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Polyarthropathy in Type 2 Diabetes Patients Treated with DPP4 Inhibitors

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ABSTRACT

Dipeptidyl peptidase-4 inhibitors (DPP-4Is) inactivate incretin hormones while also affecting the immune system, since CD26/DPP-4 is involved in immune regulation. The current study shows that the use of DPP-4Is as therapy for type 2 diabetes patients may induce joint symptoms associated with a decrease in plasma SDF-1 α level.

Keywords: DPP-4, CD26, DPP-4 inhibitors, polyarthropathy, SDF-1 α .

1. Introduction

A 110 kDa surface glycoprotein, dipeptidyl peptidase-4 (DPP-4)/CD26 is a serine protease that cleaves dipeptides from the N-terminus of peptides at the penultimate position, as well as being a T cell activation marker involved in immune regulation and inflammatory diseases [1-3]. Recently, DPP-4 inhibitors (DPP-4Is) were developed as a new class of anti-diabetic drugs which act by inhibiting DPP-4, the enzyme that inactivates incretin hormone (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) [4-6]. In the current study, we report that therapy with DPP-4Is is associated with the development of polyarthropathy, and define the risk factors for joint inflammation for this new drug-induced symptom.

2. Methods

Human study protocols were approved by the Ethics Committees at the Kobari General Hospital (Authorization Number 10) and Juntendo University (Authorization Number 2012192). Informed consent was obtained from all patients. All studies on human subjects were carried out according to the principles set out in the Declaration of Helsinki. The base cohort consisted of all type 2 diabetes mellitus (T2DM) patients regularly seen and treated at the Kobari General Hospital between February 2010 and January 2013. Polyarthropathy symptoms were confirmed in more than 2 joints with swelling and/or tenderness as diagnosed by a Japan College of Rheumatology (JCR)-board certified rheumatologist. These patients were then defined as polyarthropathy cases after excluding definitive polyarthritides such as RA, autoimmune-, malignancy-, injury- infection- or crystal-associated arthritis as well as osteoarthritis (OA). Since OA is a common disease associated with joint symptoms in adults, OA was excluded after a careful evaluation by a JCR-board certified rheumatologist, according to the diagnostic criteria for OA as recommended by the American College of Rheumatology [7, 8]. Two control cohorts were selected as the nested controls, consisting of T2DM patients who did not complain of polyarthralgia; series 1 controls selected among DPP-4I users were matched for age (± 5 yr), gender, duration of DM treatment (± 1 yr), duration of DPP-4I therapy (± 3 mo) or type of DPP-4I medication (sitagliptin, SG); series 2 controls selected among non-DPP-4I users were matched for age (± 5 yr), gender, or duration of DM treatment (± 1 yr). The plasmas of the cases were

collected at the time when polyarthropathy developed during treatment with DPP-4Is and at the time when joints symptoms disappeared following cessation of DPP-4I therapy. Methods for measuring soluble CD26 (sCD26) and DPP-4 activity were described previously [9]. Cytokine levels were quantified using Bio-Plex Suspension Array system (Bio-RAD Laboratories, Hercules, CA, U.S.A.), and chemokines were measured using Quantikine ELISA Kits (R&D Systems, Minneapolis, MN, U.S.A.).

3. Results

The recruitment process of the cases as well as controls is summarized in the Supplementary Figure. There were 146 patients who experienced undefined arthralgia (70 in DPP-4I users, and 76 in non-DPP-4I users). After a careful evaluation by JCR-board certified rheumatologists, we identified 13 polyarthropathy cases among 385 T2DM patients taking DPP-4I. No polyarthropathy patient was identified among 356 T2DM patients not treated with DPP-4I. The demographic information on these cases is shown in Table 1. None of the 13 patients started taking the other anti-diabetic drugs prior to or during the development of joint symptoms. The clinical characteristics of the cases are shown in Table 2. Following cessation of DPP-4I, the clinical symptoms of polyarthropathy resolved within a mean period of 3 months (S.D., ± 1.6) (Table 2). Steroids were not used as therapy during the development of polyarthropathy in all 13 patients, while four patients took non-steroidal anti-inflammatory drugs only when joint pain was intolerable (Cases No. 5, 7, 10, and 11). In addition, following resolution of the joint symptoms, levels of CRP, ESR and MMP-3 normalized in all those patients with abnormal values initially (Table 2).

We next attempted to identify potential serum biomarkers among the 13 cases, including cytokines and chemokines which are substrates for DPP-4 enzyme [10, 11]. The plasma level of SDF-1 α among the cases of patients with developing polyarthropathy was significantly decreased compared to the controls (Figure 1A). Interestingly, following resolution of polyarthropathy symptoms, plasma level of SDF-1 α was significantly restored to the level of the controls (Figure 1B). There were no significant differences in the levels of the other cytokines and chemokines, including sCD26 level and DPP-4 enzyme activity, tested between the cases and controls (Supplementary Table). These results suggest that treatment with DPP-4Is for T2DM

may be associated with polyarthropathy in patients whose plasma levels of SDF-1 α were decreased during their arthritic episodes. In addition, our data may indicate that lower level of SDF-1 α is a biomarker predicting the development of arthritic symptoms in T2DM patients treated with DPP-4Is.

4. Discussion

In the present study, we demonstrate that DPP-4I therapy is associated with an increase in the risk of joint inflammation of polyarthropathy, and that the patients with developing polyarthropathy associated with DPP-4I treatment had lower plasma SDF-1 α level.

A pooled analysis of data from 10,246 patients treated with DPP-4Is in the US was published recently [12]. Among the reported adverse events that might be related to SG, arthralgia occurred at a frequency of 0.2 incident events per 100 patient-years in the US, which was not significantly different compared with that in non-exposed patients. The joint symptoms in patients treated with DPP-4I were therefore considered to be relatively rare. However, our detailed evaluation of patients complaining of polyarthralgia indicated that polyarthropathy may be the cause of the multiple joint inflammation observed in T2DM patients treated with DPP-4I, a condition which might be overlooked at routine follow-ups in diabetic clinics. There have been 2 reported cases of RA with SG, a first-generation DPP-4I, suggesting the association of DPP-4I use with development of RA [13, 14]. More recently, 3 cases of DPP-4I-induced polyarthrititis have been reported [15]. Among these patients, 2 patients had chronic inflammatory conditions such as Sjögren's syndrome, or hepatitis B virus infection [15]. In our current study, we found that 146 patients experienced undefined arthralgia (Supplementary Figure). Among them, 8 patients were diagnosed as having OA (1 patients among DPP-4I users and 7 patients among non-DPP-4I users), while there were 105 patients who had disappearance of arthralgia or no joint findings at the time of evaluation by a rheumatologist, and 20 patients who did not have an evaluation of their joints by a rheumatologist. The clinical outcome of these patients may be of interest and may be potentially examined in a future non-concurrent cohort study.

It has been reported that plasma level of SDF-1 α in RA patients was significantly elevated as compared to healthy adults or OA patients [16, 17]. In the

current study, plasma SDF-1 α level at the onset of polyarthropathy was lower than the control cohorts. Moreover, while serum sCD26 level was decreased in active RA patients [18-20], no statistically significant differences in sCD26 level among the polyarthropathy cases and control cohorts were observed in our current study. Our study therefore revealed potential differences in biomarkers between RA patients and the polyarthropathy patients with T2DM treated with DPP-4I.

In conclusion, the results of this study are consistent with an association between DPP-4I therapy and the risk of polyarthropathy, with a concomitant decrease in plasma SDF-1 α level in the affected patients. We propose that reversible inflammatory changes may be occurring in the joints mediated by DPP-4Is. Further pharmacoepidemiological and pathological studies should be conducted to confirm or refute these findings.

Conflict of Interest

The authors declare no competing financial interests associated with this manuscript.

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Contribution statement

TS acquired, analyzed and interpreted the data and co-wrote the draft of the manuscript; HS and RH analyzed and interpreted the data; NHD analyzed and interpreted the data and co-wrote the draft of the manuscript; and HN analyzed and interpreted the data. KO and CM made substantial contributions to the design of the study, analyzed and interpreted the data, and co-wrote the draft of the manuscript. KO, HS and CM are the JCR-board certified rheumatologist, and HS examined all patients with complaints of joint symptoms. KO and CM reviewed the medical charts of patients with complaints of joint symptoms.

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Figure legend

Figure 1. Plasma levels of SDF-1 α in T2DM patient.

(A) The levels of soluble SDF-1 α were measured in the plasma of non arthritic T2DM patients not treated with DPP-4 inhibitor (DPP-4I) (No-DPP-4I user control, n=30) or treated with DPP-4I (DPP-4I user control, n=40). The levels of soluble SDF-1 α were also measured in the T2DM patients with polyarthropathy symptoms treated with DPP-4I (Cases, n=13). The mean values (\pm S.D.) of No-DPP-4I user control, DPP-4I user control or Cases were 1797 (\pm 423.0), 1730 (\pm 553.3), or 714 (\pm 341.4), respectively. The plasma levels of soluble SDF-1 α in Cases were significantly decreased than in no-DPP-4I user control ($p < 0.0001$, 95%CI, -1459.8 to -705.6) or DPP-4I user control ($p < 0.0001$, 95CI, -1384.2 to -648.2) (ANOVA test). Each dot indicates individual value. The horizontal lines in the middle of scattergrams indicate each mean value, and error bars indicate S.D. N.S. denotes 'not significant'.

(B) Changes in the plasma levels of soluble SDF-1 α in Cases at the time of polyarthropathy development while treated with DPP-4I, and after resolution of polyarthropathy following cessation of DPP-4I therapy. The mean value (\pm S.D.) at resolution following cessation of DPP-4I was 1844 (\pm 535.6). The plasma levels of soluble SDF-1 α in Cases were significantly increased compared to those measured at the time of polyarthropathy symptoms while on DPP-4I therapy ($p < 0.0001$, 95%CI, 847.6 to 1412.0) (two-tailed Student's t test), and were restored to the levels of no-DPP-4I user control or DPP-4I user control, which are shown in (A).

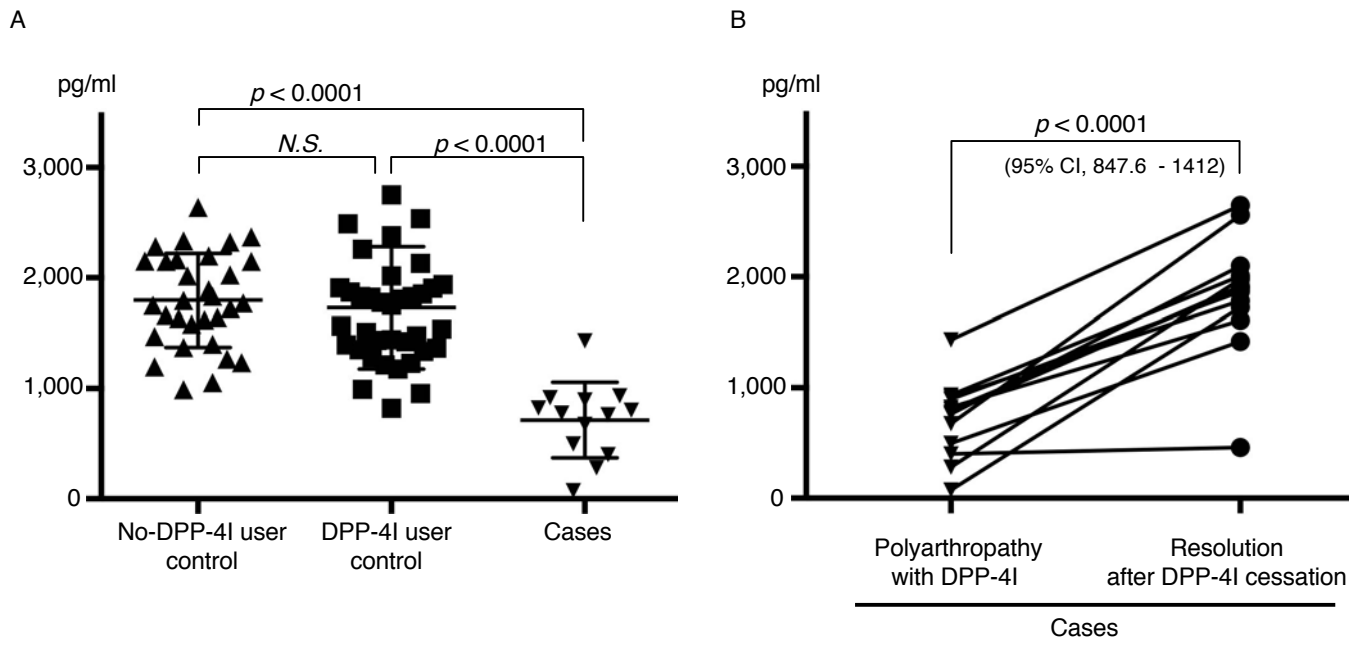


Table 1. Demographic characteristics of the Cases

(Case No.)	Gender	Age (yr)	BMI ^{a)} (kg/m ²)	Duration of DM (yr)	Other antidiabetic drugs		Type of DPP-4I ^{c)}
					OHA ^{b)}	Insulin	
1	F	48	26	1	G,S	no	SG 50
2	M	76	22	8	S	no	SG 50
3	F	60	26.6	14	B,S	no	SG 50
4	M	60	25	5	B,S	no	SG 50
5	M	81	24	20	F,G	no	SG100
6	F	64	28.3	5	B	no	SG 50
7	M	64	35	5	B,G	no	SG 50
8	M	74	22.6	4	B	no	SG 50
9	M	74	24.5	7	S	no	SG 50
10	M	59	22.9	2	no	no	SG 50
11	F	55	22.2	9	B,S,T	no	SG100
12	F	65	31	7	B,S,T	no	SG 50
13	M	41	28	0.4	B,S	no	SG 50

a) BMI, body-mass index

b) OHA, oral hypoglycemic agents (other than DPP-4Is); B, biguanides; F, phenylalanine analog;
G, α -glucosidase inhibitors; S, sulfonylureas; T, thiazolides.

c) SG50, 50mg/day of sitagliptin; SG100, 100mg/day of sitagliptin.

Table 2. Clinical characteristics of the Cases

(Case No.)	Duration of DPP-4I therapy before joint symptoms	No. of Swollen joints		No. of Tender joints		Time to resolution following cessation of DPP-4I	Values at onset / after resolution			
		Large joints ^{a)}	Small joints ^{b)}	Large joints ^{a)}	Small joints ^{b)}		CRP ^{c)}	ESR ^{d)}	HbA1c ^{e)}	MMP-3 ^{f)}
1	3 mo	0	0	1	4	2 mo	0.05/0.05	n.d. ^{g)}	6.0/6.0	n.d.
2	13 mo	0	0	1	4	2 mo	0.05/n.d.	12/n.d.	6.0/6.9	77.9/n.d.
3	7 mo	0	0	1	4	1 mo	0.05/0.05	7/3	6.6/6.7	42.3/n.d.
4	6 mo	0	0	2	2	3 mo	0.05/0.05	10/8	5.9/6.2	n.d.
5	15 mo	0	0	6	20	4 mo	0.05/0.05	5/6	6.3/6.4	165.9/119.0
6	12 mo	0	0	4	4	6 mo	0.40/0.28	21/13	6.8/5.9	115.5/26.4
7	2 mo	2	10	2	10	1 mo	0.05/0.05	2/3	5.6/5.6	79.1/41.7
8	23 mo	0	0	3	4	2 mo	0.33/0.05	20/11	6.5/6.4	71.5/36.9
9	31 mo	0	0	4	6	3 mo	0.05/0.05	5/4	7.4/6.8	65.4/67.5
10	28 mo	0	0	0	4	4 mo	0.05/n.d.	3/n.d.	7/6.6	35.4/n.d.
11	25 mo	2	20	6	24	6 mo	0.10/0.11	16/13	6.7/6.7	29.3/28.7
12	3 mo	4	20	6	20	2 mo	0.30/0.05	20/5	6.2/6.8	33.0/38.0
13	9 mo	0	0	4	2	4 mo	0.05/n.d.	10/n.d.	5.9/5.8	88.8/n.d.

a) "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

b) "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

c) CRP, C-reactive protein (mg/dl); normal lab value, ≤ 0.30 .

d) ESR, erythrocyte sedimentation rate (mm/1 hour); the normal ranges, 1–10 for male and 2–15 for female.

e) HbA1c, hemoglobin A1c (%) (NGSP);

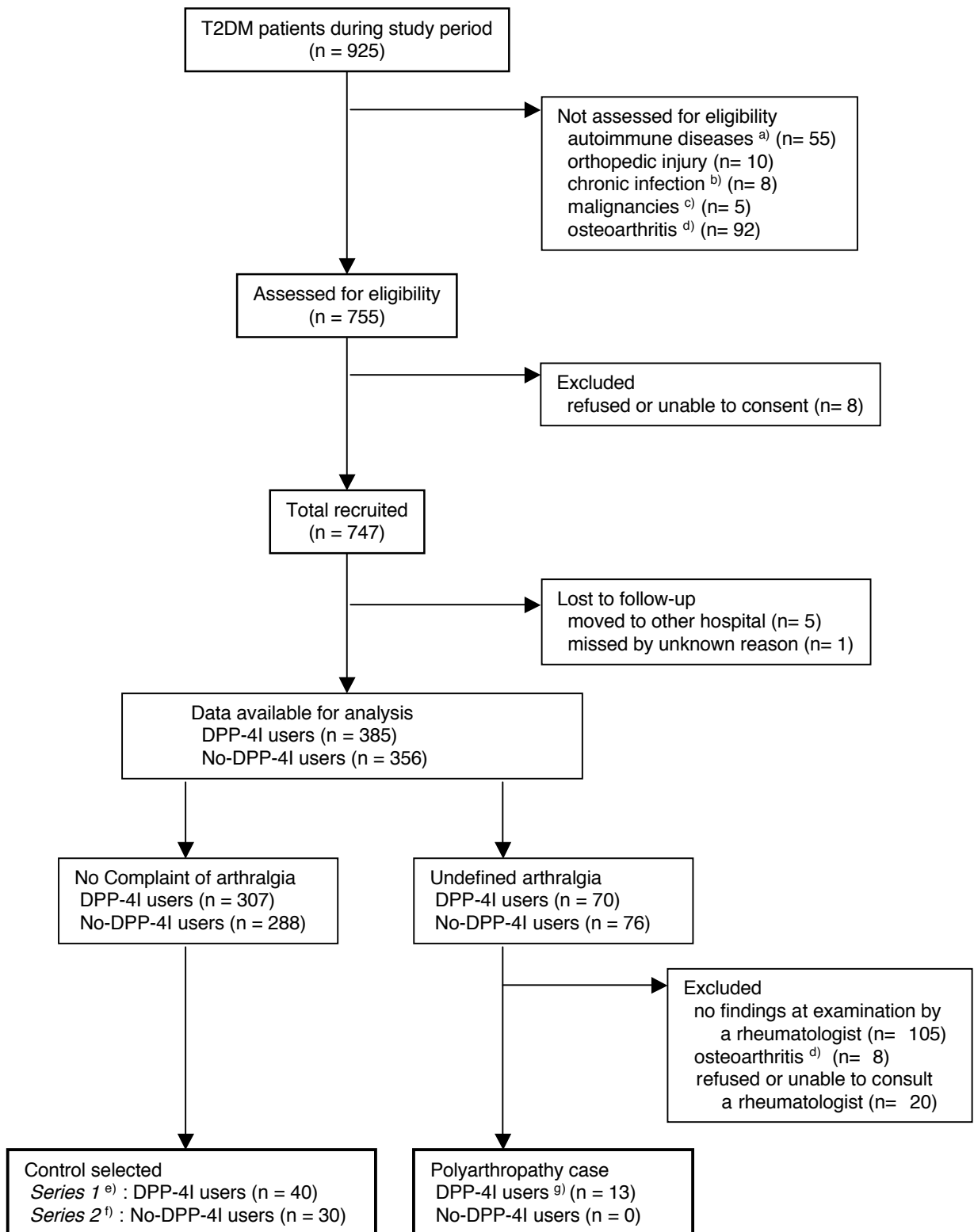
f) MMP-3, matrix metalloproteinase-3 (ng/ml); the normal ranges, 36.9–121.0 for male and 17.3–59.7 for female.

g) n.d., not determined.

Legend to Supplementary Figure

Supplementary Figure. Patient recruitment and follow-up flow diagram.

- a) autoimmune diseases included rheumatoid arthritis, Graves' disease, Hashimoto's disease, idiopathic interstitial pneumonitis, autoimmune hepatitis, ulcerative colitis, adult-onset Still's disease, Behçet's disease, IgG4-related disease, psoriasis vulgaris, scleroderma, and Sjögren's syndrome.
- b) chronic infection included hepatitis B and hepatitis C.
- c) malignancies included acute promyelocytic leukemia, gastric cancer, and malignant lymphoma.
- d) osteoarthritis of the hand, hip or knee was diagnosed by a JCR-board certified rheumatologist according to the ACR criteria.
- e) The mean age of series 1 control cohort was 62.5 yr (range, 41-81); the mean duration of DM treatment, 6.1 yr (range, 0.6-20); the mean duration of sitagliptin (SG) therapy, 12.0 mo (range, 2-25) and male, n=25; female, n=15.
- f) The mean age of series 2 control cohort was 60.5 yr (range, 40-76); the mean duration of DM treatment, 5.9 yr (range, 0.3-21); male, n=20; female, n=10.
- g) The mean age of the case cohort was 63.2 yr (range, 41-81); the mean duration of DM treatment, 6.7 yr (range, 0.5-21); the mean duration of SG therapy, 13.6 mo (range, 2-28) and male, n=8; female, n=5.



Supplementary Table. Plasma levels of soluble CD26, DPPIV activity, cytokines and chemokines

DPP-4I :	Cases ^{a)}	Controls	
	Use (n=13)	Series 1 : Use (n=40)	Series 2 : No use (n=30)
sCD26 (pg/ml)	1.50±0.54	1.56±0.38	1.58±0.43
DPPIV activity (μ M/min)	18.04±3.93	18.29±4.48	18.90±4.55
CCL2/MCP-1 (pg/ml)	197.50±114.00	173.00±141.60	182.80±68.76
CXCL10/IP-10 (pg/ml)	103.4±47.01	114.10±47.66	102.76±41.95
CCL5/RANTES (ng/ml)	30.15±26.55	29.53±12.35	32.50±13.39
CXCL12/SDF-1 α (pg/ml)	714.1±341.4 ^{b)}	1730±553.3	1797±423.0
IL-2 (pg/ml)	4.46±8.75	5.28±6.90	6.05±7.90
IL-6 (pg/ml)	6.87±4.11	5.90±4.40	6.38±5.90
IL-8 (pg/ml)	20.42±24.22	17.50±16.27	18.16±17.52
IL-10 (pg/ml)	5.88±10.71	4.73±7.90	4.57±5.30
IFN- γ (pg/ml)	75.49±127.9	69.29±128.82	73.07±84.83
TNF- α (pg/ml)	8.38±12.99	12.80±27.40	11.20±13.90

a) Plasma was collected at the time of polyarthropathy development while being treated with DPP-4I.

b) significantly decreased compared to DPP-4I user control (p<0.0001), or DPP-4I no-user control (p<0.0001) (ANOVA test).