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Effects of patient age on the therapeutic effects of GIP/GLP-1 receptor agonists (tirzepatide)

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SUMMARY: Glucagon-like peptide-1 receptor agonist (GLP-1RA) has attracted attention owing to its hypoglycemic and weight-loss effects, and various dosage forms are available in the market. Recently, glucose-dependent insulin secretion-stimulating polypeptide (GIP), an incretin hormone in the same family as GLP-1, has attracted attention, and tirzepatide, a GIP/GLP-1RA, has been launched. Given the short duration of tirzepatide on the market and the fact that its therapeutic effects in patients of different ages have not been reported, we conducted this study. HbA1c improved significantly in patients aged ≥ 65 years, whereas HbA1c, weight, and LDL cholesterol also improved significantly in patients aged ≤ 64 years when compared between the beginning of use and 3 months following use. Tirzepatide has a hypoglycemic effect regardless of age; however, its weight loss effect may be more pronounced in younger age groups. Therefore, optimal diabetes treatment with tirzepatide should consider the age and weight of patients.

Keywords: tirzepatide, HbA1c, weight

As the global diabetes population continues to increase, prevention and treatment strategies are attracting attention. Type 2 diabetes mellitus (T2DM), in particular, is associated with various factors such as dietary habits and lack of exercise, which not only increase the incidence of the disease but can also lead to social problems such as increased medical costs. In recent years, drug therapy for diabetes mellitus has included, in addition to biguanides and other drugs, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter 2 (SGLT2) inhibitors, and the incretin-related drug glucagon-like peptide-1 (GLP-1). The development and approval of drugs with new mechanisms of action, such as GLP-1 receptor agonists (GLP-1RAs), have led to a dramatic improvement in therapeutic efficacy. Specifically, GLP-1 is rapidly secreted into the blood from L cells in the lower part of the small and large intestines upon stimulation by lipids and carbohydrates in the diet and binds to GLP-1 receptors expressed on the pancreatic beta cell membrane. This promotes insulin secretion in a glucose concentration-dependent manner and lowers blood glucose levels. GLP-1 has been shown not only to improve blood glucose levels but also to have extrapancreatic effects, such as weight loss, improvement of lipid levels (*1*), and hepatoprotective effects (*2*). Therefore, various dosage regimens (daily or weekly) and formulations (injectable or oral) of GLP-1RA are available. In contrast, glucose-dependent insulin secretion-stimulating polypeptide (GIP), an incretin hormone in the same family as GLP-1, is not a target for diabetic drugs because of its lack of insulin secretion-promoting effects and concerns about weight gain due to its fat storage effect (*3*). However, a chimeric peptide that combines elements of both GLP-1 and GIP and can activate both receptors has been demonstrated to exhibit significant weight loss and hypoglycemic effects in patients with obesity and T2DM (*4*), and tirzepatide of GIP/GLP-1RA was recently launched. Tirzepatide has been reported to improve blood glucose levels and weight loss (*5*), which are important in the conventional treatment of diabetes, as well as blood pressure and lipid levels (*6*). However, since tirzepatide is a drug launched in 2023, and there are no reports of its therapeutic effects in patients of different ages, we conducted a study.

The study subjects were patients with T2DM who visited the Department of Diabetes and Metabolism at Sainokuni Higashi Omiya Medical Center as outpatients between April 1, 2024, and September 30, 2024, and were using tirzepatide (Manjaro®). The study population consisted of individuals whose medication remained unchanged for 3 months prior to 3 months following the initiation of tirzepatide use. The age groups for

Table 1. Laboratory results of patients using tirzepatide

	Project	Three months before	Beginning of use	Three months after	*p*-value
Young	Weight (kg)	89.0 ± 15.3	89.1 ± 15.8	86.8 ± 15.5	0.039
(*n* = 14)	HbA1c (%)	8.8 ± 1.7	8.6 ± 1.6	7.3 ± 1.6	< 0.001
	eGFR (mL/min/1.73m^2)	86.7 ± 22.4	82.2 ± 21.4	80.1 ± 17.3	0.304
	HDL cholesterol (mg/dL)	48.8 ± 9.1	52.1 ± 13.0	49.2 ± 11.5	0.108
	LDL cholesterol (mg/dL)	115.6 ± 32.9	104.0 ± 27.0	87.4 ± 25.1	0.006
	Triglycerides (mg/dL)	236.1 ± 145.7	201.6 ± 185.8	186.8 ± 146.4	0.636
Eldrly	Weight (kg)	71.6 ± 14.9	71.6 ± 15.8	70.3 ± 14.3	0.093
(*n* = 12)	HbA1c (%)	8.6 ± 1.1	8.7 ± 1.2	7.9 ± 1.0	< 0.001
	eGFR (mL/min/1.73m^2)	64.7 ± 19.6	62.8 ± 18.6	63.9 ± 17.8	0.665
	HDL cholesterol (mg/dL)	61.6 ± 18.4	61.0 ± 15.7	59.1 ± 14.4	0.304
	LDL cholesterol (mg/dL)	109.5 ± 19.3	106.5 ± 20.4	103.1 + 16.0	0.451
	Triglycerides (mg/dL)	172.3 ± 99.0	202.5 ± 122.5	188.1 + 106.0	0.543

(*p*-value: beginning of use *vs* 3 months after)

comparison were elderly (65 years and older) and young (64 years and younger), according to the World Health Organization (WHO) definition of the elderly. The variables assessed in this study were weight (kg), HbA1c (%), eGFR (mL/min/1.73 m^2), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), and triglycerides (mg/dL) 3 months before, at the beginning of tirzepatide use, and following 3 months of tirzepatide use. This study was conducted retrospectively. Test values are shown as mean ± standard deviation, and statistical analysis was performed by paired-samples t-test with a significance level of 5%. This study conformed to the provisions of the Declaration of Helsinki, and which was approved by the Ethics Committee of Sainokuni Higashi Omiya Medical Center (Approval number: 65).

Twenty-six patients received tirzepatide during the study period: 14 in the young group and 12 in the elderly group. The dose of tirzepatide was 2.5 mg for all patients. Table 1 presents the survey results. There were no significant differences in any of the measured variables between the 3 months before and at the beginning of use in both the young and elderly groups (p-values not shown). However, a comparison between the beginning of use and 3 months following use showed significant improvements in weight, HbA1c, and LDL in the young group, whereas only HbA1c improved in the elderly group.

The results of this study show that the elderly group only showed an improvement in blood glucose levels, whereas the young group showed an improvement not only in blood glucose levels but also in weight and LDL, thus suggesting that the drug may be more effective in younger age groups. Although it has been reported that the appetite suppression effect of tirzepatide is responsible for the reduction in weight and body fat mass (*7*), the difference in weight improvement between the older and younger groups in this study may be due to the difference in weight of the study subjects. Although not shown in the data, 11 of 14 (78.6%) patients at the young age group weighed 80 kg or more compared with 4 of 11 (36.4%) patients in the elderly group. This may be due to the fact that the young age group ate more than the elderly, and thus the appetite suppression effect of tirzepatide may have resulted in a significant reduction in weight. Regarding the difference in the improvement of LDL cholesterol, a decrease in weight and LDL cholesterol occurred simultaneously with the intake of high doses of green tea extract (*8*), suggesting a close relationship between weight loss and LDL reduction. This suggests that LDL cholesterol may have been improved by a decrease in food intake (weight loss) due to the appetite suppression effect of tirzepatide. In contrast, an improvement in blood glucose levels was observed in the elderly group, although there was no significant decrease in weight, suggesting that tirzepatide is a useful drug for treating diabetes mellitus. Tirzepatide (Manjaro®) has been reported to improve blood glucose and reduce weight better than dulaglutide (*9*), the most widely prescribed GLP-1RA in Japan (*10*). We also reported that tirzepatide may be more effective than dulaglutide in inhibiting the progression of renal impairment (*11*). Furthermore, tirzepatide, like dulaglutide, is a formulation that can be administered once a week and uses a dedicated, single-use injector, Ateos®, thus making it unnecessary to set doses or attach needles, and it can be used regardless of age. These aforementioned results suggest that tirzepatide has a hypoglycemic effect regardless of age, but that weight loss may be more pronounced in heavier young patients. Therefore, it is desirable to select a drug that considers not only the patient's age but also his or her weight.

This study is limited by the small number of cases obtained from a single medical institution and the lack of detailed patient backgrounds. Therefore, the results of this study may not reflect the overall picture of T2DM during tirzepatide use. It is necessary to conduct ongoing studies at multiple institutions with a large

number of patients to further improve the reliability of the study.

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