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Brief report

Polyarthropathy in type 2 diabetes patients treated with DPP4 inhibitors☆

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ABSTRACT

Dipeptidyl peptidase-4 inhibitors (DPP-4Is) inhibit the inactivation of 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 with decrease in plasma SDF-1α level.

1. Introduction

Dipeptidyl peptidase-4 (DPP-4), also known as T-cell activation antigen CD26, is a 110 kDa surface glycoprotein involved in immune regulation and inflammatory diseases, being a serine protease that cleaves dipeptides from the N-terminus of peptides at the penultimate position [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 hormones (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

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examine risk factors for this drug-associated joint inflammation.

2. Methods

The study was 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. The base cohort consisted of all type 2 diabetes mellitus (T2DM) patients regularly attending the Kobari General Hospital between February 2010 and January 2013. Polyarthropathy was confirmed in more than 2 joints with swelling and/or tenderness diagnosed by a Japan College of Rheumatology (JCR)-board certified rheumatologist. Other causes of polyarthritis such as rheumatoid (RA), autoimmune-, malignancy-, injury-, infection- or crystal-associated arthritis as well as osteoarthritis (OA) were excluded. 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 plasma of cases was collected at the time 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, USA), and chemokines were measured using Quantikine ELISA Kits (R&D Systems, Minneapolis, MN, USA).

3. Results

The recruitment process of cases and 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 (3.3%) 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 (SD ± 1.6) (Table 2). Steroids were not used as therapy during the development of polyarthropathy in any of 13 patients, while four patients took non-steroidal anti-inflammatory drugs only when joint pain was intolerable (Case Nos. 5, 7, 10, and 11). Following resolution of joint symptoms, levels of CRP, ESR and MMP-3 normalized in all patients with abnormal values initially (Table 2).

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

Table 1 – Demograhic 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	SG 100
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	SG 100
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] SG 50, 50 mg/day of sitagliptin; SG 100, 100 m/day of sitagliptin.

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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 DDP-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	nd[g]	6.0/6.0	n.d
2	13 mo	0	0	1	4	2 mo	0.05/n.d.	12/nd	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/nd.
4	5 mo	0	0	2	2	3 mo	0.05/0.05	10/8	5.9/6.2	n.d.
5	I5 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	0.05/0.09	2/3	5.6/5.6	79.1/41.7
8	23 mo	0	0	3	4	2 mo	0.33/0.09	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	65.4/87.5
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] C-reactive protein (mg/dl); normal lab value, ≤0.30.
[d] Erythrocyte sedimentation rate (mm/1 h); the normal ranges, 1–10 for male and 2–15 for female.
[e] Hemoglobin Alc (%) (NGSP).
[f] Matrix metalloproteinase-3 (ng/ml): the normal rages 36.9–121.0 for male and 17.3–59.7 for female.
[g] n.d., not determined.

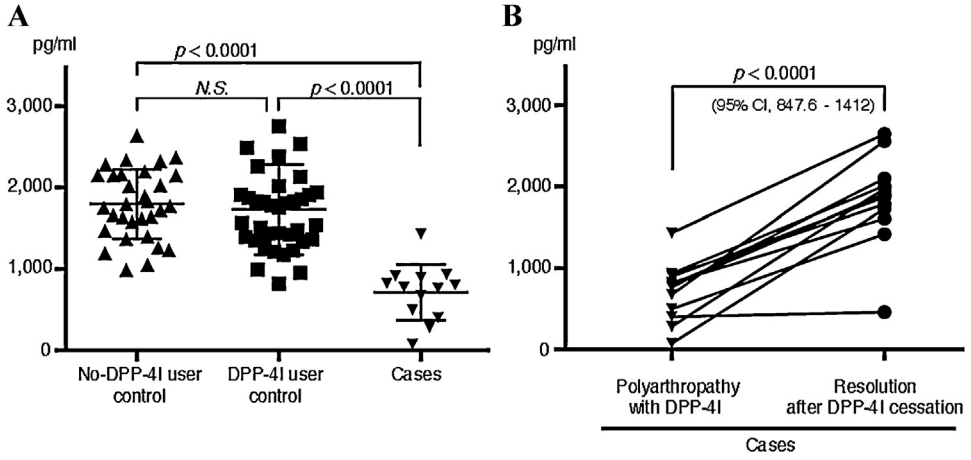

Fig. 1 – Plasma levels of SDF-1α in T2DM patient. (A) The levels of soluble SDF-1α were measured in the plasma of non-arthritic T2DM patients not treated with DPP-4 inhibitor (DPP-4I) (No-DPP-4I user control, $n = 30$) or treated with DPP-4I (DPP-4I user control, $n = 40$). The levels of soluble SDF-1α were also measured in the T2DM patients with polyarthropathy symptoms treated with DPP-4I (Cases, $n = 13$). The mean values (±S.D.) of No-DPP-4I user control, DPP-4I user control or Cases were 1797 (±423.0), 1730 (±553.3), or 714 (±341.4), respectively. The plasma levels of soluble SDF-1α 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 ($p < 0.0001$, 95 CI, −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-1α 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 (±S.D.) at resolution following cessation of DPP-4I was 1844 (±535.6). The plasma levels of soluble SDF-1α 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, 847.6–1412.0) (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).

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4. Discussion

We report that DPP-4I therapy is associated with an increased risk of polyarthralgic joint inflammation and that patients developing polyarthropathy associated with DPP-4I treatment had lower plasma SDF-1α level.

A pooled analysis of data from 10,246 patients treated with DPP-4Is in the US has recently been published [12]. Among the reported adverse events that might be related to sitagliptin, arthralgia occurred at a frequency of 0.2 incident events per 100 patient-years, which was not significantly different to 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-up in diabetic clinics. There have been 2 reported cases of RA associated with sitagliptin treatment [13,14] and more recently, 3 cases of DPP-4I associated polyarthritis have been reported [15], 2 of whom had chronic inflammatory conditions, Sjögren's syndrome (SS) and hepatitis B virus infection (HBV) [15].

Plasma SDF-1α in RA patients has been reported to be significantly elevated compared with healthy adults or OA patients [16,17]. In our study, plasma SDF-1α level at the onset of polyarthropathy was lower than in controls. Moreover, while serum sCD26 level was decreased in active RA patients [18–20], no statistically significant difference in sCD26 level among the polyarthropathy cases and control cohorts was observed in our study, indicating potential differences in biomarkers between RA patients and the polyarthropathy patients with T2DM treated with DPP-4I.

In conclusions, our results are consistent with an association between DPP-4I therapy and the risk of polyarthropathy, with a concomitant decrease in plasma SDF-1α level in affected patients. Further pharmacoepidemiological and pathological studies should be conducted to confirm or refute these findings.

Authors' contributions

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 a substantial contribution to the design of the study, analyzed and interpreted the data, and co-wrote the draft of the manuscript.

Conflict of interest

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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2013.07.010.

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