A dipeptidyl peptidase-4 inhibitor, teneligliptin, decreases plasma triglyceride-rich lipoprotein remnants in diabetic patients with chronic kidney disease undergoing hemodialysis

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Introduction

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 in patients with diabetes and CKD undergoing maintenance hemodialysis treatment. Small dense LDL is extremely atherogenic and apolipoprotein (apo) B-rich . The LDL-C/apo B ratio was estimated to determine whether DPP-4 inhibitors affect the LDL size.

Materials and Methods

Study protocol

The study protocol was approved by the Ethics Committee of Hiratsuka Life Style-related Diseases and Hemodialysis Clinic. The study commenced after informed consent was obtained from all participants. Fifteen and 10 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 × 25 kcal/day diet. Patients with hereditary hyperlipoproteinemia, secondary hyperlipoproteinemia with kidney diseases, and those taking lipid-lowering and hypotensive drugs, which 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.

Laboratory procedures

Plasma levels of creatinine, glucose, lipids, and blood glycated 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. The C-peptide level was measured using an electrochemiluminescence immunoassay (Roche, Germany). Plasma levels of apo B were estimated using a turbidimetric immunoassay. RLP-C was measured using a precipitation method with monoclonal antibodies against apo AI and apo B-100. 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; 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.

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.

Results

The backgrounds of the subjects are shown in Table 1, and an accurate onset of DM was not known. DM treatment had been ongoing for more than 30 and 20 years in patients older than 70 years and those in their 60s, respectively. DM had been treated for more than 10 years in seven patients in the control group who were aged 40 to 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 were. Body-mass index (BMI), hemodialysis duration, and plasma levels of creatinine, urea nitrogen (UN), uric acid (UA), 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 to 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 12-week trial.

Conclusions

Teneligliptin 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 teneligliptin could be beneficial for prevention and treatment of atherosclerotic diseases in diabetic CKD patients undergoing hemodialysis.

Table 1. Demographics of study subjects

	Teneligliptin group	Control Group	p-values[1]
N (M/F)	15 (8/7)	10 (5/5)	
Age (years)	71 (65, 75)[2]	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 (M)	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
UN (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	

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

Treatment duration (w)	0	4	12	p-values[1]
FPG (mg/dL)	111 (94, 143)[2]	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

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

Treatment duration (w)	0	4	12	p-values[1]
FPG (mg/dL)	131 (113, 163)[2]	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

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