



Higher hemoglobin level may be associated with use of dipeptidyl peptidase-4 (DPP-4) inhibitor by diabetic patients on hemodialysis



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Background / Objective

- Background**
 - Recently, the ability of Dipeptidyl peptidase-4 inhibitors (DPP4i) to effect anti-inflammation and hematopoietic stimulation has been reported in several experimental studies.
 - it is still unknown whether DPP4i actually increase the hemoglobin level in diabetic patients on dialysis..
- Objective**
 - Examine the association between DPP4i use and hemoglobin level.

Methods

- Study Population:** N=87,830 diabetic patients who had received maintenance hemodialysis for at least 12 months, 2012.12 to 2013.12 in Japan, after excluding patients who had been dialyzed <3 /week or <2hr per treatment, or those with a history of organ transplantation
- Analysis:**
 - Model:** multivariate regression analysis
 - Dependent variable:** hemoglobin level
 - Matching:** propensity-score (PS) matching and inverse probability weighting (IPW) for the use of DPP4i
 - Adjustments:** age; sex; dialysis vintage; modality; BMI; smoking; types of diabetes; albumin; TSAT; ferritin; CRP; glycemic control (standardized); Erythropoietin dose per weight (standardized); use of insulin, DPP4i, or OHA; vascular complications; and antihypertensive drugs at the beginning of observation. (Dose of erythropoietin was only available in the dataset 2012.)

Results

Figure 1: Average hemoglobin among anti-hyperglycemic agents groups

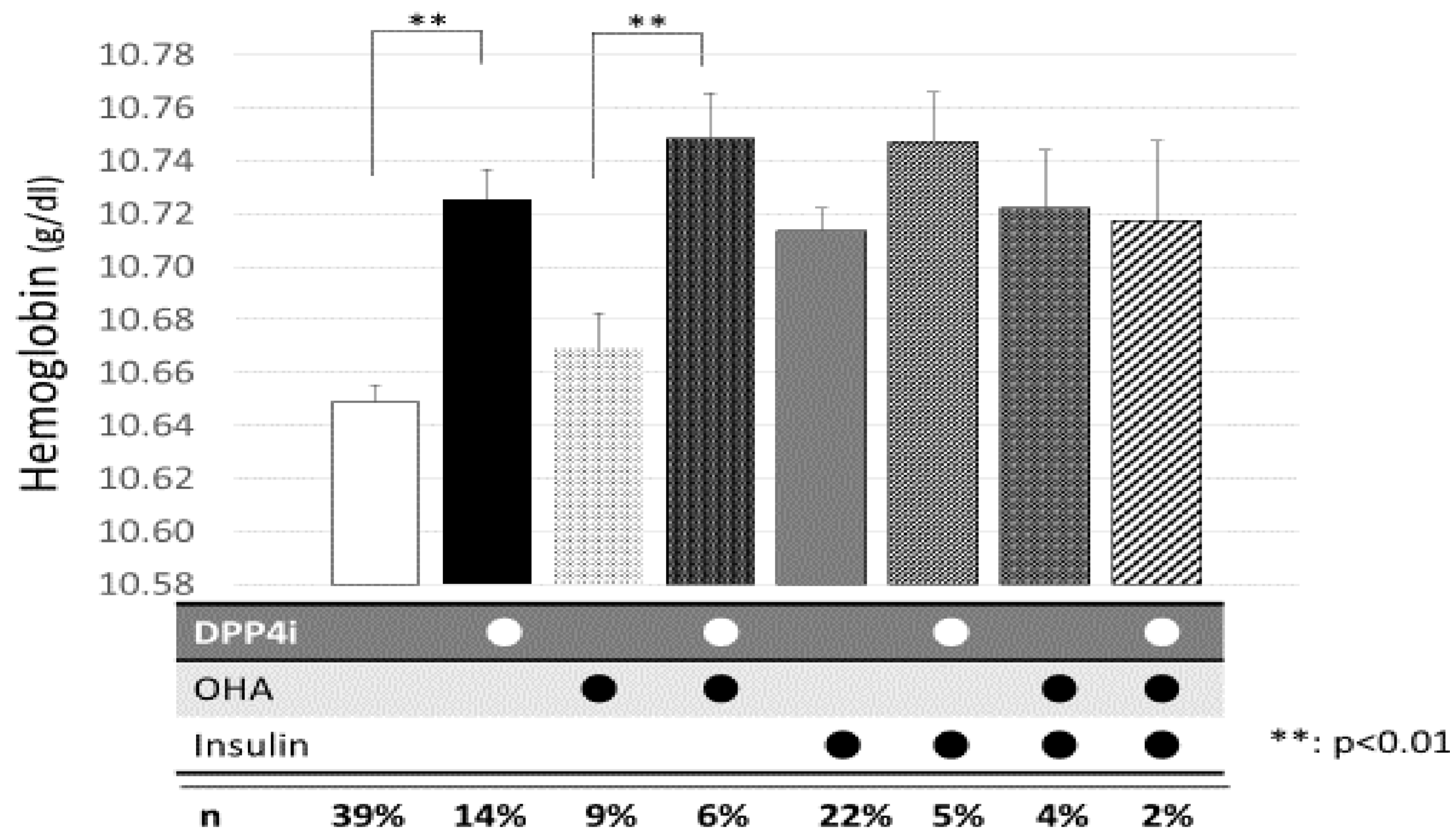


Table 1: Patient Characteristics

	Total	DPP4i (-)	DPP4i (+)	p
n	87,830	63,647	24,183	
Age (years)	67.5±11.3	67.5±11.3	67.5±11.1	0.99
Vintage (years)	5.5±4.7	5.7±4.7	4.9±4.6	<0.001
Female	30.5%	30.3%	31.1%	0.03
Primary disease: DM nephropathy	84.8%	84.6%	85.5%	0.001
Modality: hemodiafiltration	9.2%	9.1%	9.6%	0.04
Body mass index (kg/m ²)	22.4±4.0	22.4±4.0	22.5±4.1	<0.001
Smoking	14.2%	14.0%	14.6%	0.04
Type 2 diabetes mellitus	80.3%	79.2%	83.1%	<0.001
History of Cardiovascular diseases	34.4%	34.7%	33.8%	0.01
Glycated albumin (%)	21.3±5.3	21.0±5.3	22.0±5.2	<0.001
Erythropoietin (IU/week/kg)	82.5±53.5	82.6±53.7	82.1±53.2	0.35
ERI (IU/kg*(g/dL))	7.90±5.47	7.93±5.51	7.81±5.35	0.02
Albumin (g/dL)	3.61±0.43	3.60±0.43	3.61±0.41	0.03
Hemoglobin (g/dL)	10.69±1.22	10.67±1.23	10.74±1.20	<0.001
Transferin saturation	19.9±7.6	20.0±7.6	19.6±7.6	<0.001
Ferritin	77 [33-161]	77 [33-163]	76 [34-158]	0.38
C-reactive protein (mg/dL)	0.15 [0.06-0.47]	0.14 [0.06-0.46]	0.17 [0.06-0.50]	<0.001
Antihypertensive drug use	73.9%	73.3%	75.4%	<0.001
Hyperglycemic agents use				
with insulin only	26.5%	29.5%	18.1%	<0.001
with OHA only	15.0%	12.8%	20.9%	<0.001
with insulin and OHA	5.4%	6.9%	4.9%	<0.001
without insulin nor OHA	53.1%	52.8%	54.1%	<0.001

Abbreviation: DPP4i, dipeptidyl peptidase-4 inhibitors; ERI, erythropoietin resistance index; OHA, other hypoglycemic agents
 **The dose of erythropoietin per body weight was standardized using Z-scores and transferred to dose of erythropoietin in order to compare ERIs among erythropoietin, darbepoetin, and epoetin beta pegol groups.

Table 2: Factors associated with hemoglobin level

Variable	Coefficient (95% CL)	p value
Age (per 10 years)	-0.007 (-0.019, 0.005)	0.23
Vintage (per 10 years)	-0.027 (-0.055, 0.000)	0.05
Female	-0.104 (-0.130, -0.078)	<0.001
HDF (reference:HD)	0.018 (-0.002, 0.038)	0.07
Vascular complications	0.034 (0.009, 0.059)	0.008
Antihypertensive drug use	-0.068 (-0.096, -0.040)	<0.001
Body mass index (+ 1.0 kg/m ²)	0.0003 (-0.003, 0.004)	0.86
Glycated albumin (+1.0 %)*	-0.002 (-0.004, 0.001)	0.18
Use of DPP4i	0.044 (0.017, 0.070)	0.001
Use of OHA	0.013 (-0.016, 0.042)	0.38
Erythropoietin (IU/kg, + 1.0 SD) (logarithm)	-0.108 (-0.121, -0.095)	<0.001
Albumin (+ 1.0 g/dL)	0.360 (0.322, 0.397)	<0.001
Transferrin saturation (+ 1.0%)	-0.001 (-0.003, 0.0002)	0.09
C-reactive protein (logarithm)	-0.075 (-0.070, -0.066)	<0.001

Abbreviations: 95% CL, 95% confidence limit; HDF, hemodialysis filtration; HD, hemodialysis; BS, blood sugar;

Table 3: Results of the estimation of average treatment effects with use of DPP4i

Average treatment effect (ATE)	Coefficient (95% CL)	p value
Propensity-score matching		
Full match	0.034 (-0.008, 0.077)	0.11
Matching except TSAT, ferritin, CRP	0.030 (-0.006, 0.066)	0.10
Matching except albumin, ESA, TSAT, ferritin, and CRP	0.046 (0.014, 0.078)	0.005
Inverse probability weighting		
Full match	0.024 (-0.013, 0.060)	0.20
Matching except TSAT, ferritin, CRP	0.021 (-0.011, 0.052)	0.19
Matching except albumin, ESA, TSAT, ferritin, and CRP	0.037 (0.010, 0.065)	0.01

Abbreviations: CL, confidence limit; TSAT, transferrin saturation; CRP, C-reactive protein; ESA, standardized erythropoietin dose (IU/week/kg) (logarithm)

- After adjusting possible confounders, DPP4i use turned out to be a significant factor associated with improvement of hemoglobin level (0.044 (95% CL: 0.017, 0.070) g/dL, p=0.001).
- To minimize selection bias for choice of DPP4i prescription, we performed PS matching and IPW to balance patients' background characteristics. Average treatment effects became significant when all factors except inflammation factors were matched.
- Sensitivity analyses: We analyzed only patients whose hemoglobin levels were consistent between 2012 and 2013, and obtained similar results.

Summary / Conclusions

- There is a weak but significant association between DPP4i use, and higher hemoglobin level in hemodialysis patients, even after adjusting possible confounders.
- it is suggested that higher hemoglobin level in DPP4i users may be intermediated by the anti-inflammatory effect of DPP4i.

