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Original Research Article

Type 2 Diabetes Affects Joint Pain Severity in People with Localized Osteoarthritis: A Retrospective Study

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Abstract

Objective. To examine the association between type 2 diabetes (T2D) and pain severity in people with localized osteoarthritis (OA) and to explore the association between glycemic control, measured by hemoglobin A1c (HbA1c) level, and pain severity in people with localized OA and T2D. **Design**. Retrospective study. **Setting**. A tertiary medical center. **Subjects**. Data from 819 patients (mean age = 65.08±9.77 years, 54.3% women) were used. **Methods**. Patients were grouped to localized OA only (N = 671) and localized OA+T2D (N = 148) based on diagnosis codes. An index date was set as the first diagnosis date of localized OA and linked to pain severity, measured by numeric rating scale from 0 to 10. HbA1c values were obtained for patients with T2D within six months of the index date. Multiple linear regression was used. **Results**. After controlling for age, gender, body mass index (BMI); diagnoses of depression, hypertension, dyslipidemia; OA locations; and medication list (+/- 90 days of the index date), T2D was significantly associated with increased pain severity (B = 1.07, 95% confidence interval [CI] = 0.25 to 1.88, $P = 0.014$). For patients with T2D and localized OA with available data for HbA1c (N = 87), the results showed that an increased HbA1c value was significantly associated with higher pain severity (B = 0.36, 95% CI = 0.036 to 0.67, $P = 0.029$) after controlling for age, gender, BMI, medications, and OA locations. **Conclusion**. T2D was associated with higher pain severity in people with localized OA, and poor glycemic control was associated with higher pain severity in people with localized OA+T2D. Clinicians should emphasize that better HbA1c control might help with pain management in people with T2D and OA.

Key Words: Pain Intensity; Glycemic Level; Osteoarthritis

Introduction

Osteoarthritis (OA) and type 2 diabetes (T2D) are chronic diseases that coexist with increasing prevalence globally [1–4]. OA, characterized by joint pain, may affect any joint, potentially leading to disability [4]. Recent evidence has suggested that joint pain in people with OA could be affected by comorbidities [5]. Metabolic syndrome has been shown to be associated

with increased pain severity in people with knee OA [6,7]. Hypertension, dyslipidemia, diabetes, and obesity were also associated with increased pain severity in people with knee OA [6,7]. However, limited research has examined the association between T2D and pain in people with OA.

Recent evidence has shown that diabetes is associated with increased pain severity in people with knee OA [6,8–10]. However, these reports were focused on the knee or hip joint, which could be affected by many factors, such as obesity, other metabolic components, and medications. T2D may affect any joint due to the impact of hyperglycemia and low-grade inflammation [11,12]. Thus, glycemic control, measured by HbA1c, could potentially affect pain severity in people with OA; however, this has yet to be explored in depth. One study found a positive correlation between HbA1c and knee pain severity in individuals with end-stage knee OA [8]. Long-term chronic hyperglycemia may affect pain severity because of increased inflammatory markers such as production of oxidative stress, advanced glycation end products (AGEs), and pro-inflammatory cytokines in the joints [13]. Because of this possibility, it is important to investigate the association between T2D and pain severity in people with OA at any joint (e.g., localized OA) to understand the holistic impact of the disease on pain in this population. Localized OA, affecting one or two joints, could affect any joint, including the knee, hip, ankle, hand, or shoulder.

Previous evidence concerning the impact of diabetes on pain severity in people with OA was limited due to lack of controlling for other metabolic syndromes and pain medications. Recent evidence has suggested that metabolic syndromes and their medications may affect the progression and pain of OA [14,15]. Therefore, the aims of this study were to examine the association between T2D and pain severity in people with localized OA and to explore the association between HbA1c and pain severity among people with localized OA and T2D. We hypothesized that T2D would be associated with increased pain severity in people with localized OA and that increased levels of HbA1c would be associated with increased pain severity in people with localized OA and T2D.

Methods

Design and Setting

This is a retrospective study of de-identified data using the Healthcare Enterprise Repository for Ontological Narration (HERON) database at a tertiary medical center [16]. This database includes de-identified electronic medical records. HERON includes data from other administrative, research, and public sources such as the clinics' billing system (GE IDX), the University Health System Consortium, tumor registries, and the death index from the Social Security Administration. HERON data contain demographic data (age, gender, and race), service use, clinical data (diagnosis codes, flowsheet data, laboratory data, and patients' vitals), and pharmacy data. An approval for using this data set was obtained from the Data Request Oversight Committee.

Study Cohort

Participants were selected using the i2b2 query and analysis tool [17] for HERON [16]. Participants who were seen between 2011 and 2017 were included if they had at least two diagnosis codes of localized OA. These codes must be separated by at least one day using either the International Classification of Disease, Ninth Revision (ICD-9), or the International Classification of Disease, Tenth Revision (ICD-10). To set up the index date for localized OA, the first OA diagnosis code that was linked with pain severity score was set as the index date. Participants who were 45 years old and older were included. Participants were excluded if they had at least one specific ICD-9 or ICD-10 code for type 1 diabetes, neoplasm, gout, systemic lupus, arthritis with infection, fibromyalgia, secondary OA, generalized OA, rheumatoid arthritis, trigeminal nerve disorders, or carpal tunnel syndrome.

Variables and Covariates

Age and gender (males or females) were obtained for all participants. OA locations included the shoulder, hand or elbow, knee or lower leg, hip or pelvis, and foot or ankle. Chronic diseases data were selected based on at least two diagnosis codes, and these codes were separated by at least one day. The chronic disease of interest for this study was T2D, and codes for T2D were included accordingly. Participants were categorized as having T2D if they had at least two diagnostic codes or had used insulin within 90 days of the index date. Body mass index (BMI) was obtained within two years before or after the index date because of several missing values within one year of the localized OA index date.

Pain severity was measured using a numeric rating scale from 0 = no pain to 10 = severe pain. Data for pain severity were obtained from a flow sheet and linked to the index date for localized OA. Data for HbA1c for participants with T2D and localized OA were obtained from the flow sheet. Due to missing values for HbA1c within three months of the index date, HbA1c data were obtained within six months of the index date.

Other chronic diseases including hypertension, dyslipidemia, and depression were included as covariates in this study if there were at least two diagnosis codes separated by one day using the ICD-9 or ICD-10. Lists of medications were included within +/- 90 days of the index date of localized OA and pain severity. Each participant had pharmacy data, and each medication was searched for specific types of medications. Data for medications have specified categories for each type of

medication, and each category includes the name of the medication. Types of medications included pain medications (opioids, nonopioids, and benzodiazepine), antidiabetics (insulin or hypoglycemic), antihypertensives, antilipemic, and antidepressants. Use of medications was further categorized as yes or no. Table 1 shows ICD-9 and ICD-10 codes for all variables.

Statistical Analyses

Descriptive analyses included frequencies and percentages for categorical variables and mean and standard deviation for continuous variables. For comparing people with localized OA and T2D with people with localized OA only, variables were analyzed using the chi-square for categorical variables and an independent *t* test for continuous variables. Further, the Mann-Whitney test was conducted to compare pain severity between people with and without T2DM at each OA location.

To examine the association between T2D and joint pain severity, linear regression analyses were performed. Two models were created with associated unstandardized coefficient (B) and 95% confidence intervals (CIs). T2D was entered into the model as a predictor variable and pain severity as a dependent variable. Model 1 was adjusted for age and gender. Model 2 was a multivariable linear regression with adjustment for age, gender, OA locations, BMI, depression, hypertension, dyslipidemia, and taking medications (pain medications including opioids, nonopioids, and benzodiazepine; antidiabetics; antihypertensive; antilipemic; antidepressants) within 90 days of the index date.

To examine the association between HbA1c and joint pain severity in people with localized OA and T2D, linear regression analyses were performed. Three models were created with associated unstandardized coefficient (B) and 95% CI. HbA1c was entered into the model as a predictor variable and pain severity as a dependent variable. Model 1 was univariate or unadjusted because of the small sample with an HbA1c value. Model 2 was a multivariate linear regression with adjustments for age, gender, BMI, and OA locations. Model 3 was a multivariable linear regression model with adjustment for OA locations and taking medications (pain medications including opioids, nonopioids, and benzodiazepine; antihypertensive; antilipemic) within 90 days of the index date.

Excluding cases affects results and could create biased estimation [18]. Therefore, missing values for BMI (N = 50, 6.11%) were imputed using a multiple imputations method. The imputation model included age, gender, BMI, T2D, hypertension, dyslipidemia, depression, OA locations, HbA1c value, and medications (antidiabetics, antihypertensives, antilipemic, and antidepressants). This imputation created five complete data sets according to Rubin's method [19]. Pooled results were used for data analysis. We conducted a sensitivity analysis comparing the results from the imputed data to the original data set, and the results were similar. Therefore, we chose to report the multivariable results based on the imputed model. All analyses were performed using SPSS 25 for Mac (Chicago, IL, USA). All analyses were conducted at an alpha level of 0.05.

Table 1. Clinical diagnostic codes using ICD-9 and ICD-10

	ICD-9 Codes	ICD-10 Codes
Localized OA	715.1	M16, M17, M18
T2D	250.xx	E11
Hypertension	401.xx	I10
Dyslipidemia	272.xx	E78
Depression	296.2, 296.3	F32, F33

ICD = International Classification of Disease; OA = osteoarthritis; T2D = type 2 diabetes.

Results

A total of 819 patients were included in the analyses; of those, 148 (18.07%) had T2D. Table 2 shows the patients' characteristics for the whole sample, the localized OA subsample, and the localized OA with T2D subsample. To summarize, people with localized OA+T2D (N = 148) were older and had higher BMIs and pain severity when compared with people with localized OA only (N = 671). People with localized OA+T2D had higher prevalence of hypertension, dyslipidemia, depression, and medication usage (for T2D, hypertension, dyslipidemia) when compared with individuals with localized OA only. However, people with localized OA+T2D had lower prevalence of using opioids compared with people with localized OA only. Participants with localized OA+T2D had higher pain severity when compared with participants with localized OA only at three locations (i.e., shoulder, hand or elbow, and knee or lower leg). The hip or pelvis and ankle or foot locations showed no significant difference in pain severity when compared with localized OA+T2D. A total of 37 (42.53%) participants within the T2D group who had available HbA1c values (N = 87) had poor glycemic control (HbA1c $\geq$ 7). Table 3 shows a summary of pain severity across OA locations and T2D statuses.

For the impact of T2D and joint pain severity in people with localized OA, the results of the multiple linear regression analyses are presented in Table 4 with associated 95% CIs. Model 2 shows that T2D was significantly associated with increased joint pain severity (B = 1.07, 95% CI = 0.25 to 1.88, $P = 0.014$) after adjustments for covariates including age, gender, OA locations, BMI, depression, hypertension, dyslipidemia, and medication usage (pain medications including opioids, nonopioids, and benzodiazepine; antidiabetics; antihypertensives; antilipemic; antidepressants) within 90 days of the index date.

For the impact of HbA1c level on joint pain severity in people with localized OA+T2D, the results of the linear regression are listed in Table 5. Model 3 shows that an

Table 2. Participants' characteristics

	Total Sample N = 819	Localized OA+T2D N = 148	Localized OA Only N = 671	*P* Value
Age, mean ± SD, y	64.1 ± 10.2	66.38 ± 9.42	63.58 ± 10.32	0.002
Gender, female, No. (%)	374 (54.3)	81 (54.7)	364 (54.2)	0.49
Body mass index, mean± SE, kg/m^2	31.71 ± 0.35	33.90 ± 0.70	31.21 ± 0.41	0.003
Hypertension, No. (%)	401 (49.0)	115 (77.7)	286 (42.6)	< 0.001
Dyslipidemia, No. (%)	251 (30.6)	82 (55.4)	169 (25.2)	<0.001
Depression, No. (%)	84 (10.3)	28 (18.9)	56 (8.3)	<0.001
Medications, No. (%)				
Insulin	91 (11.1)	91 (61.5)	0 (0.00)	<0.001
Hypoglycemic	99 (12.1)	77 (52.0)	22 (3.3)	<0.001
Antihypertensive	186 (22.7)	57 (38.5)	129 (19.2)	<0.001
Antilipemic	366 (44.7)	92 (62.2)	274 (40.8)	<0.001
Antidepressants	230 (28.1)	49 (33.1)	181 (27.0)	0.08
Opioid	759 (92.7)	127 (85.8)	632 (94.2)	0.001
Nonopioid	624 (76.2)	114 (77.0)	510 (76.0)	0.44
Benzo	670 (81.8)	114 (77.0)	556 (82.9)	0.06
HbA1c, n = 87 mean ± SD	-	7.03 ± 2.01	-	-
Pain intensity, mean ± SD	5.36 ± 2.84	6.22 ± 2.85	5.17 ± 2.80	<0.001

OA = osteoarthritis; T2D = type 2 diabetes.

Table 3. Comparison between groups for pain severity across each OA location using the Mann-Whitney test

	No T2D		T2D		*P* Value
OA Locations	No.	Pain Severity ± SD	No.	Pain Severity ± SD	
Total all locations	671	5.17 ± 2.81	148	6.22 ± 2.85	0.001
Shoulder	96	5.70 ± 2.72	30	7.60 ± 2.21	0.001
Hand or elbow	112	4.40 ± 2.42	21	5.86 ± 2.97	0.041
Ankle or foot	110	5.29 ± 3.08	19	6.26 ± 2.98	0.17
Knee or lower leg	258	5.01 ± 2.80	63	5.92 ± 2.88	0.018
Hip or pelvis	95	5.80 ± 2.85	15	5.13 ± 2.95	0.45

OA = osteoarthritis; T2D = type 2 diabetes.

Table 4. Linear regression analyses for the association between T2D and joint pain severity

Dependent Variable		No.	B	SE	95% CI	*P* Value
Pain severity	Model 1	819	1.025	0.26	0.52 to 1.53	<0.001
	Model 2	819	1.07	0.43	0.25 to 1.88	0.014

Model 1 was adjusted for age and gender. Model 2 was adjusted for model 1 and body mass index, OA locations, depression, hypertension, dyslipidemia, and taking medications (pain meds, antidiabetics, antihypertensive, antilipemic, and antidepressants within 90 days of the index date).

CI = confidence interval; OA = osteoarthritis; T2D = type 2 diabetes.

Table 5. Linear regression analyses for the association between HbA1c and joint pain severity in people with T2D and localized OA

Dependent Variable		No.	B	SE	95% CI	*P* Value
Pain severity	Model 1	87	0.25	0.15	–0.044 to 0.55	0.095
	Model 2	87	0.23	0.14	–0.055 to 0.52	0.11
	Model 3	87	0.36	0.16	0.036 to 0.67	0.029

Model 1 was unadjusted. Model 2 was adjusted for age, gender, BMI, and OA locations. Model 3 was adjusted for age, gender, BMI, OA locations, and taking medications within 90 days of the index date (pain meds, antihypertensive, antilipemic, insulin, and hypoglycemic).

BMI = body mass index; CI = confidence interval; OA = osteoarthritis; T2D = type 2 diabetes.

increase in HbA1c value was significantly associated with increased joint pain severity (B = 0.36, 95% CI = 0.036 to 0.67, $P = 0.029$) only after adjustments for age, gender, BMI, OA location, and pain medication (opioids, nonopioids, and benzodiazepine; antidiabetics; antihypertensives; and antilipemic).

Discussion

This study examined the association of T2D with joint pain severity in people with localized OA and explored whether glycemic control measured by HbA1c was associated with pain severity in people with localized OA and T2D. The results of this study found that T2D was associated with increased pain severity in people with localized OA. Poor glycemic control measured by HbA1c was associated with increased pain severity in people with localized OA and T2D only after controlling for using medications.

The current study found that T2D was associated with higher pain severity in people with localized OA. Although limited research has investigated the impact of

diabetes on pain severity in people with localized OA, few studies have found an association between diabetes and knee pain symptoms [6,8,9] and hand OA [20]. The findings from the current study are consistent with previous studies examining the association between diabetes and pain severity in people with knee or hand OA [6,8–10,20]. Additionally, the current study found higher pain severity in people with T2D at different locations, including the knee, shoulder, and hand. However, patients with hip and foot or ankle OA showed no significant difference in pain severity between people with and without T2D. The differences between the current study and previous reports are related to controlling for other covariates such as demographics, chronic diseases, and using medications. Furthermore, the current study included all possible OA locations and adjusted for OA location in the analysis. Eitner et al. found that people with end-stage knee OA and diabetes had higher pain severity when compared with those without diabetes [8]. Another study on women with knee OA found that diabetes was associated with increased knee pain severity using a numeric rating scale after controlling for age, BMI, and exercise [9]. However, the amount of pain increase due to diabetes was below the clinically important difference (>1 score) in this study (B = 0.4) [9]. Our study found that T2D was associated with higher pain severity using a numeric rating scale that exceeded clinically important difference (B = 1.16) [21].

Most of the previous published reports have focused on specific joints (i.e., knee or hip OA), regardless of other parts that might be affected by OA such as the hands and shoulders. The present study examined localized OA that affects one or two joints, in any possible joint such as the knee, hip, ankle, hand, or shoulder. The joint category was added as a covariate in the analyses to control for the effect of OA location on pain severity. The results of this study may give clinicians and researchers a holistic picture of the burden of T2D on localized OA symptoms for possible joints that can be affected by OA. However, the interpretation of the findings regarding the association of T2D with shoulder OA pain might be limited due to the association of T2D with other painful shoulder disorders not specific to OA. Future research should examine in depth the association between T2D and other shoulder disorders.

Pain medications and other metabolic syndrome medications were adjusted in the current study, and T2D remained significantly associated with pain severity in people with localized OA. Previous reports have not controlled for medications such as opioids and other metabolic syndrome medications [6,8–10]. Especially when pain severity is an outcome, pain medications such as opioids and nonopioids should be adjusted in the analyses to obtain the relationship between T2D and pain in this population. To our knowledge, this study was the first that controlled for using pain medications within 90 days of the index date. Other medications including antidiabetic, antilipemic, and antihypertensive drugs might be associated with decreased pain and progression in people with OA [14,15,22–24]. Thus, the present study has the ability to control for using these medications to examine the influence of T2DM on pain severity in people with localized OA, independent of other possible confounders.

The potential mechanism for the association between T2D and pain severity in people with localized OA is beyond the scope of this work. However, the current study might relate this association to the effect of hyperglycemia or poor glycemic control. The results of the association between higher levels of HbA1c and pain severity were significant after controlling for pain medications, antihypertensive, antilipemic, insulin, and hypoglycemic drugs. However, the unadjusted model was not statistically significant ($P = 0.09$), indicating that these medications may influence the relationship between HbA1c and pain severity. Only one study showed a significant correlation between HbA1c and knee pain score in people with end-stage knee OA [8]. Chronic hyperglycemia may affect pain severity due to an increase in inflammatory markers, including increased production of oxidative stress, AGEs, and pro-inflammatory cytokines in the joints [13]. In a high–glucose concentration state, AGEs can accumulate in cells and joints. Increased levels of AGEs have been linked to modifying joint properties including stiffness, resistance, and cartilage degradation [11,12,25]. Previous evidence showed higher concentration of interleukin-6 in the synovial fluid and higher synovitis scores among patients with diabetes and end-stage knee OA when compared with patients with knee OA only [8].

This study has some limitations. The design was retrospective; thus, causality cannot be determined. The data were obtained from a single site, which limits generalizability. Using diagnostic codes is prone to measurement errors or bias. However, we used at least two ICD-9 or ICD-10 codes to improve accuracy. BMI data were obtained within two years of the index date, and this may change dramatically during this relatively long period. Although every possible effort was made to capture pain severity data by linking pain to OA diagnostic codes, there is a possibility of including pain data not related to OA. HbA1c value was obtained within six months of the index date to increase the sample size for subgroup analyses. However, the HbA1c is usually a measure for three months of glycemic control. Therefore, the results regarding HbA1c should be interpreted with caution. This study is limited by a lack of information about OA grades or radiographs, as these variables were not available in the database. Although this study controlled for medications such as opioids, this was categorized as yes or no, and dosage of medications was not considered. This study included only people with localized OA, and the results are limited to this subpopulation. Future research may consider generalized OA and

T2D. The type of diabetes medications (insulin vs oral) may show other spectra of this association and should be considered in future research. Some possible unknown factors that cannot be captured in HERON database may have influenced the results.

Conclusions

This study found that T2D was a significant factor for increased pain severity in people with localized OA after controlling for other confounders. Participants with T2D had higher pain severity at any localized OA location including weight-bearing and non-weight-bearing joints (i.e., knee, hand, and shoulder), except hip and ankle locations. Increased HbA1c level was not significantly associated with increased pain severity in people with localized OA and T2D. However, after controlling for other covariates including age, sex, BMI, and medications, including pain medications, antilipemic, antihypertensives, and antidiabetics, HbA1c was a significant factor for increased pain severity in this population. T2D as a systemic disease results in chronic hyperglycemia, which is associated with increased production of oxidative stress and inflammatory cytokines at any joint, and these mechanisms could elucidate the association between T2D and pain severity in this population. Clinicians should emphasize that better HbA1c control might help with pain management in people with T2D and OA. As increased HbA1c was associated with increased pain severity only after controlling for specific medications including pain meds, antihypertensive, antilipemic, insulin, and hypoglycemic, these factors might become potential targets for managing pain in people with localized OA and T2D. Clinicians may need to reinforce the importance of medication adherence to minimize the level of pain in people with localized OA and hyperglycemia.

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