed.

The authors and coresearchers established an ethics committee for this case at Kanaiso Hospital in Komatsushima, Japan. The committee comprised various medical professionals, including the hospital director, physician in charge, head nurse, pharmacist, dietitian, and legal professional. The committee members engaged in thorough discussions regarding the protocol, ensuring a satisfactory approach. Informed consent for the current case was obtained through written documentation.

Discussion

This report highlights a case of a 55-year-old male with T2D, demonstrating a remarkable response to imeglimin (Twymeeeg) over a short period [17]. In this case, HbA1c decreased from 10.9% to 6.8% in just 3 months. The association between HbA1c levels and estimated average blood glucose levels (eAG) has been previously reported [18], with the estimated average glucose (eAG) decreasing from 265 to 148 mg/dL in this instance [19].

Table-1: Changes in Laboratory Data

		2023		Units
		Mar	May	
Liver	AST	54	24	(U/L)
	ALT	121	28	(U/L)
	GGT	45	18	(U/L)
	ChE	453	323	(U/L)
Diabetes	HbA1c	10.9	7.2	(%)
	glucose	324	148	(mg/dL)
CBC	WBC	9900	9500	(x10 ^{*2} /μL)
	RBC	532	486	(x10 ^{*4} /μL)
	Hb	16.8	15.6	(g/dL)
	PLT	27.2	29	(x10 ^{*4} /μL)
Lipids	HDL	32		(mg/dL)
	LDL	145		(mg/dL)
	TG	395		(mg/dL)
Renal	BUN	8		(mg/dL)
	Cre	0.67		(mg/dL)
	UA	3.5		(mg/dL)

Regarding his past history, his weight significantly increased during his 30s to 50s. Excess weight may be linked to the onset of T2D over the decades. Unfortunately, he struggled to consistently manage his diabetes and often discontinued regular treatment [4]. A previous study reported a relationship between T2D and weight gain [20]. In a study involving 51 thousand male professionals, 272 cases showed a relative risk of 42.1, compared with two BMI groups at 21 years old ($BMI > 35 \text{ kg/m}^2$ vs $< 23 \text{ kg/m}^2$). As BMI increased by 5, relative risks (RR) increased to 3.07 and 2.12 for early and late periods, respectively [21]. Concurrently, increased BMI risk correlated with a relative ratio of 3.38 for early body weight gain, indicating that increased weight serves as a quantifiable predictor for T2D onset.

Another report from a large epidemiological study spanning 21 years with 1.47 million cases revealed interactions between male/female, BMI, and the incidence of T2D. Hazard ratios (HRs) for males showed values of 1.7, 2.8, 5.8, 13.4, and 25.8 for the 50-74th, 75-84th percentile, overweight, mild obesity, and severe obesity, respectively. Projected fractions for adult-onset T2D displayed higher BMI values (more than 85th percentile), reaching 56.9% in men [22].

In the current case, imeglimin (Twymeeeg) was administered, revealing significant clinical efficacy. HbA1c decreased remarkably in a short period, accompanied by weight reduction over 3 months. Furthermore, liver function tests (ALT, AST, and GGT) exhibited substantial improvement in only 2 months, suggesting an enhancement in fatty liver. International investigations, such as the Trials of IMeglimin for Efficacy and Safety (TIMES) 1, TIMES 2, and TIMES 3, have reported fundamental clinical efficacy, with monotherapy resulting in a 0.46% reduction in HbA1c. Additional results include a 0.92% reduction with DPP4-i and 0.57% with SGLT2 [24]. Imeglimin is known to exhibit useful function through mitochondria in glucose metabolism [25]. Consequently, further research will be necessary to elucidate the apparent mechanism in this pathway.

A certain limitation exists in this report. The observed clinical efficacy may be attributed to Twymeeeg, SGLT2-I, and LCD continuation. However,

other factors may contribute to this acute improvement in glucose variability. Therefore, additional scrutiny will be required for this case in the future.

In summary, a 55-year-old male T2D patient was presented with a remarkable decrease in HbA1c, weight reduction, and improved liver function tests. This article is expected to serve as an important reference for diabetic research.

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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