DPP-4 INHIBITORS INCREASE THE INCIDENCE OF ARTHRITIS/ARTHRALGIA BUT DO NOT AFFECT AUTOIMMUNITY

Z.A. Sayiner^{1,*}, B. Okyar², B. Kısacık³, E. Akarsu¹, M. Özkaya², M. Araz¹

Gaziantep University School of Medicine, ¹Dept. of Endocrinology and Metabolism, ²Dept. of Internal Medicine, ³Medical Park Gaziantep Hospital, Department of Rheumatology, Gaziantep, Turkey

Abstract

Aims. In August 2015, FDA published a black box declaring that DPP-4 inhibitors may cause severe joint pains. The impact on autoimmunity marker positivity of these drugs has not been comprehensively evaluated. We compared the incidence of arthritis/arthralgia in patients with T2DM who were using DPP-4 inhibitors and patients who were not using.

Methods. A number of 93 DPP-4 inhibitor users and 107 non-users were included into the study. Arthritis/arthralgia were found in 41 of 93 (44.1%) DPP-4 inhibitor users and in 19 of 107 (17.8%) non-users ($p < 0.05$).

Results. No inflammatory rheumatological condition was identified in 27 of 41 (65.9%) patients in DPP-4 inhibitor user group as well as in 13 of 19 (68.4%) patients in non-user group ($p > 0.05$). After adjusting for gender the incidence for arthritis/arthralgia was significantly increased in the DPP-4 inhibitor user group (p value for any DPP-inhibitor < 0.05). There was 3.77 times increased risk for arthritis/arthralgia in the DPP-4 inhibitor using group (p value = 0.001) and this risk increases 2.43 times for each year of DPP-4 inhibitor usage.

Conclusions. Arthritis/arthralgia were more common among T2DM patients who were using DPP-4 inhibitors compared to non-users, but the seropositivity did not differ between DPP-4 inhibitor users and non-users.

Key words: Type 2 Diabetes Mellitus, DPP-4 inhibitors, arthralgia/arthritis.

INTRODUCTION

Also known as T-cell activation antigen CD26, dipeptidyl peptidase-4 (DPP-4) is a ubiquitous enzyme that is expressed in immune system cells such as lymphocytes as well as in muscle cells. DPP-4 inhibitors (DPP-4i) are oral antihyperglycemic agents which selectively inhibit DPP-4. As a result of this inhibition, incretin may remain in the body for a longer duration. This is significant for alleviating some negative side effects of Type 2 diabetes mellitus

(T2DM) such as high blood pressure and abnormal lipid profiles, as inadequate incretin levels have been known to play a role in T2DM pathophysiology (1). Moreover, DPP-4i hinder glucagon release, consequently increasing insulin secretion and limiting the production of glucagon-like peptide (GLP) as well as glucose-dependent insulinotropic polypeptide (GIP) hormones in pancreatic beta-cells. Besides deactivating GLP-1 and GIP, DPP-4i also reduce the production of several bioactive peptides (2).

Despite the benefits mentioned above, DPP-4i use has been linked to an elevated risk of inflammatory disease (3), and recent studies have demonstrated that it may increase the risk of arthritis/arthralgia (4-5). For example, in August 2015, the United States Food and Drug Administration (FDA) warned that DPP-4i may cause severe joint pain. This study examined the incidence of arthritis/arthralgia in T2DM patients using DPP-4i (sitagliptine, vildagliptine and saxagliptine). In those who exhibited arthritis/arthralgia, it was also investigated whether they possessed an autoimmune inflammatory condition.

METHODS

Subjects

After this study had been approved by the Faculty of Medicine Ethics Committee at Gaziantep University in Turkey, written consent was obtained from all participants. These included T2DM patients who were attending an endocrinology outpatient clinic between February and June 2016. Patients' medical histories, physical examination results, and test results of routine biochemical and hematological monitoring were recorded. After the occurrence of arthritis/arthralgia was examined in patients, those exhibiting arthritis/arthralgia histories were referred to a rheumatology clinic for further examination. There, in accordance with the guidelines established by the

*Correspondence to: Zeynel Abidin Sayiner, Gaziantep University, Gaziantep, 27100, Turkey, E-mail: zeynelasayiner@hotmail.com

American Collage of Rheumatology, a rheumatologist assessed each patient in terms of rheumatoid factors (RF), cyclic citrullinated peptides (CCP's), antinuclear antibodies (ANA's), and C-reactive proteins (CRP's) in order to distinguish between osteoarthritis as well as infectious causes of diffuse joint pain and autoimmune rheumatic causes.

During the inclusion period of this study, 423 T2DM patients attended the Endocrinology and Metabolism clinic. As 223 patients did not meet all of the inclusion criteria, they were excluded. Ultimately, this study consisted of 93 T2DM patients identified as DPP-4i users and 107 T2DM patients labeled as non-users. The number of patients in each group was decided by a statistician via power analysis. An adjusted odds ratio (OR) was calculated based on gender, and the effects of gender on arthralgia/arthritis among DPP-4i users were evaluated. DPP-4i-using patients all had been using DPP-4i for at least one year. No participants possessed a known rheumatic or active infectious disease. Moreover, all participants were willing to participate in this study and possessed verbal skills enabling them to give adequate responses to questioning regarding their conditions. None were being treated for active malignancy or infectious diseases.

Statistical analysis

To determine the risk factors for arthralgia, univariate binary logistic regression analysis was performed. Moreover, multivariate binary logistic regression models were used to estimate adjusted OR's and a 95% confidence interval. Variables were presented as frequency, percentage (%) and mean $\pm$

standard deviation (mean $\pm$ SD). Statistical analysis was performed via SPSS for Windows Version 22.0, and a p-value < 0.05 was accepted as statistically significant.

RESULTS

The descriptive statistics presented in Table 1 indicate that 93 out of 200 T2DM patients had been using DPP-4i at the time of the study. The mean duration of DPP-4i usage was 1.95 years (min. 1 year/ max. 6 years), while the mean age of the patients was 54 ± 9.7 years. The mean duration of diabetes mellitus (DM) was 8.3 ± 5.8 years. No statistically significant difference in terms of gender was observed between the user and non-user groups.

Arthritis/arthralgia was observed in 41 out of 93 (44.1%) DPP-4i users and in 19 out of 107 (17.8%) non-users ($p < 0.05$). Moreover, 27 out of 41 (65.9%) patients with arthritis/arthralgia in the DPP-4i user group lacked inflammatory rheumatological conditions, and 13 out of 19 (68.4%) patients with arthritis/arthralgia in the non-user group ($p > 0.05$) lacked these conditions, as well. A statistically significant gender difference was observed among participants of the arthralgia/arthritis group. Table 2 displays the results of univariate logistic regression analysis, which was used to determine the risk factors of arthralgia/arthritis among DPP-4i users. After adjusting for gender, the incidence of arthritis/arthralgia significantly increased in the DPP-4i user group (p-value for any DPP-inhibitor < 0.05). However, there was no increase in any real inflammatory condition with the use of DPP-4i. There was a 3.77-time increase in the risk of arthritis/arthralgia among DPP-4i users

Table 1. Patients characteristics and descriptive statistics

		N	%
Gender	Male	85	42.5%
	Female	115	57.5%
CO-morbidity	No	61	30.5%
	Yes	139	69.5%
Weight loss	No	171	85.5%
	Yes	29	14.5%
DPP4inh Usage	No	107	54.0%
	Yes	93	46.0%
DPP4inh group	Saxagliptin	15	7.5%
	Sitagliptin	45	22.5%
	Vildagliptin	33	16.5%
Arthritis/Arthralgia	No	140	70.0%
	Yes	60	30.0%
Rheumatologic Marker	Negative	182	91.0%
	Positive	18	9.0%

Table 2. Results of univariate logistic regression analysis to determine risk factors for arthralgia/arthritis

		Arthralgia/Arthritis		OR[95%CI]	P
		Yes (n=60)	No (n=140)		
Age*		55.50±8.29	53.73±10.51	1.02 [0.99-1.05]	0.247
BMI*		33.62±6.12	33.48±20.69	1.00 [0.98-1.02]	0.958
Duration of DM*		9.63±6.40	8.51±6.54	1.03 [0.98-1.07]	0.266
Gender†	Female	44 (73.3)	71 (50.7)	2.67 [1.38-5.18]	0.004‡
	Male	16 (26.7)	69 (49.3)	1 (reference)	
Comorbidity†	Yes			1.47 [0.74-2.29]	0.270
Weight loss†	Yes			1.52 [0.67-0.34]	0.316

OR: Odds ratio; CI: Confidence Interval a: Adjusted by Gender

* Continuous variables (mean± std)

† Ordinal or Binary variable (n(%))

‡ Significant at p<0.05.

Table 3. Results of univariate and multivariate logistic regression analysis to show relationship between DPP4 drugs and arthralgia/arthritis

		Arthralgia/Arthritis		OR[95%CI]	P	OR ^a [95%CI]	P ^a
		Yes(n=60)	No(n=140)				
DPP4 usage	Yes			3.77 [1.98-7.17]	0.001‡	2.7 [1.34-5.40]	0.001‡
Type of DPP4	Saxagliptin	6	88	3.09 [0.98-9.71]	0.054	3.55 [1.09-11.59]	0.036‡
	Sitagliptin	21	9	4.05 [1.88-8.73]	0.001‡	4.03 [1.84-8.85]	0.001‡
	Vildagliptin	14	24	3.41 [1.46-7.98]	0.005‡	3.32 [1.39-7.91]	0.007‡
	Non-users	19	19	1(reference)		1(reference)	
Duration of DPP4 (year)		1.95±1.41	0.98±0.83	2.43 [1.44-4.12]	0.001‡	2.51 [1.47-4.30]	0.001‡

OR: Odds ratio; CI: Confidence Interval a: Adjusted by Gender;

* Continuous variables (mean± std);

† Ordinal or Binary variable (n(%));

‡ Significant at p<0.05.

compared with non-users (p-value= 0.001), and this risk increased 2.43 times for each year of DPP-4i usage (Table 3).

Following Cox regression analysis, no relationship between DPP-4i usage and rheumatologic marker positivity was found to exist (p = 0.865).

DISCUSSION

Between 2010 and 2012, 22.7% of individuals (adults aged ≥18 years) living in the United States complained to a physician regarding joint pain (7). This percentage among diabetic patients is unknown, although musculoskeletal complications have been known to increase in these patients. In the present study, arthritis/arthritis were identified in 60 (30%) out of 200 T2DM patients, which seems to be higher compared to the U.S. population referenced above (7). Moreover, arthritis/arthritis was identified in 41 (44%) out of 93 DPP-4i users and in only 19 (17%) non-users. This result is consistent with the above-mentioned statistics regarding individuals in the U.S.,

but the incidence of arthritis/arthritis was determined to be higher than that of general DPP-4i users. Studies conducted among patients with rheumatoid arthritis have found that DPP-4 levels are inversely correlated with the number of arthritic joints (2). Given that DPP-4i similarly decreases DPP-4 levels, complaints of joint pain may occur independently from rheumatic diseases in patients without a known rheumatologic inflammatory disease. Furthermore, in a study by Busso *et al.*, an increase of technetium was detected in the synovial exudative fluid of DPP-4-deficient mice (3). No statistically significant difference was found to exist among DPP-4i molecules (saxagliptin, sitagliptin or vildagliptin), which implies that this outcome is an effect of DPP-4i drugs, regardless of the molecule used.

The present study found that gender is the most compromising determinant for arthralgia/arthritis incidence in DPP-4i users. Thus, the results were adjusted by gender. Complaints of arthritis/arthritis were almost 3.77-times higher in DPP-4i users than in non-users. However, no statistically significant

difference was observed in the diagnosis rate of a real inflammatory rheumatological condition among patients with complaints of arthritis/arthralgia who were referred to a rheumatology clinic. In a study of 10.246 patients, arthralgia occurred at a frequency of 0.2 incidents per 100 patient-years among patients using sitagliptin. This incidence paralleled that of newly developed arthralgia in patients who were not using DPP-4i, and the usage of DPP-4i was shown not to pose an increase in the risk of arthralgia (8).

The present study employed a multidisciplinary approach, as participants were examined both by an endocrinologist and by a rheumatologist. All three DPP-4i currently available in Turkey were utilized, and no given molecule was of exclusive focus. As indicated by current research, DPP-4i have been studied especially in patients diagnosed with rheumatoid arthritis. The effects of present immunological conditions are largely still controversial, though recent attention has been given to the question of whether arthritis/arthralgia is immune-related. In particular, the relationship between DPP-4i and arthralgia/arthritis declared by the FDA has indicated the need for further research. Thus far, studies have identified an association between DPP-4i and the molecule which plays a role in numerous inflammatory processes at a molecular level. Studies have focused especially on stromal cell- derived factor-1 (SDF-1) as well as matrix metalloproteinase-1 and -3 (MMP-1 and -3). In addition, it has been speculated that human leukocyte antigen (HLA) allele differences alter clinical side effects (9-10).

In another study, it has been stated that several molecules (including SDF-1 a/b) are modulated by DPP-4. SDF-1 a/b play a role in the pathophysiology of rheumatoid arthritis and SDF-1, also known as a pro-inflammatory marker (11). On the other hand, no clinical studies have examined markers of autoimmunity such as ANA, anti-CCP, and RF, all of which were used in the present study. Regardless of the underlying molecular mechanism, no reflection on autoimmune markers was observed in this study. This suggests that the presence of arthralgia does not reflect a real auto-inflammatory rheumatological process. Herein, it can be speculated that the effect of DPP-4i on the immune system might result from a similarity at a molecular level rather than from a real inflammatory process.

In conclusion, the occurrence of arthritis/arthralgia was more common among T2DM patients using DPP-4i compared to non-users. Nevertheless, the incidence of seropositivity/real inflammatory

rheumatological conditions did not differ between users and non-users. Further studies are required in order to better understand the side effects of autoimmunity among T2DM patients taking DPP-4i. Moreover, this study was limited in the number of patients included; thus, future studies including larger samples would yield more accurate results. Finally, the lack of clarity regards whether all patients possessing positive autoimmune markers may have limited this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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