HOKKAIDO UNIVERSITY

Efficacy of tirzepatide on patients with type 2 diabetes and chronic kidney disease; a prospective, two-arm, observational study

Yuki Oe[1,2], Takashi Omori[1], Koki Nakamura[1], Shin Furukawa[1], Taro Nishio[1], Hirohiko Kitakawa[1], Kiyoshi Sakai[1]

1) Department of Internal Medicine, Kushiro Red Cross Hospital, Kushiro, Japan.
2) Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

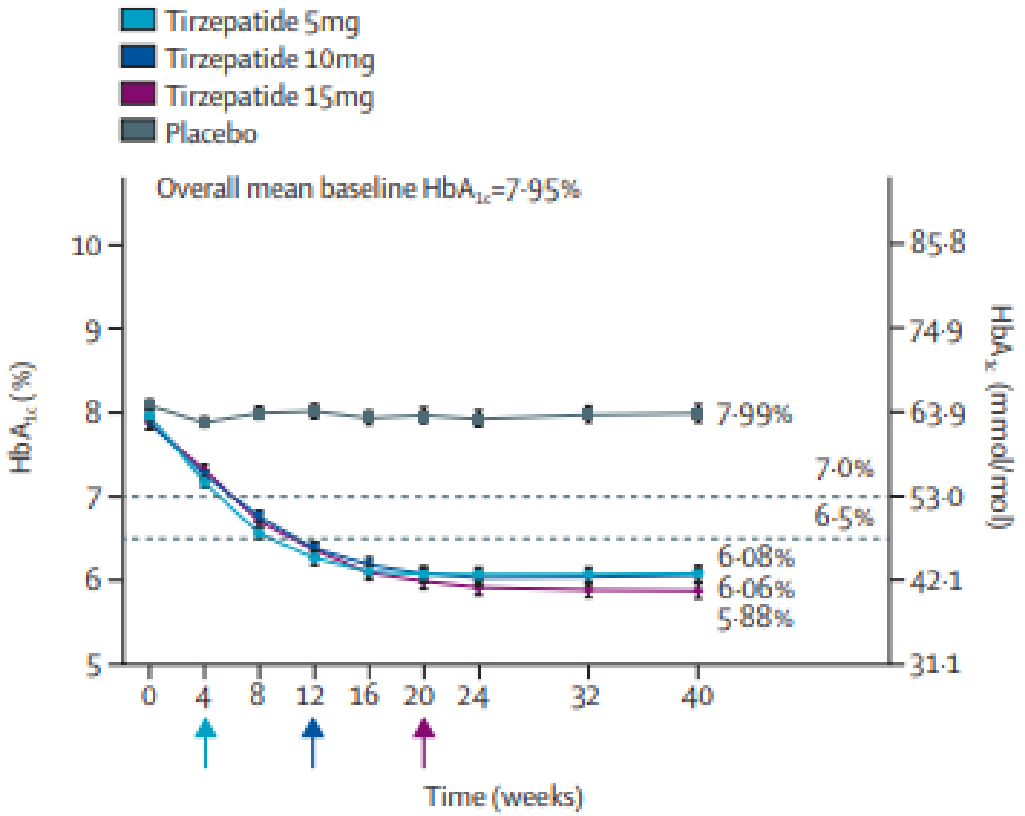
Disclosure

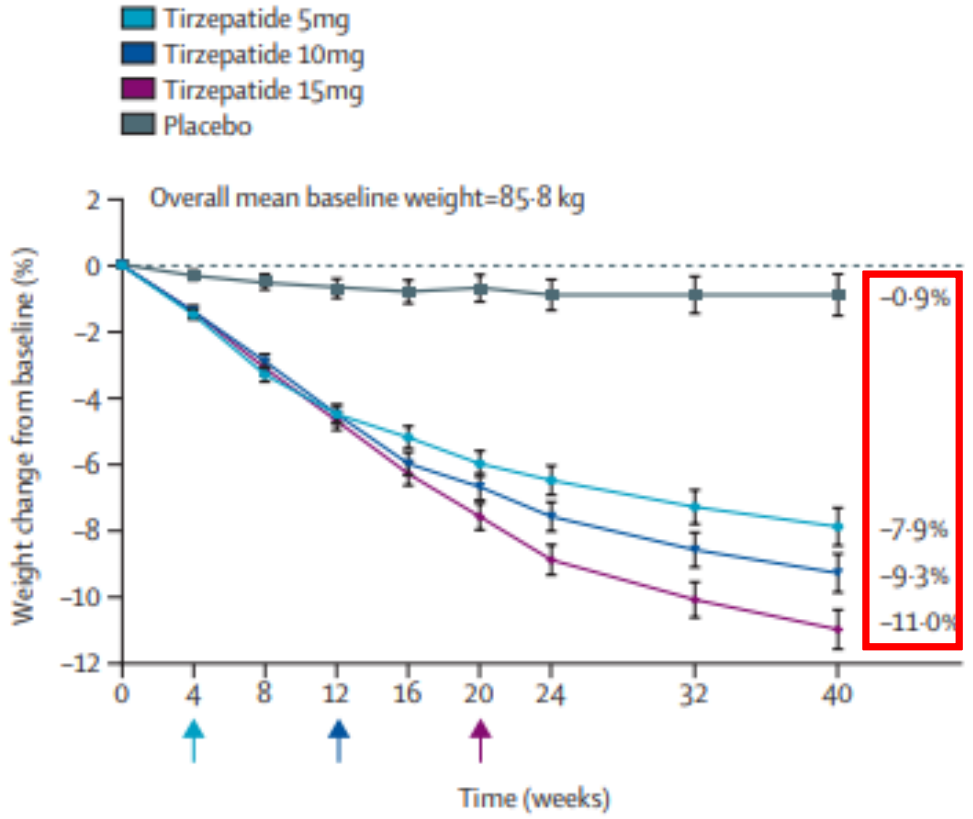
Yuki Oe, Takashi Omori, Koki Nakamura, Shin Furukawa, Taro Nishio, Hirohiko Kitakawa, Kiyoshi Sakai

Lecture fee:

Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma, Sumitomo Pharma Co. Ltd., Kowa Pharmaceuticals Co. Ltd, Taisho Pharmaceuticals Co. Ltd., Abbott Japan Co., MSD K.K., Otsuka Pharmaceutical Co.

Introduction





Tirzepatide, the world's first dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypepide (GIP) receptor agonist, has demonstrated overwhelming efficacy of weight loss and glycemic control for people living with obesity and type 2 diabetes (T2D).

However, the efficacy and safety in these people complicating chronic kidney disease (CKD) has not been investigated.

Lancet. 2021 Jul 10;398(10295):143-155.

Aim

We conducted the present study on Japanese subjects with T2D and CKD
to evaluate the efficacy and safety of trizepatide
switching from conventional GLP-1 receptor agonists.

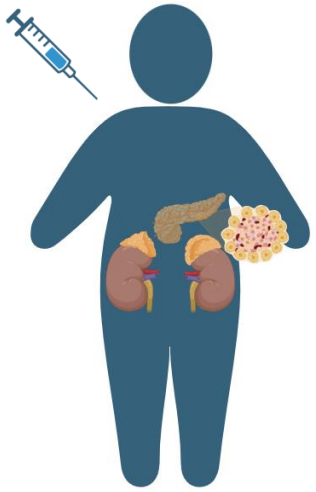
Methods: study design and outcomes

A prospective, two-arm, observational study
(Registration number:UMIN000051344)

Observation period; 6 months

Inclusion criteria

Subjects with
- eGFR < 60 mL/min/1.73m^2
- HbA1c ≥ 7%
- Age ≥ 20 years old
- Receiving dulaglutide for at least 3 months as pre-treatment



Obtained consent

Primary outcome; Difference of change in HbA1c after 24 weeks between the groups.

Secondary outcomes;
Difference of change in following items after 24 weeks between the groups.
- Body mass and glucose tolerance; waist circumference, fasting plasma glucose, C-peptide,.
- Renal functions; BUN, Cr, cystatin C, eGFRcrr, eGFRcys, UACR.
- CT findings; total fat area, subcutaneous fat area, visceral fat area, VAT/SAT ratio.

Regression analysis between the change of HbA1c and baseline parameters in tirzepatide group.

BUN, blood urea nitrogen; Cr, creatinine; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio; VAT/SAT, visceral adipose tissue/ subcutaneous adipose tissue.

Methods: exclusion criteria, statistics and sample size

Exclusion criteria

- Subjects on erythropoietin stimulating agents or hypoxia-inducible factor-prolyl hydroxylase domain inhibitor.
- Subjects on maintenance hemodialysis or peritoneal dialysis.
- And following other reasons; refusal to participate or withdrawal of consent, dissatisfaction with eligibility after registration, deterioration of complications or adverse events, pregnancy or potential pregnancy, a defaulted clinic appointment, and poor compliance with dietary and exercise therapy.

Statistics

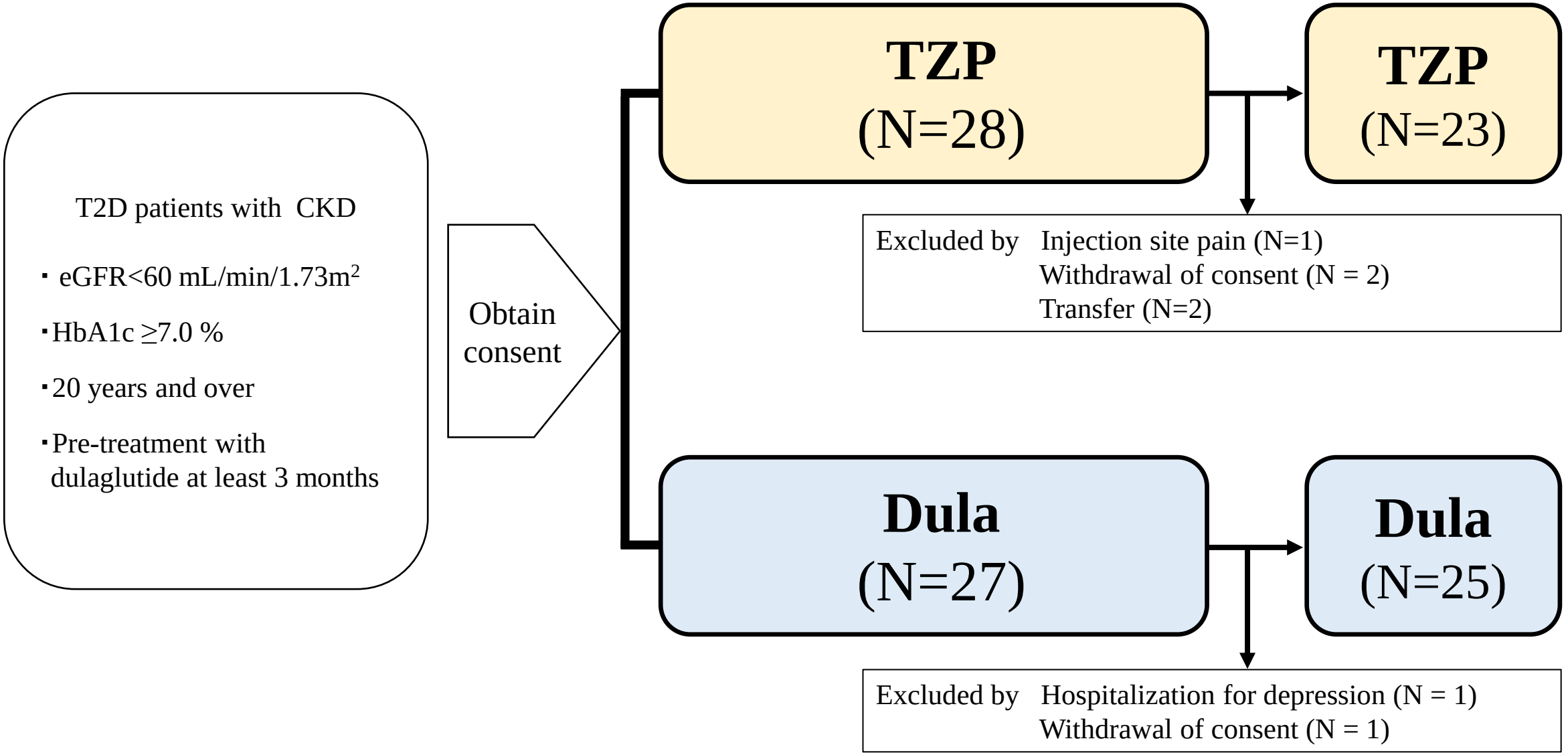
For comparison between the two groups, Student *t*-test was performed for parametric data and Wilcoxon signed-rank test was performed for non-parametric data. For comparison to baseline in each group, paired *t*-test was performed for parametric data and Wilcoxon signed-rank test was performed for non-parametric data. Fisher's exact test was applied to the categorical variables. Data were analyzed using JMP Pro 17.0.0 (SAS Inc., Cary, NC, USA).

Sample size

In a phase III study (SURPASS-J mono), the change in HbA1c for Japanese subjects with type 2 diabetes were following:
TZP 5 mg/week, -2.4% (SE: 0.1); Dula 0.75 mg/week, -1.3% (SE: 0.1).
Assuming a mean difference of 1.1% and a standard deviation of 1.30% for the reduction of HbA1c, 22 cases per group were needed under a power of 80% and a two-sided significance level of 5%.Considering a dropout rate of 15% (3 patients), the target number of subjects per group was 25, for a total of 50 subjects in both groups. As a comparison to the switched group, the number of subjects in the control group was set to be the same.

Lancet Diabetes Endocrinol. 2022;10(9):623-633.
TZP; tirzepatide, Dlua; dulaglutide

Results: flowchart diagram



TZP; tirzepatide, Dlua; dulaglutide

Results: baseline characteristics

	Variables	Tirzepatide (N=23)	Dulaglutide (N=25)	*P* value
Body mass etc.	Female sex (n)	14	12	0.40
	Age (years)	73.0 [67.0, 76.0]	72.0 [58.0, 75.5]	0.54†
	Height (cm)	157.2 ± 10.4	159.7 ± 9.0	0.38
	Body weight (kg)	67.5 ± 15.4	69.9 ± 16.3	0.61
	BMI (kg/m^2)	27.5 [22.7, 30.6]	26.3 [22.4, 30.3]	0.70†
	Waist circumference (cm)	95.2 ± 11.5	96.5 ± 13.2	0.72
	Diabetes duration (years)	18.0 [12.0, 30.0]	22.0 [16.0, 26.0]	0.26†
Biochemical data	FPG (mg/dL)	144.0 [120.0, 174.0]	135.0 [117.0, 154.0]	0.38†
	HbA1c (%)	8.2 [7.4, 8.8]	7.4 [7.2, 8.4]	0.11†
	C-peptide (ng/mL)	2.7 [1.4, 4.6]	2.1 [1.2, 3.3]	0.27†
	BUN (mg/dL)	19.5 [15.4, 22.5]	22.9 [17.3, 28.4]	0.09†
	Cr (mg/dL)	1.1 [0.8, 1.3]	1.2 [1.0, 1.4]	0.34†
	eGFRcr (mL/min/1.73m^2)	43.5 ± 10.6	42.6 ± 12.1	0.77
	Cystatin C (mg/L)	1.5 [1.2, 1.7]	1.4 [1.3, 1.9]	0.53†
	eGFRcys (mL/min/1.73m^2)	45.1 ± 12.7	43.6 ± 15.7	0.72
	UACR (mg/g•Cr)	279.1 [57.2, 1320.8]	142.1 [28.1, 652.7]	0.54†
CT findings	Total fat area (cm^2)	363.2 ± 141.5	349.7 ± 164.1	0.76
	Subcutaneous fat area (cm^2)	189.0 ± 68.9	168.2 ± 75.4	0.33
	Visceral fat area (cm^2)	180.3 [121.3, 209.8]	195.8 [76.8, 234.7]	0.61†
	VAT/SAT ratio	0.9 [0.5, 1.2]	1.0[0.7, 1.4]	0.49†

Values are expressed as mean ± SD or median (interquartile range).

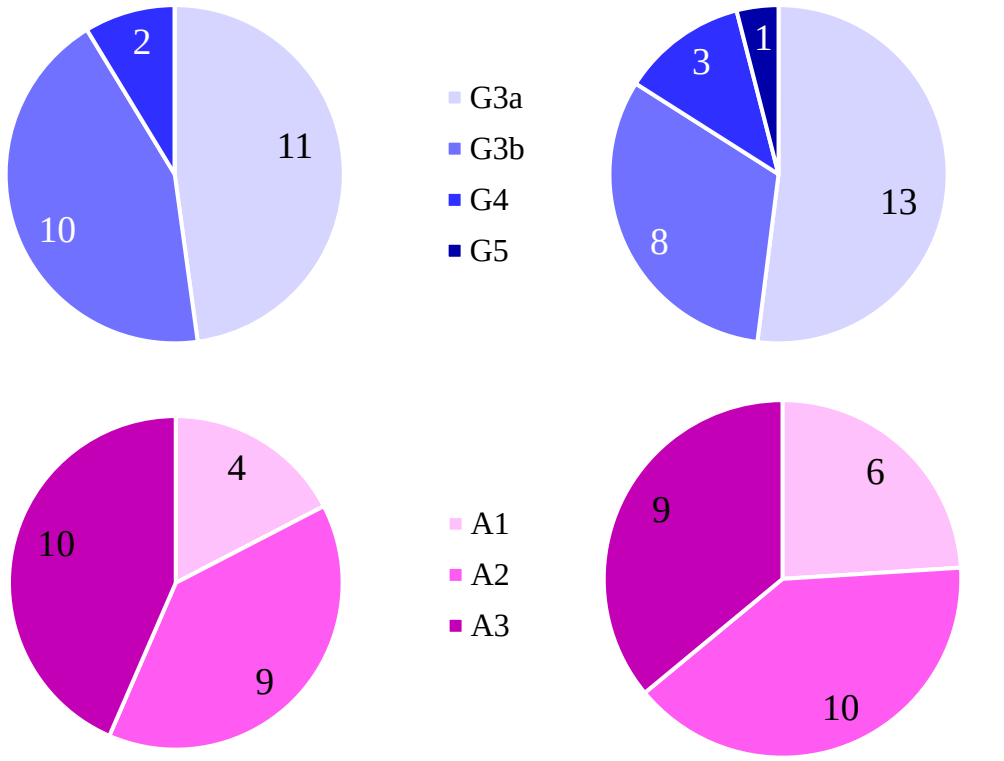
† Wilcoxon signed-rank test was applied to the following factors.
Student t-test was performed for parametric data and Wilcoxon signed-rank test was performed for non-parametric data.
eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate
UACR, urinary albumin creatinine ratio; VAT/SAT, visceral adipose tissue/ subcutaneous adipose tissue.

Results: baseline characteristics

The proportion of anti-diabetic agent (n, %)

	Tirzepatide	Dulaglutide	*P* value
The number of drugs	4.0 [3.0, 4.0]	3.0 [2.0, 4.0]	0.20
Biguanide	13(56.5)	14(56.0)	1.00
SU	5(21.7)	2(8.0)	0.24
Glinides	9(39.1)	8(32.0)	0.76
Thiazolidine	1(4.3)	0(0.0)	0.48
α-GI	9(39.1)	6(24.0)	0.35
SGLT2i	15(65.2)	10(40.0)	0.09
Insulin	13(56.5)	19(76.0)	0.22
Basal insulin	13 (56.5)	18 (72.0)	0.21
Dose	18.2 [6.0, 23.6]	12.5 [5.9, 17.8]	0.28
Bolus insulin	10 (43.5)	9 (36.0)	0.80
Dose	9.9 [7.8, 14.9]	13.0 [4.8, 31.0]	0.65

The proportion of CKD classification by eGFR and ACR (n)

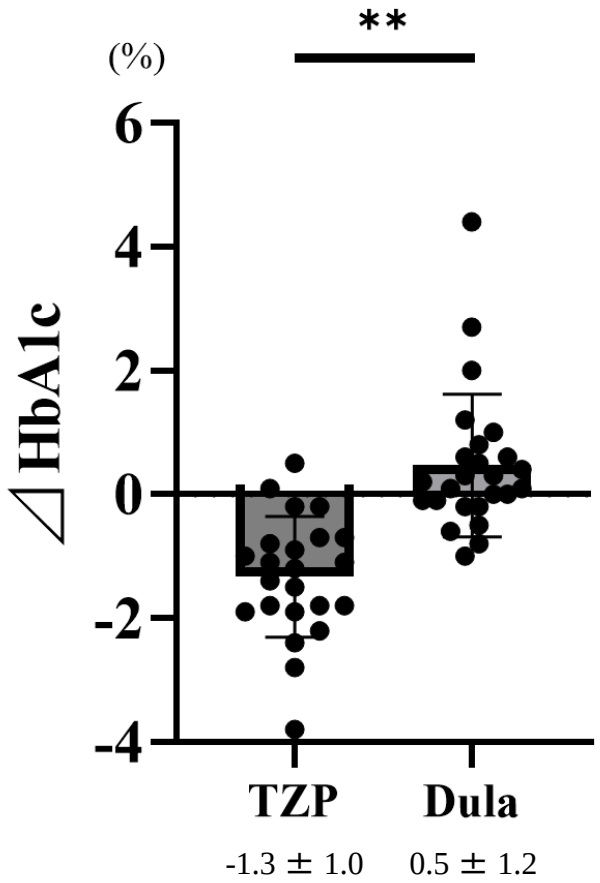


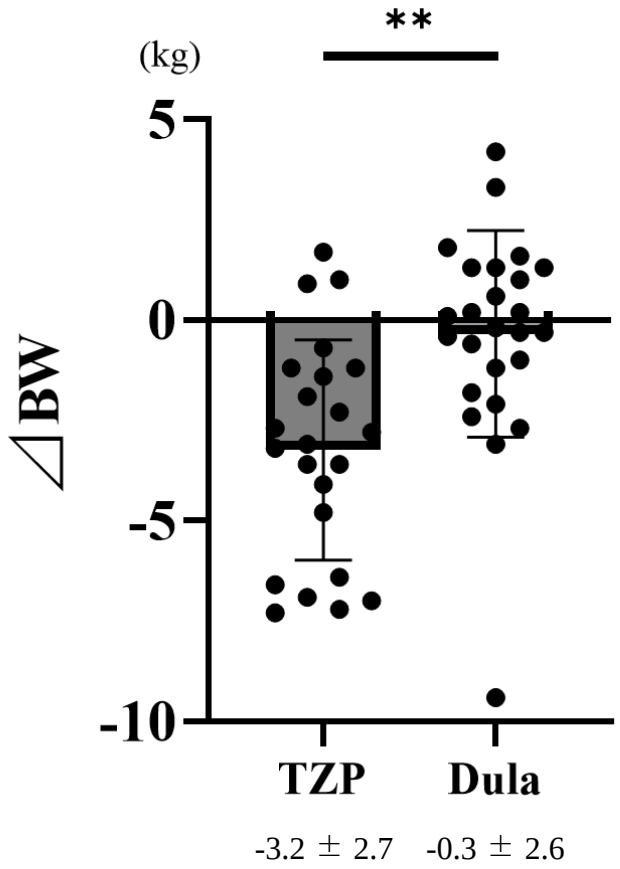
Tirzepatide (N=23)　　Dulaglutide (N=25)

G3a, eGFR=45-59; G3b, =30-44; G4, 15-29; G5, <15 mL/min/1.73m^2
A1, ACR< 30 mg/gCr; A2, 30 mg/gCr ≤ACR≤299 mg/gCr; A3, ACR≥mg/gCr.

Values are expressed as median (interquartile range). Fisher's exact test was applied to the variables.
ACR, albumin creatinine ratio; α-GI, alpha glucosidase inhibitors; CKD, chronic kidney disease;
SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea

Results: primary and secondary outcomes





Tirzepatide significantly reduced HbA1c and body weight.

Values are expressed as mean ± SD or median (interquartile range). For comparison between the two groups, Student t-test was performed for parametric data and Wilcoxon signed-rank test was performed for non-parametric data. ***P*<0.01

Results: secondary outcomes

	Variables	amount of change for 6 months TZP (N=23)	*P* value	amount of change for 6 months Dula (N=25)	*P* value	Change difference between groups *P* value
Body mass etc.	BMI (kg/m^2)	-1.3 ± 1.1	<0.01	-0.1 ± 0.9	0.53	<0.01
	Waist circumference (cm)	-4.0 [-7.0, 0.0]	<0.01	-1.5 [-5.0, 1.0]	0.04	0.22
Biochemical data	FPG (mg/dL)	-22.0 [-39.0, -9.0]	<0.01	2.0 [-21.5, 20.0]	0.82	<0.05
	CPR (ng/mL)	0.0 [-0.5, 0.3]	0.77	-0.1 [-0.4, 0.7]	0.90	0.91
	BUN (mg/dL)	2.1 ± 5.8	0.09	0.5 ± 5.2	0.67	0.29
	Cr (mg/dL)	0.0 [-0.1, 0.1]	0.11	0.0 [-0.1, 0.1]	0.69	0.10
	eGFRcr (mL/min/1.73m^2)	2.3 [-2.4, 5.0]	0.09	-0.5 [-2.2, 2.8]	0.93	0.18
	CysC (mg/L)	0.1 [-0.1, 0.2]	0.07	0.1 [0.0, 0.2]	<0.01	0.54
	eGFRcys (mL/min/1.73m^2)	-2.4 [-7.2, 2.3]	0.08	-3.3 [-6.7, 0.9]	<0.01	0.74
	UACR (mg/g•Cr)	-3.5 [-129.4, 117.7]	1.00	76.5 [4.8, 476.4]	<0.01	<0.05
CT findings	Total fat area (cm^2)	-41.4 ± 46.9	<0.01	-5.7 ± 44.5	0.53	<0.01
	Subcutaneous fat area (cm^2)	-13.9 [-39.4, -1.2]	<0.01	-6.5 [-20.0, 3.9]	0.18	0.12
	Visceral fat area (cm^2)	-27.3 [-31.0, -5.5]	<0.05	-1.8 [-12.1, 6.5]	0.41	<0.05
	VAT/SAT ratio	0.0 [-0.1, 0.1]	0.35	0.0 [-0.1, 0.1]	0.41	0.17

Prevention for the progression of nephropathy was expected with tirzepatide.

Values are expressed as mean ± SD or median (interquartile range). For comparison between the two groups, Student t-test was performed for parametric data and Wilcoxon signed-rank test was performed for non-parametric data.

Results: Regression analysis in TZP group

Baseline parameters	r	*P* value
Age	0.1684	0.44
Height	-0.4634	<0.05
Body weight	-0.3614	0.09
BMI	-0.1145	0.60
Waist circumference	-0.2748	0.22
Diabetes duration	-0.4500	<0.05
FPG	-0.6281	<0.01
HbA1c	-0.7472	<0.01
CPR	-0.1791	0.41
BUN	0.0183	0.93
Cr	-0.2532	0.24
eGFRcr	-0.0600	0.79
CysC	-0.0255	0.91
eGFRcys	-0.1672	0.45
UACR	-0.3506	0.10
Total fat area	-0.2809	0.19
Subcutaneous fat area	0.0604	0.78
Visceral fat area	-0.4804	<0.05
VAT/SAT ratio	-0.4676	<0.05

Variables	Estimates	SE	95%CI	P value
HbA1c	0.604	0.197	0.195 to 1.013	0.0057
Visceral fat area	-0.007	0.002	-0.010 to -0.003	0.0020

Multiple regression analysis was performed on items with significant differences in the single regression analysis by stepwise method, considering multicollinearity.

Possibly effective for T2D
with visceral fat accumulation.

Regression analysis was performed between the change of HbA1c and baseline parameters in tirzepatide group.

HOKKAIDO UNIVERSITY

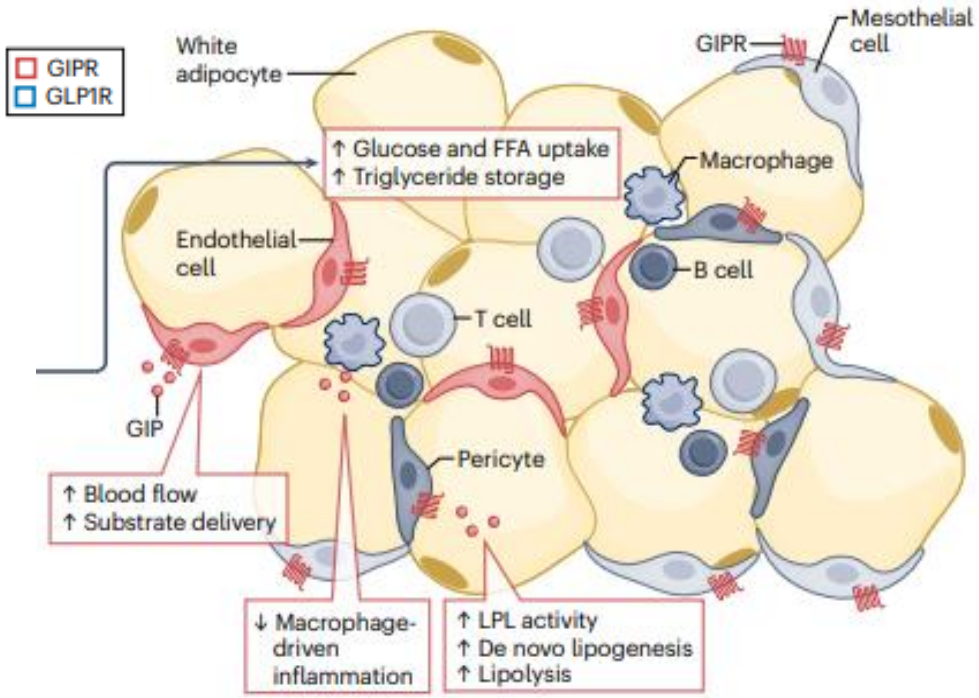
Results: Changes of HbA1c at 6 months adjusted for ANCOVA

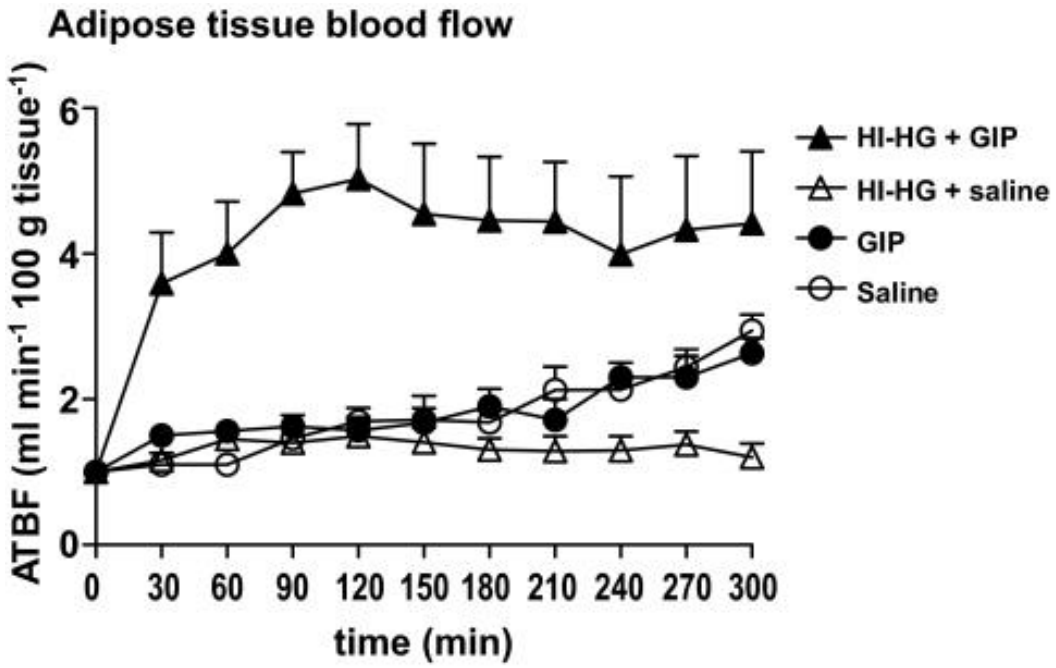
Variables	Tirzepatide	Duraglutide	P value
Model 1			
ΔHbA1c	-1.3 ± 0.22	0.5 ± 0.2	
ETD	-1.9 (-2.5, -1.2)		<0.001
Model 2			
ΔHbA1c	-1.3 ± 0.2	0.5 ± 0.2	
ETD	-1.8 (-2.5, -1.2)		<0.001
Model 3			
ΔHbA1c	-1.3 ± 0.2	0.5 ± 0.24	
ETD	-1.8 (-2.5, -1.1)		<0.001
Model 4			
ΔHbA1c	-1.3 ± 0.2	0.5 ± 0.2	
ETD	-1.8 (-2.5, -1.2)		<0.001

Model 1: adjusted for sex, age, BMI, and WC.
Model 2: Model 1 plus HbA1c.
Model 3: Model 1 plus HbA1c and diabetes duration period.
Model 4: Model 1 plus HbA1c, diabetes duration period, and visceral fat area.

Values are presented as adjusted mean ± standard error or the estimated treatment difference (95% confidence interval).
Data were adjusted for ANCOVA.
ETD, estimated treatment difference; WC, waist circumference.

Discussion; the possible optimization of lipid metabolism



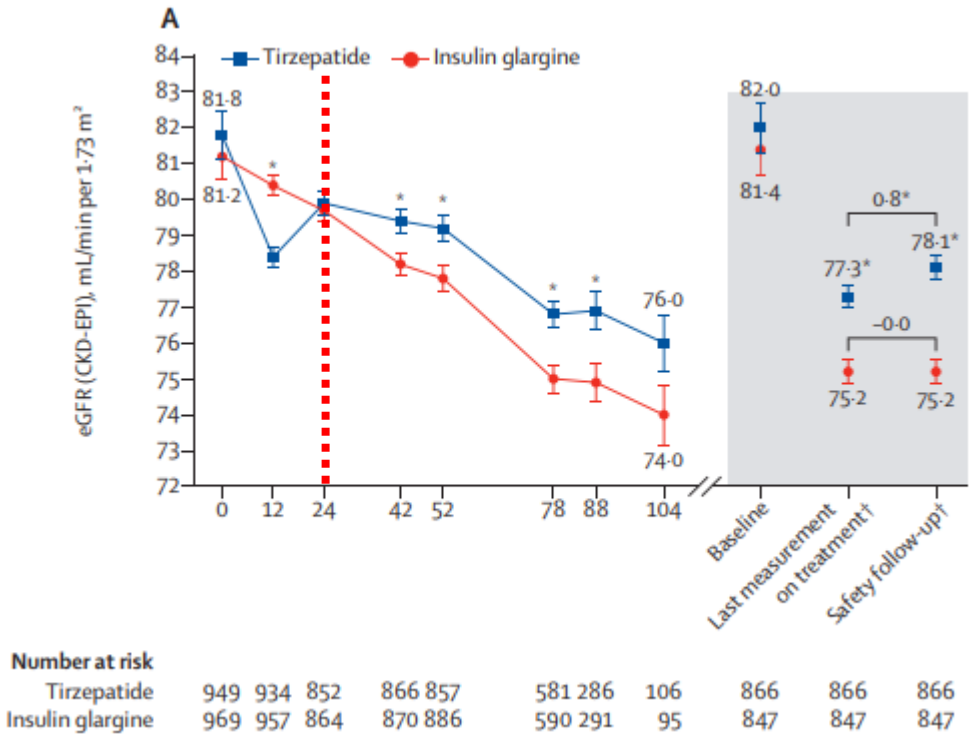


- The function of white adipose tissue (WAT) is to regulate circulating lipids by the release and storage of free fat acid.
- The infusion of GIP might be able to restore the original fat buffering capacity by correcting WAT blood flow.

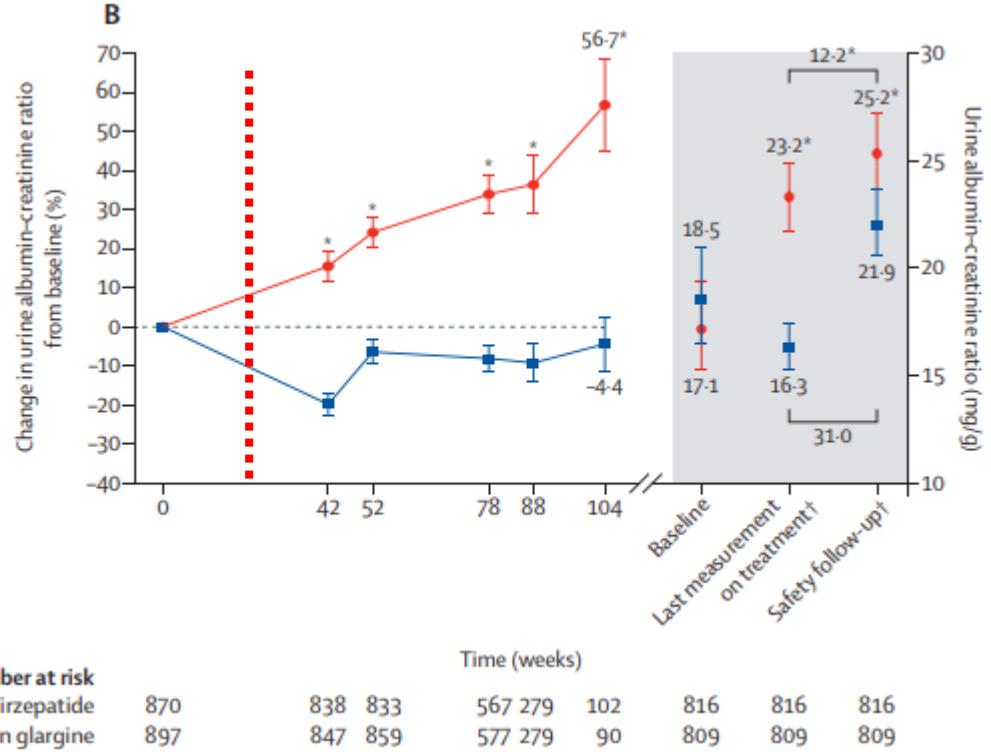
Trends Endocrinol Metab. 2020;31(6):410-421. *Diabetologia*. 2002;45(9):1201-10.
Nat Rev Endocrinol. 2023;19(4):201-216. *Nat Rev Mol Cell Biol. 2019;20(4):242-58.*

Discussion: the possible prevention for progression of nephropathy

Decline of eGFR.



Trend of UACR



- No GIP receptors are expressed in the kidney, suggesting an indirect mechanism.
- Decreasing UACR may require more long-term observation.

Lancet Diabetes Endocrinol. 2022 Nov;10(11):774-785.

Limitation

- This is not an RCT, and selection bias may be introduced.
- Guaranteed detectability, but only a small sample size.
- Participants were exclusively Japanese, which limits the generalizability of the findings.

Conclusion

Our results demonstrated dramatically weight loss and hypoglycemic effects of tirzepatide even in subjects with CKD.

Additionally, it is effective for subjects with visceral fat accumulation and may have a preventive effect on progression of nephropathy.