

A Dipeptidyl Peptidase-4 Inhibitor, Tenaigliptin, Decreases Plasma Triglyceride-Rich Lipoprotein Remnants in Diabetic Patients with Chronic Kidney Disease Undergoing Hemodialysis

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Abstract

Objective A high plasma level of remnant-like particle cholesterol (RLP-C), which is equivalent to triglyceride-rich lipoprotein remnant, is an important coronary risk marker. RLP-C level is high, independent of other plasma lipids, in patients with chronic kidney disease (CKD) undergoing hemodialysis. The effect of teneligliptin, a dipeptidyl peptidase (DPP)-4 inhibitor, on plasma levels of RLP-C in patients with diabetes mellitus and CKD under hemodialysis was studied.

Methods Tenaigliptin 20 mg/day was administered to 15 patients with diabetes and CKD undergoing hemodialysis for 12 weeks. Ten patients with diabetes and CKD undergoing hemodialysis were allocated to the control group. Blood was sampled following a 12-h fast. Fasting plasma glucose (FPG), C-peptide, triglyceride, low-density lipoprotein (LDL)-cholesterol (C), high-density lipoprotein (HDL)-C, RLP-C, apolipoprotein (apo) B, oxidized LDL, lipoprotein lipase, and glycated hemoglobin (HbA1c) were measured.

Results HbA1c decreased in the teneligliptin group but significantly increased in the control group. FPG and RLP-C significantly decreased in the teneligliptin group. Plasma lipoprotein-related parameters except RLP-C were not affected by teneligliptin treatment.

Conclusion Tenaigliptin treatment significantly reduced plasma levels of RLP-C, FPG, and HbA1c in patients with diabetes with CKD who are undergoing hemodialysis.

Key Points

High plasma remnant-like particle cholesterol (RLP-C), equivalent to triglyceride-rich lipoprotein remnants is an important coronary risk marker.

Plasma RLP-C levels are high, independent of other plasma lipid levels, in patients with chronic kidney disease undergoing hemodialysis.

A dipeptidyl peptidase-4 inhibitor, teneligliptin, reduced the plasma RLP-C, fasting plasma glucose, and glycated hemoglobin (HbA1c) in patients with diabetes mellitus who were undergoing hemodialysis.

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1 Introduction

Recently, dipeptidyl peptidase-4 (DPP-4) inhibitors have been widely used for the treatment of diabetes mellitus [1–3]. They are very effective for the treatment of diabetic patients with and without insulin treatment.

Dyslipoproteinemia is a common complication associated with diabetes [4–6] and chronic kidney disease (CKD) [7, 8]. Therefore, DPP-4 inhibitors might be effective for the treatment of plasma lipoprotein abnormality in diabetic patients with CKD.

Triglyceride (TG)-rich lipoprotein remnants, which are produced by the catabolism of intestine-derived chylomicron and hepatic-derived very low-density lipoprotein (VLDL), are small and very atherogenic [9]. Remnant-like particles (RLP) are equivalent to TG-rich lipoprotein remnants [10–13]. Plasma levels of RLP-cholesterol (C) are measured clinically to assess the plasma levels of TG-rich lipoprotein remnant. Plasma RLP-C levels are usually high in hypertriglyceridemic subjects and patients with CKD (with or without hypertriglyceridemia) undergoing hemodialysis [14–18]. Diabetes is one of the major causes of CKD and the need for hemodialysis. Atherosclerotic diseases such as coronary artery disease (CAD) and cerebrovascular disease (CVD) are the main complications experienced by patients with CKD who are under hemodialysis treatment. Reducing the plasma levels of low-density lipoprotein (LDL)-C, TG, and RLP-C by DPP-4 inhibitors could be beneficial in preventing the progression of atherosclerosis in patients with diabetes.

This study evaluated the effects of a DPP-4 inhibitor, teneligliptin, on plasma levels of lipids and oxidized LDL (ox-LDL), which is a strong atherosclerosis-promoting lipoprotein [19–22] in patients with diabetes and CKD undergoing maintenance hemodialysis treatment. Small dense LDL is extremely atherogenic and apolipoprotein (apo) B-rich [9]. The LDL-C/apo B ratio was estimated to determine whether DPP-4 inhibitors affect the LDL size.

2 Materials and Methods

2.1 Study Protocol

The study protocol was approved by the Ethics Committee of Hiratsuka Lifestyle-Related Diseases and Hemodialysis Clinic. The study commenced after informed consent was obtained from all participants. Fifteen and ten patients with diabetes and CKD undergoing hemodialysis were recruited in the teneligliptin and control groups, respectively. Nine and three patients in the teneligliptin and control groups, respectively, were under insulin treatment. Patients treated with oral antidiabetic agents were not enrolled in this study. The participants were instructed to repeatedly consume a standard weight \times 25 kcal/day diet. Patients with hereditary hyperlipoproteinemia, secondary hyperlipoproteinemia with kidney diseases, and those taking lipid-lowering and hypotensive drugs that influence plasma lipids, such as β -blockers and diuretics, were excluded.

Teneligliptin was administered after breakfast at 20 mg/day. Fasting (12 h) blood samples were collected at week 0, 4, and 12 of teneligliptin treatment.

2.2 Laboratory Procedures

Plasma levels of creatinine, glucose, lipids, and blood glycosylated hemoglobin (HbA1c) were measured using routine laboratory methods using an auto-analyzer. Blood HbA1c was measured using a latex agglutination method using a determiner L HbA1c test kit [23]. The C-peptide level was measured using an electrochemiluminescence immunoassay (Roche, Germany) [24]. Plasma levels of apo B were estimated using a turbidimetric immunoassay [25]. RLP-C was measured using a precipitation method with monoclonal antibodies against apo AI and apo B-100 [26]. LDL that reacts with monoclonal antibodies against malondialdehyde-modified LDL (MDA-LDL) was designated as ox-LDL and was measured using an enzyme-linked immunosorbent assay (ELISA) with a monoclonal antibody against MDA-LDL [27]; 1 U/L of ox-LDL was equivalent to 1 mg/L of the MDA-LDL standard. The lipoprotein lipase (LPL) assay was performed using an ELISA method with a monoclonal antibody against LPL [28].

2.3 Statistical Analysis

Values are expressed as medians (25 and 75 percentile). The comparison of baseline values between the teneligliptin and control groups was performed using the Mann-Whitney *U* test. The statistical analysis of serial changes was performed using the Friedman test, and the statistical package for the social sciences (SPSS, IBM, New York, NY, USA) was used for all statistical calculations.

3 Results

The backgrounds of the subjects are shown in Table 1, and an accurate onset of diabetes was not known. Diabetes treatment had been ongoing for more than 30 and 20 years in patients older than 70 years and those in their 60s, respectively. Diabetes had been treated for more than 10 years in seven patients in the control group who were aged 40–59 years. All patients were hypertensive and took calcium blockers, angiotensin II receptor blockers, or both. Four patients in the teneligliptin group were patients who previously had myocardial infarctions and took aspirin. The teneligliptin group subjects were significantly older than those in the control group. Body mass index (BMI), hemodialysis duration, and plasma levels of creatinine, urea nitrogen (UN), uric acid (UA), fasting plasma glucose

Table 1 Demographics of study subjects

	Teneligliptin group	Control group	<i>p</i> values ^a
N (M/F)	15 (8/7)	10 (5/5)	
Age (years)	71 (65, 75) ^b	58 (46, 60)	0.0023
BMI (kg/m ²)	22.2 (21.1, 23.5)	22.4 (21.6, 24.8)	0.4877
HD duration (months)	24 (13, 40)	19 (7, 27)	0.5281
Creatinine (mg/dL)	7.9 (7.1, 9.6)	8.8 (6.1, 10.2)	0.8009
Urea nitrogen (mg/dL)	62.7 (55.8, 69.1)	57.3 (52.1, 61.1)	0.0543
Uric acid (mg/dL)	6.7 (5.9, 8.3)	7.0 (5.9, 8.0)	0.8500
FPG (mg/dL)	131 (113, 163)	111 (94, 143)	0.4884
HbA1c (%)	6.6 (5.7, 8.5)	6.3 (5.8, 12.3)	0.7995
C-peptide (ng/mL)	6.1 (5.5, 8.1)	5.2 (4.1, 10.5)	0.4301
TC (mg/dL)	186 (136, 202)	176 (132, 209)	0.5493
TG (mg/dL)	149 (103, 176)	109 (88, 156)	0.6143
LDL-C (mg/dL)	84 (67, 115)	105 (78, 125)	0.0884
HDL-C (mg/dL)	40 (35, 46)	36 (33, 44)	0.3280
RLP-C (mg/dL)	12.5 (6.1, 13.7)	6.7 (4.5, 12.1)	0.5081
Apo B (mg/dL)	98 (65, 108)	93 (71, 117)	0.1474
Ox-LDL (U/L)	83 (79, 99)	81 (68, 101)	0.9749
LPL (ng/mL)	61 (49, 83)	79 (65, 90)	0.8254
LDL-C/apo B ratio	1.06 (0.93, 1.12)	1.12 (1.04, 1.23)	0.2984
Insulin treatment (+/−)	9/6	3/7	

apo B apolipoprotein B, *BMI* body mass index, *C* cholesterol, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin A1c, *HD* hemodialysis, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LPL* lipoprotein lipase, *N (M/F)* number (male, female), *Ox* oxidized, *RLP* remnant-like particle, *TC* total cholesterol, *TG* triglyceride

^a Statistical significance using Mann-Whitney *U* test; *p* < 0.05 was considered significant

^b Median (25 and 75 percentile)

(FPG), C-peptide, total C (TC), TG, LDL-C, HDL-C, apo B, RLP-C, Ox-LDL, and LPL, as well as blood HbA1c were not significantly different between the two groups.

Changes in plasma levels of FPG, C-peptide, lipids, apo B, RLP-C, ox-LDL, and LPL, as well as blood HbA1c during the 12-week observation in the control group, are presented in Table 2. Blood HbA1c significantly increased in the control group during the 12-week trial (*p* = 0.0087). However, plasma levels of FPG (*p* = 0.0572), C-peptide, TC, TG, LDL-C, HDL-C, apo B, RLP-C, ox-LDL, and LPL did not change significantly during the 12-week trial.

The effects of 12 weeks of teneligliptin treatment on plasma levels of FPG, C-peptide, lipids, apo B, RLP-C, ox-LDL, and LPL, as well as blood HbA1c, are shown in Table 3. Teneligliptin treatment significantly decreased the plasma levels of FPG, RLP-C, and blood HbA1c while those of C-peptide, TC, LDL-C, HDL-C, apo B, ox-LDL, and LPL did not change during the 12-week teneligliptin treatment. The LDL-C/apo B ratio was not changed in both groups. No patients had hypoglycemic attacks during the 12-week trial. The daily insulin dose was reduced by 2–4 units for four of the nine patients on insulin treatment after 4 weeks of teneligliptin treatment. No patient complained

of subjective adverse effects, and the liver function tests were normal during the 12-week trial.

4 Discussion

The effects of a DPP-4 inhibitor, teneligliptin, on diabetic and dyslipoproteinemic parameters were studied in patients with diabetes and CKD who were undergoing hemodialysis. Treatment with teneligliptin markedly reduced FPG and blood HbA1c in patients with diabetes and CKD who were undergoing hemodialysis, while HbA1c increased in the control group. The FPG and blood HbA1c level-reducing effects of teneligliptin treatment were clearly demonstrated in this study. The fasting plasma insulin levels were not affected by the 12-week teneligliptin treatment.

A high level of plasma RLP, which is equivalent to TG-rich lipoprotein remnant, is an important coronary risk marker in patients with CKD even in those with normal plasma TG levels [18]. Treatment with teneligliptin decreased plasma RLP-C in patients with diabetes and CKD who were undergoing hemodialysis; therefore,

Table 2 Plasma levels of factors of glucose and lipoprotein metabolism during 12-month trial in controls

Treatment duration (week)	0	4	12	<i>p</i> values ^a
FPG (mg/dL)	111 (94, 143) ^b	142 (116, 168)	124 (92, 164)	0.0572
HbA1c (%)	6.3 (5.8, 12.3)	7.0 (6.2, 7.3)	7.0 (6.2, 7.6)	0.0087
C-peptide (ng/mL)	5.2 (4.1, 10.5)	6.2 (4.4, 7.3)	7.2 (5.8, 9.5)	0.8233
TC (mg/dL)	176 (132, 209)	176 (142, 213)	180 (149, 200)	0.8948
TG (mg/dL)	109 (88, 156)	139 (87, 177)	115 (59, 141)	0.0973
LDL-C (mg/dL)	105 (78, 125)	96 (82, 134)	94 (78, 126)	0.8233
HDL-C (mg/dL)	36 (33, 44)	40 (32, 43)	42 (35, 51)	0.1114
RLP-C (mg/dL)	6.7 (4.5, 12.1)	9.7 (4.8, 13.1)	6.9 (5.1, 12.6)	0.4227
Apo B (mg/dL)	93 (71, 117)	102 (72, 101)	89 (70, 117)	0.7165
Ox-LDL (U/L)	81 (68, 101)	86 (75, 97)	81 (75, 105)	0.8948
LPL (ng/mL)	79 (65, 90)	67 (47, 86)	66 (53, 89)	1.0000
LDL-C/apo B ratio	1.12 (1.04, 1.23)	1.12 (1.09)	1.14 (1.11, 1.16)	0.8948

apo B apolipoprotein B, *C* cholesterol, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LPL* lipoprotein lipase, *Ox* oxidized, *RLP* remnant-like particle, *TC* total cholesterol, *TG* triglyceride

^a Statistical significance by Friedman test; *p* < 0.05 was considered as significant

^b Median (25 and 75 percentile)

Table 3 Effects of teneligliptin on plasma levels of factors affecting glucose and lipoprotein metabolism

Treatment duration (weeks)	0	4	12	<i>p</i> values ^a
FPG (mg/dL)	131 (113, 163) ^b	110 (98, 126)	117 (101, 127)	0.0015
HbA1c (%)	6.6 (5.7, 7.7)	6.2 (5.6, 7.1)	6.0 (5.4, 6.4)	0.0011
C-peptide (ng/mL)	6.1 (5.5, 8.1)	7.2 (5.6, 9.0)	6.9 (5.8, 7.8)	0.5749
TC (mg/dL)	186 (136, 202)	150 (140, 202)	148 (131, 176)	0.4244
TG (mg/dL)	149 (103, 176)	119 (69, 170)	129 (97, 149)	0.1238
LDL-C (mg/dL)	84 (67, 115)	88 (74, 104)	74(63, 99)	0.3614
HDL-C (mg/dL)	40 (35, 46)	37 (34, 44)	33 (30, 45)	0.4640
RLP-C (mg/dL)	12.5 (6.1, 13.7)	10.8 (4.7, 13.8)	8.1 (5.7, 11.4)	0.0171
Apo B (mg/dL)	98 (65, 108)	84 (65, 109)	76 (61, 92)	0.1454
Ox-LDL (U/L)	83 (79, 99)	81 (63, 86)	75 (43, 104)	0.4640
LPL (ng/mL)	61 (49, 83)	51 (48, 73)	69 (50, 80)	0.4169
LDL-C/apo B ratio	1.06 (0.93, 1.12)	1.10 (0.90, 1.13)	1.07 (0.94, 1.13)	0.7123

apo B apolipoprotein B, *C* cholesterol, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LPL* lipoprotein lipase, *Ox* oxidized, *RLP* remnant-like particle, *TC* total cholesterol, *TG* triglyceride

^a Statistical significance by Friedman test; *p* < 0.05 was considered as significant

^b Median (25 and 75 percentile)

teneligliptin treatment might be beneficial for the prevention and treatment of atherosclerotic diseases in these patients. LPL, which mainly mediates the conversion of TG-rich lipoprotein to its remnant, was not affected by teneligliptin treatment. Therefore, this decrease in RLP-C may not be due to inhibition of the conversion of TG-rich lipoproteins to their remnants. However, this speculation is not conclusive because the conversion of TG-rich lipoprotein to its remnant should be assessed by both LPL mass and activity [29]. Teneligliptin was reported to improve insulin resistance [30, 31]. In insulin resistance

states, the production of VLDL, the precursor of TG-rich lipoprotein remnants, and the conversion of TG-rich lipoproteins to their remnants is stimulated [32]. The decrease in plasma RLP-C might be due to the improvement in insulin resistance by teneligliptin treatment. However, this mechanism is not conclusive because plasma levels of insulin, TG, and HDL-C were not changed by teneligliptin treatment. Treatment with teneligliptin did not affect plasma levels of ox-LDL, although they were not high [33]. The effect of DPP-4 inhibitors on ox-LDL should also be examined in patients with high plasma

levels. Teneeligliptin treatment did not change the size of plasma LDL because the LDL-C/apo B ratio was not changed following 12-month teneeligliptin treatment.

5 Conclusions

Teneeligliptin treatment of patients with diabetes and CKD who are undergoing hemodialysis decreased their plasma levels of TG-rich lipoprotein remnants as well as plasma FPG and blood HbA1c. Therefore, the treatment with teneeligliptin could be beneficial for prevention and treatment of atherosclerotic diseases in diabetic CKD patients undergoing hemodialysis.

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Compliance with Ethical Standards

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Conflict of interest Koichiro Homma, Joe Yoshizawa, Yutaka Shiina, Hideki Ozawa, Muneki Igarashi, Tadashi Matsuoka, Junichi Sasaki, Mamoru Yoshizawa, and Yasuhiko Homma declare that they have no conflict of interest.

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