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Inverse Correlation between Free Triiodothyronine to Free Thyroxine Ratio and Dietary Sodium Intake in Patients with Type 2 Diabetes Taking Dipeptidyl Peptidase 4 Inhibitors: A Retrospective Cohort Study

ABSTRACT

Objective: This clinical study investigated the hypothesis that patients with type 2 diabetes (T2D), who consume more dietary sodium while taking dipeptidyl peptidase 4 inhibitors (DPP4is), would demonstrate increased iodothyronine deiodinase-2 activity, elevating the free triiodothyronine to free thyroxine ratio.

Materials and methods: This study included 157 patients with T2D. Dietary salt intake was estimated following Tanaka's formula. Pearson's correlation coefficients were calculated to estimate the linear correlations between variables.

Results: The DPP4i and non-DPP4i groups included 58 (female/male = 15/43) and 99 participants (female/male = 37/62), respectively. The patient characteristics of the DPP4i versus non-DPP4i groups were as follows: mean age (years): 70.2 ± 10.7 versus 68.3 ± 11.7; mean T2D duration (years):16.8 ± 10.9 versus 16.5 ± 12.7; mean thyroid-stimulating hormone (μU/mL): 2.04 ± ± 1.75 versus 2.036 ± 1.381; mean free triiodothyronine (FT3) (pg/mL): 2.792 ± 0.378 versus 2.741 ± 0.402; free thyroxine (FT4) (ng/dL): 1.08 ± 0.216 versus 1.134 ± 0.237; FT3/FT4 ratio: 2.569 ± 0.487 versus 2.486 ± 0.486; sodium intake (g/day): 10.4 ± 2.911 versus 10.41 ± 2.671. The free triiodothyronine to free thyroxine ratio was inversely correlated with dietary sodium intake in the DPP4i group (r = −0.444) but demonstrated no correlation with dietary sodium intake in the non-DPP4i group (r = −0.153).

Conclusions: The results are different from those of mouse adipose tissue, but DPP4is may affect iodothyronine deiodinase-2 activity in patients with T2D under certain conditions. Clinicians should pay close attention to DPP4i intake and dietary sodium consumption when estimating the iodothyronine deiodinase activity of patients with T2D. (Clin Diabetol 2024; 13, 2: 101–105)

Keywords: type 2 diabetes, iodothyronine deiodinase-2, free triiodothyronine to free thyroxine ratio, sodium intake, dipeptidyl peptidase 4 inhibitor

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Introduction

Liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), increases type 2 iodothyronine deiodinase (DIO2) activity without significantly up-regulating its mRNA levels in mouse adipose tissue [1]. A study revealed that oral sodium loading increases endogenous glucagon-like peptide-1 (GLP-1) levels in humans [2], whereas our previous study demonstrated that patients with type 2 diabetes (T2D) who received increased dietary sodium intake exhibited improved dipeptidyl peptidase 4 inhibitors (DPP4i) effects on glycemic control [3].

The free triiodothyronine (FT3) to free thyroxine (FT4) ratio (FT3/FT4 ratio) is considered an index of type 1 iodothyronine deiodinase (DIO1) and DIO2 activities [4–6]. Therefore, this clinical study investigated the hypothesis that patients with T2D consuming more dietary sodium while taking DPP4i would demonstrate increased DIO activities, causing elevated FT3/FT4 ratio.

Materials and methods

Participants

The Institutional Review Board of Hidaka Hospital approved our study protocol that conformed to the principles stated in the Declaration of Helsinki (1964) (#336). Each participant signed written informed consent.

We excluded participants who had ever been diagnosed with hypertension with or without antihypertensive medication because they were instructed to reduce dietary sodium intake. Additionally, changes were not made to the prescriptions during the observation period. Moreover, this study excluded participants with an estimated glomerular filtration rate of < 45 mL/min/1.73 m^2 as well as those taking GLP-1 RA because the ligand level to the GLP-1 receptor reached a nonphysiologically high level.

Thus, this study included 157 patients with T2D and no previously diagnosed hypertension who visited our hospital from December 2021 to December 2022.

Estimation of the dietary sodium intake

Dietary salt intake was estimated according to Tanaka's formula [7]. Tanaka's formula is a method for estimating 24-h sodium excretion using urine samples at any time. It is used to evaluate salt intake in patients with hypertension and for salt reduction guidance.

Specifically, first, calculate the 24-h urinary creatinine excretion (mg/day) from the formula {[weight (kg) × 14.89] + [height (cm) × 16.14] (age × 2.043) 2244.45. Afterward, calculate the 24-h urinary Na excretion (mEq/day) by {21.98 × [urinary Na (mEq/L) at any time ÷ urinary creatinine (mg/dL) at any time ÷ ÷ 10 × 24-hour urinary creatinine excretion] ^ 0.392}. Finally, the estimated daily salt intake (g/day) was calculated from {24-hour urine Na divided by 17}.

Sample size

The sample size was calculated, considering a statistical power of 0.80, a of 0.05, and an effect size of 0.361. The resulting sample sizes were individuals for the outcomes. Therefore, our study required 58 samples for the DPP4i group.

Statistical analysis

All statistical data were analyzed using Statistical Package for the Social Sciences software (version 10.0, SPSS Inc., Chicago, IL, USA). All numerical values are expressed as means ± SD. Dunnett's test was used for multiple comparisons of variables. Analysis of variance and Wilcoxon rank-sum test were used to compare continuous variables by group for non-normally distributed data. We calculated Pearson's correlation coefficients to estimate the linear correlation between variables. All tests for significance and the resulting p-values were two-sided, with a level of significance set at 5%.

Results

Participant characteristics

The majority of the subjects were male, accounting for 74.1% and 62.6% of the DPP4i (N = 58) and non-DPP4i groups (N = 99), respectively. The patient characteristics in the DPP4i and non-DPP4i groups were as follows: mean age (years): 70.2 ± 10.7 versus 68.3 ± ± 11.7; mean T2D duration (years): 16.8 ± 10.9 versus 16.5 ± 12.7; mean body mass index (kg/m^2): 24.5 ± 3.4 versus 24.7 ± 16.2; mean systolic blood pressure (mmHg): 133.2 ± 15.6 versus 134.1 ± 16.2; mean diastolic blood pressure (mmHg): 71.3 ± 11.7 versus 72.3 ± 11.0; mean serum creatinine level (mg/dL): 0.90 ± 0.28 versus 0.85 ± 0.32; mean casual triglyceride level (mg/dL): 152.1 ± 86.7 versus 164.1 ± 98.5; mean high-density lipoprotein cholesterol level (mg/dL): 53.0 ± 12.7 versus 60.2 ± 19.0; mean low-density lipoprotein cholesterol level (mg/dL): 105.6 ± 30.5 versus 111.7 ± 32.6; mean casual plasma glucose level (mg/dL): 163.6 ± 50.1 versus 153.6 ± 56.6; mean glycated hemoglobin level (%): 6.7 ± 1.0 versus 6.8 ± 0.8; mean thyroid-stimulating hormone (TSH) (μU/mL): 2.04 ± 1.75 versus 2.036 ± 1.381; mean free triiodothyronine (FT3) (pg/mL): 2.792 ± 0.378 versus 2.741 ± 0.402; mean free thyroxine (FT4) (ng/dL): 1.08 ± 0.216 versus 1.134 ± 0.237; FT3/FT4 ratio: 2.569 ± 0.487 versus 2.486 ± 0.486; sodium intake (g/day): 10.4 ± 2.911 versus 10.41 ± 2.671. The dif-

ference in characteristics between the two groups is statistically not significant.

Proportion of patients prescribed antidiabetic medications

Among those in the DPP4i and non-DPP4i groups, sodium-glucose cotransporter 2 inhibitors (SGLT2is) were prescribed to 42.4% and 46.6%, glinides to 22.2% and 13.8%, sulfonylureas to 22.2% and 8.6%, α-glucosidase inhibitors to 11.1% and 6.9%, thiazolidinediones to 1.0% and 0%, to biguanides 30.3% and 20.7%, and GLP-1 receptor analogs (GLP-1 RAs) to 0.0% and 0.0%. Insulin was administered in 10.0% and 25.9% and imeglimin in 12.1% and 6.9% of the DPP4i and non-DPP4i groups, respectively.

Proportion of patients prescribed DPP4i

Sitagliptin, vildagliptin, linagliptin, teneligliptin, alogliptin, and anagliptin were administered in 58.0%, 18.0%, 16.0%, 4.0%, 2.0%, and 2.0% of patients, respectively. Statins were prescribed in 37.4% and 25.8% of the patients and proton-pump inhibitors in 3.0% and 3.2% of the DPP4i and non-DPP4i groups, respectively.

Analysis of multiple comparisons for factors affecting the FT3/FT4 ratio

Table 1 shows that sodium intake was independently associated with the FT3/FT4 ratio but not associated with TSH, FT3, and FT4 levels in the DPP4i group. Conversely, sodium intake was not associated with TSH, FT3, FT4, and FT3/FT4 ratios in the non-DPP4i group.

Relationship between the FT3/FT4 ratio and dietary sodium intake in the DPP4i and non-DPP4i groups

Figure 1 shows the regression coefficients for the univariate linear regression analysis between the FT3/FT4 ratio and dietary sodium intake in the DPP4i and non-DPP4i groups. The FT3/FT4 ratio was inversely correlated with dietary sodium intake in the DPP4i group ($r = -0.444$) (Fig. 1A) but not in the non-DPP4i group ($r = -0.153$) (Fig. 1B).

Discussion

Thyroid hormone deiodinases consist of a dynamic system whose components synergistically act to ultimately maintain thyroid hormone signaling to the greatest extent possible in the serum and intracellular environment, thereby supporting thyroid function concerning various demands of the organism in physiological and pathological contexts [8]. The FT3/FT4 ratio is an index of DIO1 and DIO2 activities [4–6].

Studies have revealed that liraglutide, a GLP-1 RA, increases DIO2 activity in mice [1]. However, oral sodium loading increases endogenous GLP-1 levels in humans [2]. Consistent with these results, we previously revealed that patients with T2D who had increased dietary sodium intake demonstrated heightened DPP4i

Table 1. Participant Characteristics

	DPP4i group	Non-DPP4i group
N	58	99
Gender [F/M]	15/43	37/62
Age [years]	70.2 ± 10.7	68.3 ± 11.7
Type 2 diabetes duration [years]	16.8 ± 10.9	16.5 ± 12.7
Body mass index [kg/m^2]	24.5 ± 3.4	24.7 ± 16.2
Systolic blood pressure [mmHg]	133.2 ± 15.6	134.1 ± 16.2
Diastolic blood pressure [mmHg]	71.3 ± 11.7	72.3 ± 11.0
Serum creatinine [mg/dL]	0.90 ± 0.28	0.85 ± 0.32
Casual triglyceride [mg/dL]	152.1 ± 86.7	164.1 ± 98.5
High-density lipoprotein cholesterol [mg/dL]	53.0 ± 12.7	60.2 ± 19.0
Low-density lipoprotein cholesterol [mg/dL]	105.6 ± 30.5	111.7 ± 32.6
Casual plasma glucose [mg/dL]	163.6 ± 50.1	153.6 ± 56.6
Glycated hemoglobin [%]	6.7 ± 1.0	6.8 ± 0.8
Thyroid stimulating hormone [mU/mL]	2.04 ± 1.75	2.036 ± 1.381
Free triiodothyronine [pg/mL]	2.792 ± 0.378	2.741 ± 0.402
Free thyroxine [ng/dL]	1.08 ± 0.216	1.134 ± 0.237
Free triiodothyronine to free thyroxine ratio	2.569 ± 0.487	2.486 ± 0.486
Sodium intake [g/day]	10.4 ± 2.911	10.41 ± 2.671

All numerical values are expressed as means ± standard deviation; DPP4i — dipeptidyl peptidase 4 inhibitor

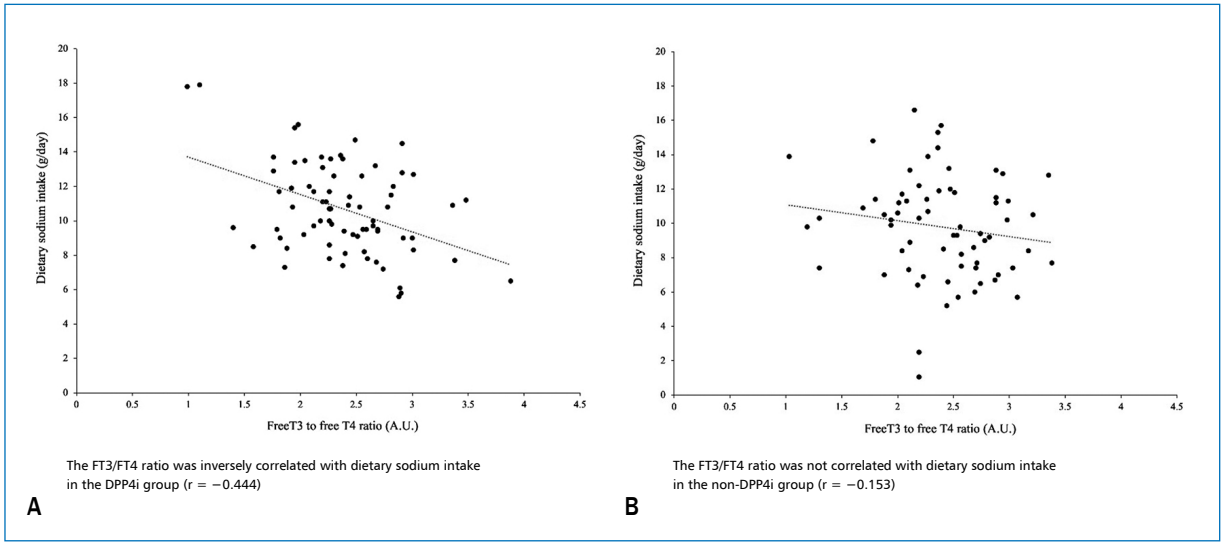

Figure 1. Relationship between the Free Triiodothyronine to Free Thyroxine Ratio (FT3/FT4 Ratio) and Dietary Sodium Intake in **A**. the DPP4 Inhibitor (DPP4i) and **B.** Non-DPP4i Groups. DPP4 — dipeptidyl peptidase 4

Table 2. Multiple Regression Analysis of the Relationship between Sodium Intake and Associated Thyroid Hormones

	DPP4i group		non-DPP4i group	
	p-value	r-value	p-value	r-value
Thyroid stimulating hormone	0.822	0.023	0.644	0.067
Free triiodothyronine	0.483	−0.062	0.343	−0.118
Free thyroxine	0.324	0.148	0.455	0.067
Free triiodothyronine to free thyroxine ratio	0.011	−0.444	0.011	−0.153

r represents the correlation coefficient; DPP4i — dipeptidyl peptidase 4 inhibitor

effects on glycemic control, based on which we assumed that dietary sodium intake affects endogenous GLP-1 levels and activity [3]. Thus, DPP4 may affect DIO2 activity under certain conditions. Therefore, the current clinical study aimed to investigate the hypothesis that patients with T2D, who consume more dietary sodium while taking DPP4is, would exhibit increased DIO2 activities, causing elevated FT3/FT4 ratios. However, contrary to our hypothesis, the FT3/FT4 ratio was inversely correlated with dietary sodium intake in the DPP4i group ($r = -0.444$) but not correlated in the non-DPP4i group ($r = -0.153$). Our results indicate differences between humans and mice as well as DIO2 measurement.

The clinical significance of this study

Clinicians need to determine the blood TSH and T4 levels and do not directly measure T3 to assess thyroid function [9]. However, a recent study has revealed that subclinical variation in the hypothalamic–pituitary–thyroid–axis effector hormone T3 is a crucial and overlooked factor connecting socioeconomic forces, human biology, and aging [9]. Importantly, T4 and TSH levels are poorly associated with free T3 levels. Alternatively, TSH and T4 may not be accurate surrogates of free T3. Thus, measuring T3 levels is recommended in addition to T4 and TSH levels. However, deiodinase produced T3 from T4 [4–6], thus determining a new factor that affects deiodinase activity is important. Concomitant with this line of thought, whether or not dietary sodium intake and DPP4i affect deiodinase activity (FT3 to FT4 ratio) becomes a clinically important issue.

Our study has limitations that warrant further discussion. First, we did not measure GLP-1 levels because we did not obtain blood samples. Second, the sample size was small (N = 157), with limited differences in ethnicity, age, and weight. Therefore, our results are not completely generalizable. Thus, future studies that include a larger

cohort with a wider range of demographic characteristics are warranted to confirm our results. Altogether, our results revealed that clinicians should pay close attention to DPP4i intake and dietary sodium consumption when estimating DIO2 activities in patients with T2D.

Article information

Data availability statement

The datasets generated or analyzed in the current study are available from the corresponding author upon reasonable request.

Ethics statement

The ethics committees at Hidaka Hospital approved our study, which conformed to the Declaration of Helsinki (as #355).

Author contributions

Shuichi Okada, Koji Kikkawa, and Kihachi Ohshima took care of the patient. Shuichi Okada, Kazuya Okada, Koji Kikkawa, Junichi Okada, Eijiro Yamada, Tsugumichi Saito, Tetsuro Andou, and Kihachi Ohshima attended the clinical conferences and made important suggestions for differential diagnosis and therapeutic strategy. Shuichi Okada and Junichi Okada prepared the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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