The Impact of Diabetes on Osteoarthritis Prevalence and Pain

By

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Abstract

A growing body of evidence shows that there is an association between osteoarthritis (OA) and Type 2 diabetes mellitus (DM). However, the impact of DM on OA prevalence, specific OA locations, and pain remain poorly understood. Therefore, the primary purpose of this work was to examine the association of DM with OA in terms of prevalence and pain using large data sets. Particularly, three specific aims were studied in this dissertation. First, we examined the prevalence and risk factors for generalized OA (involving 3 or more joints) compared localized OA (involving only one or two joints). Second, we examined the association between type 2 DM and pain severity in people with localized OA. Finally, we examined the association between DM and knee pain locations, including localized, regional and diffused knee pain in people with knee OA.

Chapter 2 describes a preliminary work for this dissertation examining the association of DM with knee pain severity and knee pain distribution (unilateral or bilateral versus no pain) in people with knee OA. This work included a cross-sectional analysis of the baseline visit of individuals who were enrolled in the Osteoarthritis Initiative. Data for participants with knee OA were used for this analysis (n=1319). Pain severity was measured using a numeric rating scale from 0 to 10 over the past 7 and 30 days for each knee. We found that DM was significantly associated with increased knee pain severity. Moreover, we observed a significant association between DM and

unilateral and bilateral knee pain. These results indicated the potential effect of DM on short-term and long-term knee pain severity as well as joint distribution.

Building upon the preliminary findings from the preliminary study in chapter 2, we examined the association between DM and OA with a focus on comparing people with generalized and localized OA. As described in chapter 3, we examined the prevalence of type 2 DM among people with generalized OA compared to localized OA along with the associated risk factors including demographic risk factors and chronic diseases (i.e. Type 2 DM, hypertension, dyslipidemia, neuropathy, and body mass index). A retrospective review of data was performed using the Healthcare Enterprise Repository for Ontological Narration (HERON), and patients with diagnostic codes for OA were selected. Data from 3855 individuals included patients with generalized OA (n=1265) and localized OA (n=2590). The prevalence of type 2 DM was significantly greater among patients with generalized OA compared to localized OA. Significant associations were found between generalized OA and type 2 DM, hypertension, and dyslipidemia. The findings from this chapter highlighted that chronic diseases including type 2 DM, hypertension and dyslipidemia might affect any joints or multiple parts due to their systemic inflammatory impact on joints and vascular systems innervating joints resulting in generalized OA.

Investigating the association between type 2 DM and OA in further details, we analyzed the association of type 2 DM with pain severity in people with localized OA to understand the association whether limited to knee joint as described in chapter 2 or at any other localized joint. Chapter 4 examined the association between Type 2 Diabetes and pain severity in people with localized OA, and explored the association between

glycemic control measured by A1c level and pain severity in people with localized OA and type 2 DM. A retrospective design using HERON database was used, and data from 819 patients were obtained and grouped into localized OA only (n=671) and localized OA+type2 DM (n=148) based on diagnoses 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. Hemoglobin A1c values were obtained for patients with T2D within six months of the index date. Type 2 DM was significantly associated with increased pain severity. Furthermore, for patients with type 2 DM and localized OA with available data for A1c (n=87), the results showed that increased A1c value was significantly associated with higher pain severity. These results suggested a negative impact of type 2 DM on pain severity in people with localized OA and extends beyond the knee joint, as shown in chapter 2 using a different dataset and population.

To study in-depth the association of DM with pain in people with OA, Chapter 5 described the results of the association of DM with knee pain locations in people with knee OA. Another exploratory analysis emerged to identify the association of DM with knee pain during walk and walking speed. This study used data from 1790 individuals from the osteoarthritis initiative with knee pain and grouped into knee OA and diabetes (n=236) or knee OA only (n=1554). Knee pain locations were categorized to no pain, localized, regional, or diffused pain. Knee pain during a 20-meter walk test was categorized as: no pain, mild, moderate, and severe knee pain. Walking speed was measured using a 20 m walk test. The results showed that DM was associated with regional knee pain, moderate, and severe pain during walk. Additionally, DM was associated with decreased walking speed. These results suggested that DM can cause

damage to the musculoskeletal system and might affect pain locations and walking performance in people with knee OA.

In summary, this body of work has shown that DM was associated with higher pain severity, bilateral and unilateral knee pain in people with knee OA. This work has identified the prevalence of DM in people with generalized OA and age, sex, DM, hypertension, and dyslipidemia were associated with generalized OA compared to localized OA. Our results found that DM was associated with higher pain severity in people with localized OA. Furthermore, glycemic control measured by A1c was associated with higher pain severity in people with DM and localized OA. Our findings demonstrated that DM was associated with specific knee pain pattern (regional knee pain), but not diffused or localized knee pain in people with knee OA. Finally, we found that DM was associated with increased knee pain during walk and walking speed in people with knee OA. This body of work is important for clinicians in many aspects. First, clinicians should consider DM as a risk factor during pain management for people with knee OA, whether bilateral or unilateral. Second, because people with DM, hypertension, and dyslipidemia appear to be at higher risk of generalized OA, they may benefit from screening and an interventional approach to manage arthritis in multiple parts of the body. Third, health care providers should emphasize that better A1c control might help with pain management in people with DM and OA. Finally, we suggest that clinicians should include walking speed assessments for patients with DM and knee OA to rule out any future risk. The findings from this dissertation highlighted the need for future research to identify whether DM causes OA or vice versa. In addition, the potential mechanisms for the association between DM and OA is an essential step for

future studies. Although parts of this dissertation focused on pain, there is a critical need to examine the longitudinal impact of DM on pain and symptoms in this population.

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Chapter 1: Introduction

Background

Diabetes Mellitus (DM) and OA are common chronic diseases resulting in several complications including hyperglycemia and pain, respectively. The prevalence of OA and DM has increased recently, affecting approximately 10% and 14% of the general population, respectively [1-4]. Recent evidence has shown an association between DM and OA [5, 6]. Studies have shown that DM, a common coexisting disease in people with OA, was a risk factor for OA incidence and progression [7-15]. DM impact was not only evident in the presence of OA, but it also has a negative impact on pain in people with OA. Recent evidence has shown that DM was associated with increased pain severity in people with knee OA [12, 16-18].

Many shared risk factors might be associated with either DM or OA. Risk factors included demographic factors (e.g., age, sex, and race) and metabolic syndrome (e.g., obesity, hypertension, and dyslipidemia). Previous research has found that these risk factors (demographic and metabolic syndrome) were associated with either DM or OA [19-21]. With a growing body of evidence regarding the association between DM and OA, it is essential to review and evaluate the pertaining literature and summarize findings about this topic. Therefore, the purpose of this review is to evaluate and update the literature about the association between DM and OA in terms of prevalence, association, pain, and shared risk factors.

Osteoarthritis

Osteoarthritis is one of the most common chronic diseases that affect joints. OA affects approximately 14% of the general population, and 26 million individuals are expected to have OA in the United States, with the average cost per patient exceeding $2000 annually [22, 23]. The prevalence of OA increases with age, and approximately 34% of older adults who are older than 65 years have OA [23]. OA is characterized by loss of cartilage, osteophyte formation, and synovial inflammation. The most common sites include knee, hip, hand, and spine. Pain is the most common symptom that requires treatment in people with OA, and pain severity may be influenced by many factors such as age, sex, obesity, and other comorbidities such as diabetes.

Generalized OA (GOA) affects three or more joints [24], and localized OA affects less than three joints. People with generalized OA may present with worse symptoms or poorer outcomes in terms of pain, functional impairments, and quality of life. Previous evidence has shown that patients with total knee replacement and OA in multiple joints had worse pain and physical function [25]. GOA affects joint replacement outcomes, quality of life, and functionality when compared to localized OA [26]. Patients with GOA may have severe impairments during activities of daily living that could affect their self-care and basic independence requirements for daily living [26].

Diabetes

Diabetes is a common metabolic syndrome around the world. DM affects approximately 9% of the general population and leads to several complications [3]. The estimate of people with DM is approximately 592 million globally by the year 2035 [27]. In America, more than 20 million people have DM with the total annual cost exceeding $245 billion [28].

A common complication of DM is hyperglycemia that may affect joints and bones. DM is characterized by disturbance in insulin machinery that leads to hyperglycemia and often leads to other complications. Hyperglycemia may induce chronic systemic inflammation that leads to systemic changes in body organs, including joints [29]. Another consequence of hyperglycemia is the production of advanced glycation end products (AGE) that can accumulate in any part of the body, including joints, and may increase cartilage stiffness and bone fragility [30].

Diabetes progresses at different rates depending on the risk factors such as demographics, chronic diseases, and poor glycemic control. Recent guidelines suggested that early treatment of DM and good glycemic control might slow DM progression [31]. A recent study has shown that younger age and females had poorer glycemic control as measured by HbA1c ≥ 7 [32]. Other factors for poor glycemic control were identified in this study, including poor adherence to medications, lifestyle modifications, and longer DM duration. Higher body mass index (BMI) and other comorbidities such as dyslipidemia and vascular complications were not significant in the multivariate analyses. Another large study found that younger age was also

consistently associated with poor glycemic control (HbA1c ≥ 7) in patients with untreated DM [33].

Osteoarthritis and diabetes in terms of association

Numerous studies have examined the association between DM and OA and found a significant association. Two meta-analyses were published investigating the association between OA and diabetes, and they showed a significant association [5, 6]. One large recent meta-analysis by Louati et al. [5] included 49 studies. The designs of the included studies varied including cross-sectional, case-control, and cohort studies. Their results showed that the prevalence of OA among 5,788 patients with DM was 29.5%, and the prevalence of DM among 645,089 patients with OA was 14.4%. The risk of OA was significantly associated with DM compared to the non-DM population with an odds ratio (OR) 1.46. In addition, this study found that the risk of DM was significantly associated with OA compared to non-OA population (OR=1.41). Several studies included in this meta-analysis had limitations, including joint replacement as the main outcome, lack of controlling other risk factors such as age, sex, and obesity as well as heterogeneous OA and DM definitions. Another recently published meta-analysis by Williams et al. [6] found similar results with fewer included studies (n=10 studies). This study included studies that examined the association between OA and DM even after controlling for BMI with a smaller population (n =16,742 patients). The primary outcome was the presence or progression of OA with DM as an independent factor. This study found a significant association between OA with the presence of DM (OR=1.21) and

remained significant after controlling for BMI. However, this study has limitations such as including the self-reported DM and joint replacement as the main outcome in some of the included studies.

Many studies have examined the prevalence of OA and DM and found a significant association. The prevalence of OA was estimated to be 52% in people with DM compared to 27% in those without DM [34]. Recent studies have shown a high prevalence of DM and OA [8, 10, 35]. Kim et al. have reported that the prevalence of knee OA was 42.4% in people with DM compared to 35.4% in those without DM [8]. Another previous research has shown that the prevalence of OA among people with DM was 49% compared to 26.5% among those without DM [10]. A larger population-based study has reported that the prevalence of hyperglycemia was 30% in people with OA compared to 13% in people without OA [35]. Previously mentioned research has focused on specific locations such as knee joints [8, 10] or hands[10] or unspecified OA joint [35]. Therefore, other factors should be considered in analyses such as BMI for weight bearing joints.

Numerous reports have examined the association between DM and OA either in unadjusted or adjusted analyses with inconsistent results within and between studies. A previous cross-sectional study (n=202) [10] showed that people with DM had 2.18 odds of having knee or hand OA compared to those without DM after adjustments for age, gender, obesity, and other risk factors. However, this study has some limitations such as including only Hispanic people, using a small sample and relying on self-reported

diabetes. Similarly, a recent research study has found a significant association between knee OA and DM (OR=1.19) in a large cross-sectional study (n=9,514) of Koreans [8] even after controlling for age and sex. However, after further controlling for other factors such as BMI, the association became non-significant [8]. Potential reasons for the non-significant association is that DM categorized to prediabetes and diabetes. Puenpatom et al. in a large population-based study (n=7,714) found that the association between metabolic syndrome and OA was greater at a younger age [35]. However, this study has not specified which joint affected by OA and type of OA (primary or secondary). A recent cross-sectional study from china with a large sample (n=5,764) has found that hyperglycemia was associated with knee OA (OR=1.36) in an unadjusted analysis [36]. However, this association disappeared in an age- and sex-adjusted model.

In contrast to previous research, a recent systematic review included 40 studies examined the association between DM and OA for knee, hip, and hand, separately [37]. This review concluded that little evidence suggested the association between DM and knee OA independent of obesity, and no evidence suggested the association between DM and hip or hand OA [37]. Consistent with these previous reports, a large case-control study (n=13,500 cases; n=13,500 matched control) by Frey et al. reported that DM was not associated with hands OA even after adjustments for age, gender, and BMI [38]. Although this study included a control group, this study had some limitations. It did not specify the type of hand OA or joints affected of the hand. This study used only one diagnostic code to define DM and hand OA, which may affect the accuracy, and other research uses two codes to improve validity. Consistent findings from Japan (n=119

women) has shown that DM was not associated with knee OA [39]. However, the participants were only women who underwent knee joint surgery, indicating end-stage knee OA. Taken together, the common limitation in these studies is focusing on localized OA in specific joints such as knee or hand and cross-sectional designs.

Few studies examine the association between DM and OA using longitudinal designs with contradicting results. A previous study with 12 years mean follow up (n=19,089 cases with OA; n=19,089 control) examined the incidence of DM in people with OA compared to those without [11]. This study showed that OA was a significant risk factor for DM incidence except for older men (> 65 years) after adjustments for covariates, including obesity [11]. The OA locations and type of OA (primary or secondary) were not specified. Another study (n=927) examined the association between DM and total hip or knee replacement over 20 years follow up [12]. This study found a significant association between DM and hip or knee replacement after adjustments for age, gender, obesity, and other confounders. This study defined OA as total hip or knee replacement. A previous longitudinal study (n=1,690) with a three-year follow-up has shown the association between knee OA occurrence and DM after adjustments for confounders such as age, gender, and BMI [13]. Another large longitudinal study over 13.5 years mean follow up (n=16,362) examined the incidence of DM among people with OA [40]. This study concluded that having knee and hip OA was a significant predictor for incident DM after adjustments for covariates such as age, gender, and BMI. This study has not measured overtime changes in other factors. Contradictory to the previous study findings and concept, a recent report (n=987) has examined whether

DM at baseline was a predictor for radiographic knee OA over seven years follow up [41]. This study has shown that baseline DM was not associated with incident radiographic knee OA after adjustments for confounders including BMI. However, levels of homeostasis model of assessment (HOMA-IR) was negatively associated with incident knee OA in women only (OR=0.80). Previous reports had different sample sizes, methodologies and definitions for OA and DM.

Osteoarthritis and diabetes in terms progression

Treatment options of OA are mainly focused on decreasing symptoms as well as preventing or slowing down disease progression, but DM may facilitate OA progression. Previous evidence has shown that DM was an independent risk for OA progression in addition to negative outcomes and complications such as joint replacement surgery [12-14, 42-44]. Schett et al., [12] evaluated arthroplasty rates among 927 patients over 20 years of follow-up visits. They concluded that DM was an independent risk factor for hip and knee joint replacement. Another recent study (n=559) examined the progression of knee OA and found that DM was an independent risk factor for knee joint space narrowing over three years compared to patients without DM [14]. Another report (n=1,690) with three years follow up has shown that DM was associated with knee OA progression [13]. However, further adjustment for BMI attenuated this association. Previously mentioned studies about DM and OA progression was focused on knee or hip OA.

Moreover, OA progression has been linked to excessive weight-bearing stress on joints, which could facilitate disease progression. High mechanical load on weight-bearing joints such as knee or hip may cause cartilage damage and misalignment that may contribute to OA progression [45-47]. However, these studies did not examine non-weight bearing joints. Regardless of the mechanical stress, previous research found an association between OA in non-weight bearing joints and obesity that may suggest a systemic pathway [10, 48].

Osteoarthritis and diabetes in terms of pain

Pain is a common symptom in patients with OA and may be affected by DM. Pain can be categorized into nociceptive and neuropathic pain in people with OA [49]. Nociceptive pain occurs due to painful stimuli resulting from inflammation in the synovium and subchondral bone and usually characterized by sharp and dull aching pain. Neuropathic pain occurs due to pathology in nerves and usually described as burning, tingling, and numbness pain. For both types of pain, pain severity plays a significant role in choosing the appropriate treatment, including medications for pain relief. However, very limited research has examined the impact of DM on either pain type in individuals with OA.

Few studies examined the impact of DM on pain severity in people with OA. Recent evidence has shown that DM was associated with increased pain severity in people with knee OA [12, 17, 18, 39, 50]. Previous evidence (n=927) has concluded that DM was

associated with more severe clinical symptoms, including pain in people with hip or knee OA [12]. This report included people who underwent hip or knee arthroplasty and may indicate end-stage OA. A recent study (n=70) concluded that patients with DM had higher pain severity in knee OA compared to those without DM [17]. Moreover, this study found that levels of inflammatory markers such as interleukin-6 and synovitis were higher in patients with DM and knee OA compared to those with only knee OA, and these values were significantly associated with pain severity [17]. This study included patients who underwent arthroplasty with a small sample. Consistent with previous reports, Abourazzak et al. reported that (n=130 women) DM was associated with higher pain severity in women with knee OA [18]. Recent evidence (n=119 women) has shown that elevated blood glucose was associated with the severity of symptomatic knee OA [39]. This study included only women who scheduled for knee joint surgery. A previous study (n=70 with knee OA; n=81 control) has found that DM was associated with higher pain severity in people with knee OA [50]. Although previous research reported a significant association between DM and pain in people with OA, the lack of controlling medications and other associated factors may limit our understanding.

Shared risk factors for Osteoarthritis and diabetes

Common risk factors have been associated with either DM or OA. These shared factors included demographic factors (e.g., age, sex, and race) and metabolic syndrome (e.g., obesity, hypertension, and dyslipidemia). Previous research has found that these risk factors (demographic and metabolic syndrome) were associated with either DM or OA

[19-21]. In addition to these risk factors, other factors have been considered risk factors for either DM or OA, including medications. Recent evidence has suggested that metabolic syndrome and their medications may affect the incidence and prevalence of OA [51]. Previous research has shown that antilipemic or antihypertensive medications were associated with decreased knee OA progression and pain [52]. Table 1 summarizes commonly shared risk factors for DM and OA

Table 1.1: Summary of shared risk factors for OA and diabetes

Risk factors	OA	Diabetes
Age	Older age increased the risk [53]	Older age increased the risk [54]
Gender	Females have higher risk than males [55, 56]	Females have higher prevalence of diabetes than males at older ages [57]
Obesity	Obesity increased the risk [45, 58]	Obesity increased the risk [59]
Hypertension	Associated with increased risk [13]	Associated with increased risk [60]
Dyslipidemia	Associated with increased risk [13]	Associated with increased risk [61]
Other risk factors	Previous injury, joint arthroplasty, sleep disorders [62] and depression [63]	Depression [64] and sleep disorders [65]

Age

Aging has a negative impact on different systems and organs because advanced age is associated with cellular function decline that has been linked to both OA and DM [19-21]. A common risk factor of both OA and DM is aging, and increased age is associated with the development and progression of both diseases. OA is associated with aging due to cellular decline in joints such as chondrocytes resulting in cartilage degradation [54]. DM is prevalent in older age because pancreatic cell decline increased with aging [53].

Gender

The prevalence of OA is greater in females, but previous studies usually controlled for sex in the analyses. Previous research has suggested that females have a higher prevalence of hip and knee OA than males [55, 56]. A meta-analysis showed differences in the prevalence and incidence of OA based on sex, and females have a notably higher risk after menopause age [66]. In contrast, recent research reported no association between hand OA and sex [38]. Sex differences in OA prevalence might be attributed to hormonal changes in females after menopause age that could partially explain this association [67, 68].

The global prevalence of DM is similar among men and women, but women have a higher prevalence of DM than men at an older age [57]. This difference might be

explained by the higher number of women than men in most populations and older age that is associated with a higher prevalence of DM [57]. However, the age-adjusted rate for DM in the United States was 6.6 for males and 5.9 for females in 2014 [69]. Since the majority of studies on OA and DM controlled for age and sex, there is a critical need to evaluate this relationship.

Race

Race is a common risk factor for DM and OA. Race has been shown to be associated with OA. Previous research reported an association between non-Hispanic African Americans and OA using a national health survey in the United States [70, 71]. A similar association exists between race and DM. A previous report showed a higher prevalence of DM among non-Hispanic African Americans [72]. Because OA and DM are independently associated with race, future research regarding the association between these diseases should consider race as a potential factor.

Obesity

A common shared risk factor in OA and DM is obesity, which is associated with 90% of DM [59] and OA [58]. Obesity is a systemic and metabolic disease that affects body organs and joints. Impaired glucose tolerance is associated with obesity as well as related metabolic syndrome [73]. Obesity is typically defined as an excessive body weight using many formulas such as body mass index (BMI). Obese people have a BMI

≥ 30, and overweight people have a BMI ≥ 25. Recent research has shown that obesity was a significant risk factor for knee OA after controlling for covariates such as metabolic syndrome [8, 74]

Obesity might be linked to OA due to the effect of weight and misalignment on joints especially weight-bearing joints that affect joint cartilage [46, 47, 58]. Furthermore, previous research has reported that obesity is associated with non-weight bearing joints such as hands OA [13, 75], which suggests that obesity might be associated with systemic metabolic dysfunctions rather than mechanical [48]. To better understand the relationship between obesity, OA, and DM, it is necessary to study this association in terms of weight-bearing versus non-weight bearing joints.

Hypertension

Elevated blood pressure is a common form of cardiovascular disease that is associated with both OA and DM. The relationship between hypertension, OA, and DM has been studied as a risk factor for the development and progression of OA. Prior research has demonstrated the accumulation of metabolic factors, including hypertension and DM, was associated with knee OA occurrence over three years after controlling for other covariates [13]. Previous studies have also reported that hypertension is significantly associated with knee OA after controlling for covariates, including BMI [7, 8, 36, 76].

The proposed mechanism for hypertension as a risk factor for the development of OA has been reported previously by Findlay [77]. Vascular impairment due to hypertension may play a role in OA development and progression. Decreased blood flow with hypertension causes subchondral ischemia that is associated with cellular dysfunction in the joint, including osteocytes and articular cartilage [77]. Previously mentioned studies shared a common limitation, which is examining knee OA only. The presence of DM and OA, as well as other metabolic risk factors, including hypertension, needs further research because these metabolic syndromes are systemic diseases, and they may contribute to further complications.

Dyslipidemia

Dyslipidemia is a form of metabolic disorder, and the evidence about its association with DM and OA is limited due to lack of research. Dyslipidemia indicates disturbances in serum level of any form of cholesterol, including high-density lipoprotein, low-density lipoprotein, total cholesterol or triglyceride. Prior evidence has shown that dyslipidemia was associated with knee OA after controlling for other covariates such as BMI [8, 74, 78]. Although some previous studies have demonstrated the association between dyslipidemia, DM and OA occurrence [13, 79, 80], other studies reported no association between DM, dyslipidemia and OA [38, 81]. These studies have focused on non-weight bearing OA with different definitions for dyslipidemia, which might contribute to conflicting results.

Medications

Medications for chronic diseases may play a role in the development or progression of OA. From those medications, antidiabetic, antilipemic, and antihypertensive medications. Previous research has shown conflicting results regarding the association between medication usage and incidence or progression of OA. Medications, including antidiabetic, antilipemic, and antihypertensive drugs might be associated with OA [51, 52, 82-84]. A previous report has found that the incidence and prevalence of OA might be affected by the presence of metabolic syndrome and their medications [51]. Recent research has demonstrated that using medications such as antilipemic or antihypertensives were associated with decreased knee OA progression and symptoms [52]. Previous study has found that individuals with DM using insulin was associated with less osteophyte formation compared to those with DM without insulin [82]. Statin use has been associated with decreased incidence and progression of knee OA [84]. Another longitudinal study over ten years follow up showed that using a high dose of statin was associated with a reduction in clinically defined OA (e.g., painful OA) [85]. Contrary to these findings, prior research has found that statin users were at increased risk of knee OA progression compared to non-statin users [83]. These conflicting findings could be related to differences in definitions of OA (e.g., diagnostic codes versus radiographic OA), OA locations, and statin dosage. Further research within the context of metabolic syndrome medications and OA is required.

Other risk factors

Many other risk factors, including sleep disorders and depression, may contribute to the development of OA in people with DM. Hyperglycemia and OA pain are common concerns in people with DM and OA because glycemic control by exercise will be limited due to pain, sleep disorders, or depression. Limited evidence has linked sleep disorders and depression to either DM [62, 63] or OA [64, 65], independently. Other factors may also have an important association with DM and OA, such as joint arthroplasty. These factors should be considered in future research examining the association between OA and DM.

Significance and Innovation

This study contributed to the literature by examining the impact of DM on OA prevalence, risk factors, and pain. Limited research has investigated the association between DM and localized OA, but GOA prevalence and pain remain unclear. For example, when a patient presented at a physical therapy clinic with DM and knee pain, some questions still need to be asked, and the treatment approach depends on the answers to these questions. First, does the patient have GOA in joints other than the knee? However, the estimated prevalence and risk factors associated with GOA are unclear. Second, does the patient have higher pain severity than other people without DM? Third, does the patient have a specific knee pain locations pattern that is different from others without DM? Therefore, understanding the association between DM and OA

is necessary. Identifying the prevalence of GOA in people with DM is necessary to have an estimate for coexisting GOA and DM. The prevalence of GOA among the overall OA population is high, with worse outcomes in individuals with GOA, including poor quality of life, higher pain, and decreased functionality. People with multiple joint OA may benefit more from systemic and interdisciplinary approaches than people with a single joint OA [86]. Knee pain locations play an important role in designing interventional approach. A traditional target for physical therapy is the anterior medial knee location. However, when the pain is diffused, clinicians should consider broader areas, including posterior knee pain [87]. This project will help clinicians for treating this population and will eventually guide interdisciplinary approach to managing the associated risk factors in people with OA and diabetes.

This study is innovative and feasible because it used two large databases to answer our research questions, which is the impact of DM on OA prevalence and pain. We have access to the Healthcare Enterprise Repository for Ontological Narration (HERON) database and the Osteoarthritis Initiative database (OAI). The HERON database is unique because we have access to extensive de-identified data for patients who visited the University of Kansas Hospital. Our approach using HERON used diagnostic codes that are valid in clinical settings and widely used in research. A unique feature in HERON database is that it includes pain scores that are known as a 5^{th} vital sign and routinely asked for the majority of patients who visited hospitals or clinics. Other variables of interest are available in this database, such as chronic disease diagnoses and medical history, which includes medications.

The OAI is another unique database. It is a multisite ongoing prospective project at four clinical centers in the United States. This database has our variables of interest, including pain locations in people with knee OA (specific aim 3), and it has longitudinal data for 4,796 patients that made our study feasible. Our approach using OAI used well-documented data and variables of interest that do not exist in the HERON database. These variables are collected at multiple sites, which will improve the generalizability of the results. We used valid and reliable outcomes for analyzing pain, which provided evidence for clinicians to target specific symptoms that may not be targeted in traditional physical therapy for people with knee OA.

This study can assist clinicians and researchers in understanding the complex relationship between DM and OA, and it could help in designing preventive and treatment approaches. Pain locations are important determinants of patients' activities because having specific pain pattern may negatively impact a patient's life and participation in the community. This study explored the relationship between knee pain locations and DM in people with knee OA.

Specific aims

Osteoarthritis (OA) and diabetes mellitus (DM) are common metabolic diseases affecting 14% and 9.3% of Americans, respectively. OA is characterized by joint degeneration and inflammation. DM results in chronic hyperglycemia, which may affect

the musculoskeletal system, increase the stiffness and fragility of bone and cartilage, and may affect multiple joints and pain experience. DM and OA have shared risk factors such as older age, females, higher body mass index (BMI), hypertension, neuropathy, and dyslipidemia. DM also increases the progression of OA and the rate of joint replacement. Consequently, the presence of both DM and OA may increase health care needs because of limiting care effectiveness and raising care cost.

Generalized OA (GOA) involves at least three joints, and localized OA involves two joints or less. OA severity and pain may increase depending on the number of affected joints and risk factors. GOA and DM are chronic systemic diseases that may benefit from systemic therapies than other localized diseases such as OA. GOA is associated with poorer quality of life, more functional limitations, and pain. DM may affect OA symptoms, such as pain intensity and locations. Treatment strategies may be improved if we have a greater understanding of pain symptoms, locations, and patterns. Because pain is a modifiable factor, this study will help clinicians to optimize prevention and treatment approaches.

The study objective is to retrospectively examine the impact of DM on OA prevalence and pain. The central hypothesis is that DM would have a negative impact on OA prevalence and pain. This project has three aims:

Aim 1: To examine the prevalence and associated risk factors of GOA compared to localized OA

We hypothesized higher prevalence of type 2 DM among people with GOA compared to LOA in the Healthcare Enterprise Repository for Ontological Narration (HERON) database [H1]. Demographic factors [H2] and chronic diseases, including type 2 DM [H3] would show stronger associations with GOA compared to localized OA.

Aim 2: To Examine the association between type 2 DM and pain severity in people with localized OA.

We hypothesized that in HERON database type 2 DM would be associated with higher pain severity in people with localized OA using a numeric rating scale [H4].

Aim 3: To explore the association between diabetes and knee pain locations including localized, regional, and diffused pain locations, using knee pain map in people with knee OA.

We used the Osteoarthritis Initiative database (OAI) because it has specific information about knee pain locations and outcomes for knee OA that do not exist in HERON database. We hypothesized that DM and knee OA would be associated with diffused knee pain when compared to knee OA only [H5].

This project will provide evidence about pain in people with DM and OA that will help in developing appropriate prevention and treatment approaches. If our hypotheses are

supported, the next step will be designing interventional studies such as examining the effect of glycemic control or appropriate doses for modified physical activity on pain in people with OA+DM.

Chapter 2: The Association of Diabetes with Knee Pain Severity and Distribution in People with Knee Osteoarthritis

Abstract

Objective: Limited research has examined the association between diabetes mellitus (DM) and knee pain in people with osteoarthritis (OA). Therefore, this study aimed at examining the association between DM and knee pain severity, and to explore the association between DM and knee pain distribution (unilateral or bilateral versus no pain) in people with knee OA.

Methods: This is a cross-sectional analysis of the baseline visit of individuals who were enrolled in the Osteoarthritis Initiative. Data for participants with knee OA were used for this analysis (n=1,319). Pain severity was measured using a numeric rating scale from 0 to 10 over the past 7 and 30 days for each knee, and the most symptomatic knee was chosen for analysis. Knee pain severity and knee pain distribution were analyzed using Linear and multinomial logistic regression, respectively, with adjustments for age, gender, BMI, depression symptoms, composite OA score, and pain medications.

Results: DM was significantly associated with increased knee pain severity over seven days (B 0.88; 95% CI 0.45-1.31) and over 30 days (B 0.77; 95% CI 0.35-1.19) after adjustments for covariates. Multinomial regression showed that participants with DM and knee OA had 3.12 (95% CI 1.30-7.47) to 3.48 (95% CI 1.46-8.29) times higher likelihood of having unilateral and bilateral knee pain than those without DM after adjustments for covariates.

Conclusion: DM was associated with higher pain severity and unilateral and bilateral knee pain distribution, independent of pain medications. Clinicians may consider DM as a factor related to knee pain in this population.

Key words: Osteoarthritis, diabetes, pain intensity

Key points:

- In people with knee osteoarthritis, diabetes was associated with increased knee pain severity after adjustments for covariates, including pain medications.
- Individuals with diabetes and knee osteoarthritis had 3-fold greater odds of unilateral and bilateral knee pain compared to those without diabetes.

Introduction

Knee Osteoarthritis (OA) is the most common cause of chronic pain affecting approximately 14% of the general population [23]. Knee pain is a leading cause of disability and the main reason for seeking medical intervention for individuals with knee OA [88]. Knee OA prevalence increases with age, affecting approximately 37% of individuals aged ≥ 45 years [71]. The increased life expectancy in the adult population increases the exposure to chronic diseases that are associated with the aging process, so the prevalence is expected to increase. Previous research has shown that the number of comorbidities is associated with higher knee pain [89]. Among these comorbidities, metabolic syndrome, including DM, hypertension, dyslipidemia, and obesity, have been related to increased pain severity among individuals with OA of the knee joint [16, 50].

Diabetes mellitus (DM) is one of the most common chronic diseases, affecting approximately 10% of the general population [3]. DM is characterized by a disturbance in insulin metabolism that leads to hyperglycemia, which often leads to other complications. Hyperglycemia may induce chronic systemic inflammation that leads to systemic changes in body organs, including joints [29]. Another consequence of hyperglycemia is the production of advanced glycation end products (AGE) that can accumulate in any part of the body, including the joints, and may increase cartilage stiffness and bone fragility [30]. Two recently published meta-analyses found a significant association between OA and DM [5, 6]. DM may be an independent risk

factor for OA progression and adverse outcomes following joint replacement [12-14, 42-44]. Although knee OA progression and severity have been linked to higher body mass index [45-47], prior research has found an association between obesity and OA in non-weight bearing joints that may suggest a systemic pathway [10, 48].

Examining associated comorbidities such as DM in people with OA is necessary to identify an increased risk of pain and multiple joint distributions, as well as to develop preventative interventions. Emerging evidence supports that patients with OA and DM have higher pain severity [9, 12, 17]. However, these studies examined severe end-stage OA [9, 12, 17]. Previous research has mainly focused on one component of metabolic syndrome, such as obesity and its association with unilateral or bilateral knee pain, regardless of the impact of other metabolic diseases such as DM [90, 91]. One common limitation in this previous research is that the effects of pain medications were not adjusted in the analyses.

Understanding the impact of DM on the pain experience of people with knee OA is valuable because it will help in designing appropriate interventions for this population. Therefore, the objectives of this study were to examine the associations of diabetes with knee pain severity and knee pain distribution (unilateral or bilateral versus no pain) in people with knee OA. We hypothesized that DM would be associated with a higher pain severity and more widespread distribution (e.g. bilateral knee pain) in people with knee OA.

Materials and methods

Study design

This study is a cross-sectional analysis of the Osteoarthritis Initiative (OAI) baseline data. OAI (https://data-archive.nimh.nih.gov/oai/) is an ongoing multisite longitudinal study in the United States that enrolled 4796 participants with or at risk of knee OA to investigate the impact of knee OA over time to understand the prevention and treatment strategies better. Data were collected from four clinical centers, including Baltimore, Maryland; Columbus, Ohio; Pittsburgh, Pennsylvania; and Pawtucket, Rhode Island. Institutional Review boards for each site approved this study, and each participant signed a consent form.

Participants

The OAI includes groups of individuals ages 45 to 79 years. This study has three cohorts: progression cohort (n=1,390 participants) who have symptomatic knee OA with both osteophytes and frequent knee symptoms in at least one knee; incidence cohort (n=3,285 participants) who have no symptomatic knee OA but are at increased risk for OA in at least one knee; and control cohort (n=122 participants) who have no symptomatic or radiographic knee OA and no elevated risk for OA. For this study, we used data only from participants in the progression cohort (n=1,390) to focus on people with established knee OA with radiographic evidence in at least one knee. All included

participants had at least grade 2 composite OA score, equivalent to Kellgren and Lawrence (KL) grade in at least one knee. Self-reported DM (either yes or no) from the Charlson Comorbidity Index was used [92, 93]. Past research has shown good validity and reliability of self-reported DM using the Charlson Comorbidity Index and using self-reported questionnaires [92, 93]. Participants with missing self-reported DM (n=46) and knee joint replacement (n=25) were excluded. Participants were further grouped into knee OA and DM (n=148) or knee OA only without DM (n=1,171) depending on the presence or absence of DM.

Study factors

Pain severity was measured using a numeric rating scale (NRS). Two questions were used in this study; one over seven days and the other over 30 days. The first question was: “During the past seven days, have you had this pain, aching, or stiffness in your right/left knee” if the participant answered yes, the following question was asked: “Please rate the pain that you've had in your right/left knee during the past seven days by pointing to the number on this card that best describes the pain at its worst. ‘0’ means ‘No pain’ and ‘10’ means ‘Pain as bad as you can imagine’”. The second question was identical except for a 30-day time frame. These questions were repeated for each knee. The most symptomatic knee was selected for the analyses in this study. If the participant answered yes to questions about pain over 30 days in both right and left knees, they were categorized as having bilateral knee pain. If they answered yes to one knee, they were categorized as having unilateral knee pain; or none if they

answered no regarding both knees. Previous longitudinal studies have utilized these questions in this way [94, 95].

Other variables

Several other variables were included in the analysis. Age, gender, body mass index (BMI), depression symptoms, composite OA score, and pain medications were included as covariates. BMI was measured using body mass (kg) divided by the square of height (m) and included as a continuous covariate. Depression symptoms factor was also included as a covariate, and the participants were classified as having depression symptoms if they scored ≥16 using the Center for Epidemiologic Studies Disease (CES-D) scale [96]. Radiographic evidence of tibiofemoral knee OA at baseline, using OAI composite OA score, which can be used as a surrogate for KL grade, was included as a covariate for each participant's knee. Use of pain medications was included as a covariate for most commonly used pain medications for arthritis for all participants [97]. Multiple types of medications were self-reported and categorized separately including prescribed non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors (coxibs), Prescribed narcotics (e.g., opioids) or nutraceutical medications (e.g., S-adenosylmethionine). Each medication was categorized as yes if the participant reported using that medication for joint pain or arthritis more than half the days of the month during the past 30 days. This allows for controlling multiple medications for the same participant. Finally, another category was included as a covariate if the participant reported taking any pain medication on the day of the clinic visit.

Statistical analyses

Descriptive statistics were calculated with means for continuous variables and frequencies (percentage) for categorical variables. To compare demographics in people with knee OA and DM to those without DM, we used a chi-square test for categorical variables and independent t-test for continuous variables. All analyses were performed using SPSS for Macintosh, version 25.0 (SPSS Inc, Chicago, IL). The significance level was set at an alpha of 0.05.

Multiple linear regression was used to examine the association between DM and knee pain severity over seven days and over 30 days. Two models were created with DM as predictor and knee pain severity over seven days and over 30 days as the dependent variables. These models included model 1 (adjusted for age, gender, and BMI) and model 2 (adjusted as in model 1 in addition to depression symptoms, composite OA score, and use of pain medications).

Multinomial regression analysis was utilized to determine the relationship between DM and knee pain distribution. Knee pain distribution included three categories: no pain, unilateral, and bilateral knee pain. Two models were created with DM as a factor and joint distribution (bilateral or unilateral versus no pain) as the dependent variable. The reference category for the dependent variable was set as no pain. These models included model 1 (adjusted for age, gender, and BMI) and model 2 (adjusted as in

model 1 in addition to depression symptoms, composite OA score, and use of pain medications). Odds ratios (OR) with associated 95% confidence intervals were calculated for each model.

Results

Data from a total of 1,319 participants were included in the analysis due to missing data for some participants. In this sample, 1171 had knee OA without DM, and 148 had knee OA with DM. Table 1 shows the participants' demographics and characteristics. Knee pain over seven days and over 30 days was significantly higher in people with knee OA and DM (NRS 6.07±2.40 vs. 4.95±2.52 for knee pain over seven days; 6.35±2.36 vs. 5.31±2.45 for knee pain over 30 days) compared to people with knee OA only. Bilateral knee pain was approximately 50% in people with knee OA and DM and 40% in people with knee OA only, and it was statistically significant.

The results of the multivariable linear regression analysis examining the impact of DM on knee pain severity over seven and 30 days are presented in Table 2 with associated 95% confidence interval (CI). Model 2 shows that DM was significantly associated with increased knee pain severity over seven days (B 0.88; 95% CI 0.45-1.31) and over 30 days (B 0.77; 95% CI 0.35-1.19) after adjustments for age, gender, BMI, depression symptoms, composite OA score, and pain medications.

The results of the multinomial logistic regression analyses to examine the association between DM and joint distribution are presented in Table 3 as well as the odds ratio (OR) with associated 95% confidence interval (CI). Model 2 showed that participants with DM and knee OA had 3.12 to 3.48 times higher likelihood of having unilateral and bilateral knee pain than those without DM (OR for unilateral knee pain 3.12; 95% CI 1.30-7.47 and OR for bilateral knee pain 3.48; 95% CI 1.46-8.29) after adjustments for age, gender, BMI, depression symptoms, composite OA score, and pain medications.

Discussion

This study examined the impact of DM on knee pain severity and joint distribution in individuals with knee OA. The results showed that DM was associated with higher pain severity and unilateral and bilateral joint distribution even after controlling for age, gender, BMI, depression symptoms, composite OA score, and pain medications.

Knee pain severity was higher in participants with DM and knee OA when compared to those with knee OA only. A few studies have examined the influence of DM on pain severity in individuals with OA and reported a negative impact of DM on knee pain [16-18]. These findings were consistent with our study results. Furthermore, our study explicitly examined both the short-term and long-term pain severity over 7 days and over 30 days, respectively, and DM had a negative influence on both. DM may facilitate low-grade systemic inflammation that could explain higher pain intensity in people with knee OA who also have DM [17, 29]. A recent study found a higher concentration of

inflammatory markers, including interleukin-6 (IL-6) in the synovial fluid and higher synovitis scores in patients with DM and end-stage knee OA [17]. Another study showed similar results among patients with DM who underwent knee or hip arthroplasty [12]. However, as these previous studies were conducted on people with advanced OA (i.e., scheduled for joint arthroplasty), their generalizability may be limited.

A common limitation in previous studies is the lack of control for pain medication usage that could affect pain severity. Pain medications introduce inter-subject variability, depending on the condition and pain severity, as well as whether they are prescription-strength or over-the-counter medications. Prescribed analgesics, in particular, could significantly affect pain severity (e.g., opioids and prescription NSAIDs). A previous report has shown that the frequency of pain medication usage was associated with increased pain severity [97]. Because using pain medication could be associated with increased pain severity, our study controlled for pain medication usage. This allows this study to have a better estimate of the influence of DM on pain severity. The results of the current study were independent of pain medication use, and DM remained significantly associated with short and long-term increased pain severity in people with knee OA.

The associations between DM and pain severity over both seven and 30 days might be clinically important with regards to both the short-term and intermediate-term impact. Previous research has determined the cutoff score for minimal clinically important difference between 1 and 2 score of pain numeric rating scale [98]. The current study

showed that the mean between-group differences in knee pain severity were greater than 1 point. [98]. However, the adjusted linear analyses showed that participants with knee OA and DM had pain ratings over seven and 30 days respectively that were 0.88 and 0.77 points greater than those of people with knee OA without DM. These scores do not meet the criteria for minimal clinically important differences, suggesting that other covariates may contribute to the association between DM and pain.

Bilateral and unilateral knee pain were associated with DM in this study even after controlling for BMI, depression symptoms, OA grade, and pain medications. This study found that people with knee OA and DM are about three-fold more likely to have bilateral or unilateral knee pain than people with knee OA without DM. These findings were different than our hypothesis that participants with DM would be more likely to have bilateral knee pain than those without DM. DM, as a systemic disease, could affect both knees in people with knee OA. However, since both unilateral and bilateral joint pain were significantly associated with DM, it could be that DM contributes to pain in knees that are otherwise compromised, rather than causing symptomatic knee OA. These findings are essential in considering prevention strategies for knee pain in patients with DM who are at elevated risk for knee OA. As DM appears related to bilateral and unilateral knee pain cross-sectionally, future research should advance understanding of this relationship by investigating the impact of DM and its management on worsening of knee pain in people with knee OA.

Limited research has investigated the association between metabolic disorders and knee pain distribution (e.g., bilateral knee pain). Previous work has mainly focused on one component of metabolic disorders (e.g., obesity) with conflicting results [90, 91]. The current study found that another metabolic disorder, DM, was associated with unilateral and bilateral knee pain, compared to no knee pain in people with knee OA, independent of BMI. Prior research has mainly focused on pain severity without considering joint distribution (unilateral or bilateral) that might influence results [99, 100]. People with bilateral knee pain could have more difficulty performing activities of daily living and functional activities such as climbing stairs and walking than those with unilateral knee pain [101, 102]. We suspected that DM, as a systemic disease, would result in a widespread pain distribution, and be more strongly associated with bilateral versus unilateral knee pain. However, our findings indicated that DM was associated with both unilateral and bilateral knee pain. These results could be explained by recent research showing that DM was associated with accelerated cartilage degeneration [103, 104] that might affect one or both knees.

Previous research focusing on the association between metabolic syndrome and unilateral and bilateral knee pain has been limited to obesity. Previous studies have found that a bilateral distribution of knee distribution was associated with higher BMI in women with knee OA [90, 105]. In contrast, Frilander et al. [91] did not find an association between obesity and bilateral knee pain among men. However, these reports did not examine any potential associations with DM.

Among the strengths of this study are adequate control for BMI as a continuous variable and the use of pain medications. The conflicting results of prior studies have examining the relationship between metabolic syndrome or diabetes and OA could be explained by inadequate controlling for BMI. In addition, this study measured pain severity in both a short-term (seven days) and long-term (30 days) time frames, extending prior research findings for the association of DM with knee pain in individuals with knee OA.

While this study has several areas of strength, some limitations should also be considered. This study included a cross-sectional analysis, and the causal relationship between DM and knee pain cannot be drawn. DM was obtained by self-report, and this is a key variable in this study. There is a chance of inaccurate answers by the patients due to the presence of undiagnosed DM, denial, or lack of awareness. The results might be affected by underestimation of DM as it was a self-reported variable. DM was not specified as type1 or type 2 in this study, so both the type and duration, which may affect the results, remained uncategorized. Other DM complications such as neuropathy, ulcers, and arterial disease were not captured in this study. Glycemic control (i.e., HbA1c) was not available in the OAI and should be acknowledged as a limitation for studies with DM. Future research should investigate this association with an objectively confirmed diagnosis of DM. Finally, other confounders were not considered, such as the duration of DM and previous knee injury or surgeries. Thus, we believe that the current study findings are generalizable to broader people with knee OA.

Conclusion

DM was associated with higher short-term and long-term pain severity when compared to people with knee OA only. DM was strongly associated with bilateral and unilateral knee pain relative to no knee pain as measured by self-reported knee pain over 30 days. In this cohort, people with knee OA and DM had a three-fold greater risk for bilateral and unilateral knee pain when compared to no knee pain. Clinicians may consider the association with DM when prescribing pain management strategies for people with knee OA. Future research should examine proper management of knee pain and DM that focuses on a pharmacological option such as DM control by medications or non-pharmacological intervention such as exercise.

Table 2.1: Participants' characteristics

	All sample (n= 1319)	Knee OA only (n= 1171)	Knee OA and DM (n= 148)	p-value
Age, years (mean ± SD)	61.20 ±9.04	61.16±9.11	61.62±8.53	0.56
Female, n (%)	747 (56.6)	663 (56.6)	84 (56.8)	0.52
BMI, kg/m^2 (mean±SD)	30.12±4.9	29.81±4.8	32.6±4.9	<0.001
Knee pain over 7 days	5.08±2.53	4.95±2.52	6.07±2.40	<0.001
Knee pain over 30 days	5.43±2.46	5.31±2.45	6.35±2.36	<0.001
Depression symptoms, yes, n (%)	176 (13.5)	141 (12.1)	35 (24.3)	<0.001
Pain medications				
Prescribed NSAIDS, yes, n (%)	113 (8.6)	101 (8.6)	12 (8.1)	0.48
Prescribed COXIBS, yes, n (%)	139 (10.6)	131 (11.2)	8 (5.4)	0.017
Prescribed narcotics, yes, n (%)	47 (3.6)	39 (3.3)	8 (5.4)	0.15
SAMe, yes, n (%)	10 (0.8)	9 (0.8)	1 (0.7)	0.69

Any pain medication today, yes, n (%)	193 (14.6)	170 (14.5)	23 (15.5)	0.41
Joint distribution				
No pain, yes, n (%)	160 (12.2)	153 (13.1)	7 (4.8)	0.002
Unilateral distribution, yes, n (%)	603 (45.9)	537 (46.0)	66 (44.9)	
Bilateral distribution, yes, n (%)	551 (42.0)	477 (40.9)	74 (50.3)	

BMI: body mass index

NSAIDS: Non-steroidal anti-inflammatory drugs

COXIBS: cox-2 inhibitors (e.g., Bextra, Celebrex)

SAMe: S-adenosylmethionine

Table 2.1: Multiple linear regression for the association between DM and knee pain severity

Dependent variables		n	R^2	B	SE	95% CI	*p*-value
Knee pain severity over 7 days	Model 1	1314	0.05	0.96	0.22	0.53-1.39	<0.001
	Model 2	1293	0.11	0.88	0.22	0.45-1.31	<0.001
Knee pain severity over 30 days	Model 1	1316	0.06	0.88	0.21	0.45-1.29	<0.001
	Model 2	1295	0.11	0.77	0.21	0.35-1.19	<0.001

n = number of patients; SE = standard error; CI = confidence interval

Model 1 = adjusted for age, gender, and BMI

Model 2 = adjusted for model 1 and depression symptoms, composite OA score, and taking pain medications (i.e., Prescribed non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors (coxibs), Prescribed narcotics (e.g., opioids), nutraceutical medications (e.g., S-adenosylmethionine) or taking any pain medication today)

Table 2.3: Multinomial regression for the association between DM and knee pain distribution

Joint distribution		n	OR	95% CI	*p*-value
No pain			Reference	-	-
Unilateral knee pain	Model1	1311	2.51	1.12-5.63	0.024
	Model 2	1294	3.12	1.30-7.47	0.011
Bilateral knee pain	Model 1	1311	2.99	1.34-6.69	0.008
	Model 2	1294	3.48	1.46-8.29	0.005

n = number of patients; OR = odds ratio; CI = confidence interval

Model 1 = adjusted for age, gender, and BMI

Model 2 = adjusted for model 1 and depression symptoms, composite OA grade, and taking pain medications (i.e., Prescribed non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors (coxibs), Prescribed narcotics (e.g., opioids), nutraceutical medications (e.g., S-adenosylmethionine) or taking any pain medication today)

Chapter 3: The Prevalence of Type 2 Diabetes and Associated Risk Factors with Generalized Osteoarthritis: A Retrospective Study Using ICD Codes for Clinical Data Repository System

Abstract

Introduction: Type 2 Diabetes Mellitus (T2DM) has been associated with osteoarthritis (OA). T2DM may be associated with generalized OA (GOA≥3 joints) rather than localized OA (LOA<3 joints). The purpose of this study was to examine the prevalence of T2DM in people with GOA compared to LOA and to investigate the association between demographic risk factors and chronic diseases (i.e., T2DM, hypertension, dyslipidemia, neuropathy, and body mass index (BMI)) with GOA compared to LOA.

Method: A retrospective review of data was performed, and patients with diagnostic codes for OA were selected. Identified codes included primary GOA, primary LOA, T2DM, hypertension, dyslipidemia, neuropathy, depression, anxiety, and sleep disorders. Information about BMI and medication list was obtained. Chi-square and logistic regression were performed to examine the prevalence and risk factors, respectively.

Results: Data from 3855 patients (mean age = 66.43±11.02, 60.9% women) included patients with GOA (n=1265) and LOA (n=2590). The prevalence of T2DM was significantly greater among patients with GOA (25.8%) compared to LOA (12.0%), however, GOA group were older. Based on age groups, T2DM was prevalent in 17.8% of GOA compared to 7.2% in LOA for younger adults (aged 45-64 years) and was prevalent in 28.8% of GOA compared 15.7% in LOA for older adults (aged 65 years or older). The odds ratio of GOA increased in people with chronic diseases compared to those without including T2DM (Odds Ratio (OR) 1.37, 95% Confidence Interval (CI) 1.05-1,78, p=0.02), hypertension (OR 1.99, CI 1.63-2.43, p<0.001) and dyslipidemia (OR 3.46, CI 2.86-4.19, p<0.001), adjusting for covariates.

Conclusions: Higher prevalence of T2DM was found in people with GOA when compared to LOA across both age groups. T2DM, hypertension, and dyslipidemia were associated with GOA. Future research with longitudinal designs is needed to test the causality of this association.

Keywords: Multisite osteoarthritis, diabetes, high blood pressure, dyslipidemia

Key points

- The prevalence of type 2 diabetes in people with generalized osteoarthritis was almost double compared to localized osteoarthritis, although generalized osteoarthritis group were older.
- Among people with osteoarthritis, the risk of generalized osteoarthritis is increased by 37% when people had type 2 diabetes, by 99% when people had hypertension, and by 246% when people had dyslipidemia.

Introduction

Osteoarthritis (OA) and type 2 diabetes mellitus (T2DM) are common chronic diseases affecting 15% and 8.5% worldwide, respectively [2, 106]. OA is characterized by joint degeneration and inflammation, and it may be classified as either localized or generalized OA depending on the number of joints affected. Generalized OA (GOA) affects three or more joints, and localized OA affects less than three joints [24]. Previous evidence with a small sample found that GOA affects 50% of people with knee OA [107]. People with GOA may present with worse symptoms or outcomes in terms of pain, functionality, and quality of life [26].

T2DM results in chronic hyperglycemia, which may affect the musculoskeletal system. Hyperglycemia may induce chronic systemic inflammation that leads to systemic changes that may affect joints through the remolding of collagen types in cartilage and synovia [29]. Another consequence of hyperglycemia is the production of advanced glycation end products (AGE) that may increase cartilage stiffness and bone fragility [30]. In addition to OA risk in people with T2DM, a recent report highlighted the lack of comprehensive risk factor assessment or treatment in the US. This study reported that only 1 in 5 persons with T2DM achieve comprehensive risk factor control such as blood pressure, glycemic control, and lipid profile [108].

Diabetes and OA are common diseases that are associated with common risk factors and complications. Although a few studies have highlighted the association between

diabetes and OA [7-14], others have found no association [38, 79, 109, 110]. Inconsistent findings could be partially explained by small sample sizes [10] and a primary focus on weight-bearing joints such as the knees [7, 8, 13, 14] or on a specific single body part such as the hands [38, 79]. Definitions for OA were inconsistent across studies as one study defined OA as arthroplasty in hip or knee joint [12]. Other factors, such as age, ethnicity, sex, body mass index (BMI), hypertension, neuropathy, and dyslipidemia, that impact both diabetes and OA have not been fully examined or controlled for in previous analyses [7-14]. Although neuropathy is a common complication of diabetes, it has not been studied as a risk factor for OA. Previous studies have shown that women have a higher prevalence of hip and knee OA than men [55]. Race has been shown to be associated with OA in non-Hispanic African Americans [70]. Older age has been associated with LOA (e.g., knee, hip, or hand) [55, 109]. However, whether other factors are associated with GOA versus LOA is still unclear. Understanding the association between these risk factors and GOA may enhance our knowledge about this understudied population with GOA as the treatment approach is different for each condition (GOA vs. LOA).

Previous reports have found associations between other metabolic syndromes (e.g., dyslipidemia, hypertension, or obesity) and OA [13, 111]. However, the research is also hampered by the limited sites for OA, a focus on LOA (hand or knee OA) [13, 111], and/or lack of control for other risk factors such as T2DM, hypertension, and dyslipidemia within the same model [13, 111]. Because some medications such as

antihypertensive and antilipemic could affect the OA progression and symptoms [52, 84], use of medications should also be adjusted in the analyses.

People with generalized OA may benefit more from systemic and interdisciplinary approaches than people with single joint OA [86]. The association between T2DM and OA has been investigated, but the association with which type of OA such as GOA versus LOA is still unknown. Examining the prevalence of T2DM and associated risk factors with GOA is crucial because of the high prevalence of GOA among the overall OA population with worse outcomes, and GOA might be a marker of more severe disease with increased progression [26]. Therefore, the objectives of this study were 1) to examine the prevalence of T2DM among patients with GOA compared to the prevalence of T2DM in patients with LOA, and 2) to investigate the association between demographic risk factors (age, gender, and race) and chronic disease risk factors (T2DM, hypertension, dyslipidemia, neuropathy, and BMI) with GOA compared to LOA.

Materials and Methods

Design and setting

This study is a retrospective analysis of de-identified data using the Healthcare Enterprise Repository for Ontological Narration (HERON) [112]. This database provides researchers access to de-identified electronic medical records from a tertiary hospital or

its affiliated clinics using Epic EMR. 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. The data warehouse contains demographic data (age, sex, and race), service use, clinical data (diagnoses codes, flowsheet data, laboratory data, and patients' vitals) as well as pharmacy data. As this data is de-identified, the study received an exempt determination from the institutional review board. An approval from the Data Request Oversight Committee was obtained for this analysis.

The study participants were selected using the i2b2 query and analysis tool [113] of the HERON database [112]. Patients 45 years old and older who were seen between 2011 and 2017 were selected if they had at least two diagnosis codes of osteoarthritis separated by at least one day using either International Classification of Disease 9th revision (ICD-9) or International Classification of Disease 10th revision (ICD-10). Osteoarthritis diagnosis was categorized as either GOA or LOA based on ICD-9 or ICD-10 codes. GOA cohort and LOA cohort were extracted separately. For example, a query was built for GOA cohort only to include patients with only GOA and exclude LOA and vice versa to ensure accuracy of categorizing each cohort and minimizing the likelihood of having different codes for the same patient (GOA and LOA). The first OA diagnosis code was set as the index date followed by a second similar diagnosis between 2011 to 2017. Previous research has validated using ICD codes against chart review, self-reported OA, American College of Rheumatology criteria or joint radiographs with good specificity and accuracy [114, 115]. Patients were excluded if they had at least one

specific ICD-9 or ICD-10 codes for type 1 diabetes, fibromyalgia, secondary OA, neoplasm, gout, systemic lupus, arthritis with infection, rheumatoid arthritis, trigeminal nerve disorders or carpal tunnel syndrome.

Variables and covariates

Demographic data included age, sex (males or females) and race (Caucasian, African American, or other). Data for chronic diseases (Type 2 diabetes, hypertension, dyslipidemia, and neuropathy) was selected based on at least two diagnoses codes separated by at least one day using ICD-9 or ICD-10. Body mass index (BMI) was obtained within one year before or after the index date (first OA diagnosis) due to lack of BMI data at the index date. Covariates of depression, anxiety or sleep disorder were included if there were at least two diagnoses codes separated by one day using ICD-9 or ICD-10, as these factors have been shown to be associated with OA [62, 63, 74]. A list of medications was included within +/- 90 days of the index date. For each participant, pharmacy data was obtained and searched for the following medication types: pain medications (opioids, non-opioids, and benzodiazepine), antidiabetics (insulin or hypoglycemic), antihypertensives, antilipemic, and antidepressants. Use of medication for each type was categorized as yes or no. Table 1 shows the ICD-9 and ICD-10 codes for all variables of interest.

Statistical analyses

Descriptive results included frequencies and percentages for categorical variables or means and standard deviations for continuous variables. Differences between groups were analyzed using the Fisher's exact tests for categorical variables or independent t-tests for continuous variables.

Chi-square statistics were used to examine the prevalence of T2DM among patients with OA based on two age groups including younger adults (45-64 years) and older adults (65 or older). To examine the individual contribution of OA category (GOA vs. LOA) and DM status (yes vs. no) based on age groups, we used individual Chi-square tests for each cell in the contingency table and the associated standardized residuals (R). R can be calculated by: $R = \frac{observed\ cases\ (O) - expected\ cases\ (E)}{\sqrt{E}}$, as utilized by Haberman [116] to test the deviation from the expected values separately for each cell. In other words, R indicates the difference between observed and expected cases and the standard deviation of the expected cases. R is considered when the strength of the measure between observed and expected cases needs to be tested to indicate which specific cell is significant the most and the least. Residuals greater than 2 indicated that observed cases were greater than expected frequency or less than -2 indicated that observed cases were less than expected frequency and were considered significantly different and selected as cutoffs [116].

Logistic regression analyses were used to examine the association between demographic factors (age, sex, and race) and chronic diseases (T2DM, hypertension, dyslipidemia, neuropathy, and BMI) with OA categories (GOA vs. LOA). Reference

category for the outcome was set as LOA. Results were presented in terms of calculated odds ratios (ORs) with 95% confidence intervals (95% CIs) for risk factors. Three models were created: (1) unadjusted bivariate model for each demographic and chronic disease factors; (2) adjusted for demographic factors (age, sex and race); and (3) the primary analysis adjusted for all covariates (depression, anxiety, sleep disorders, medications (antidiabetics, antihypertensives, antilipemic and antidepressants)) [52, 62, 74, 82, 83, 117] and each risk factors (age, sex, race, T2DM, hypertension, dyslipidemia, neuropathy and BMI).

Because excluding cases may affect the results and create bias [118], missing values for BMI (n=1237, 32.1%) were imputed using a multiple imputations method. The imputation model included age, sex, race, chronic diseases (T2DM, hypertension, dyslipidemia, neuropathy, depression, anxiety, and sleep disorders) and medications (antidiabetics, antihypertensives, antilipemic, and antidepressants). Imputation created five complete datasets, according to Rubin's method [119]. Pooled results were used for data analysis. We conducted a sensitivity analysis comparing the results from the imputed data to the original dataset, and the results were similar. Therefore, we chose to report the multivariable results based on the imputed model. All statistical analyses performed using SPSS 25 for mac (Chicago, IL). All analyses conducted at a 0.05 alpha level.

Results

A total of 3855 patients were included in the analyses, of whom 639 (16.6%) had type 2 diabetes. Table 2 shows the characteristics of the full sample and GOA and LOA subsamples. There were statistically significant differences between people with GOA (n=1256) and LOA (n=2590) in terms of age, sex, race, chronic diseases including diabetes, hypertension, dyslipidemia, neuropathy, depression, anxiety and sleep disorders. Data for BMI were available for 2088 (80.61%) participants with LOA and 530 (41.90%) participants with GOA.

For the prevalence of T2DM and GOA, Table 3 shows the results from chi-square statistics and standardized residuals. T2DM was significantly higher in people with GOA (n=327, 25.8%) compared to LOA (n=312, 12.0%). However, GOA subsample was older than LOA. Standardized residuals for the overall prevalence of T2DM in people with GOA was 8.1. This standardized residual exceeded 2, indicating that the number of cases in the group of T2DM and GOA were significantly greater than what would be expected. Standardized residuals for the overall prevalence of T2DM in people with LOA was -5.7, indicating that the number of cases in the group of T2DM and LOA were significantly smaller than what would be expected. The prevalence of T2DM based on age groups were presented in Table 3 as follow; 17.8% in people with GOA vs. 7.2% in people with LOA in younger adults group (45-64 years) and 28.8% in people with GOA vs. 15.7% in people with LOA in older adults group (65 years or older). Standardized residuals for T2DM in people with GOA and LOA were greater than 2 and less than 2 in both age groups, respectively, indicating similar results to the overall prevalence.

Results from both unadjusted and adjusted logistic regression models are shown in Table 4. Demographic factors of age (OR 1.07; 95% CI 1.06-1.08) and gender (OR 2.04; 95% CI 1.77-2.36) increased the odds of having GOA. The odds ratios of having GOA increased for patients who had chronic diseases including T2DM, hypertension, dyslipidemia, or neuropathy than those who did not have chronic diseases after controlling for demographic factors.

Multivariable logistic regression results for the primary analysis are presented in Table 5. The odds ratio of GOA for patients with type 2 diabetes, hypertension, and dyslipidemia increased compared to those without after controlling for age, gender, race, depression, anxiety, sleep disorders, medications (antidiabetics, antihypertensives, antilipemic and antidepressants), and other risk factors (T2DM, hypertension, dyslipidemia, neuropathy, and body mass index).

The results of sensitivity analysis for included patients (n=2618) who had BMI without imputation showed similar significant results when compared to patients with imputation for BMI (n=3855). The multivariable logistic regression for the primary sensitivity analysis indicated that odds of GOA was significantly increased in people with T2DM (OR 1.46, 95% CI 1.03-2.08, p=0.03), hypertension (OR 1.91, CI 1.46-2.49, p<0.001), and dyslipidemia (OR 2.91, CI 2.24-3.79, p<0.001), adjusting for covariates.

Discussion

This study examined the prevalence of T2DM in people with OA and investigated the risk factors (T2DM, hypertension, dyslipidemia, and neuropathy) associated with GOA. Our findings highlight the importance of screening for these risk factors, as previous research has found that only 1 in 5 persons with T2DM achieves comprehensive risk factor control, involving blood pressure, glycemic control and lipid profile [108].

We observed a higher prevalence of T2DM in people with GOA (25.8%) when compared to LOA (12.0%) but patients in the GOA subsample were older. However, the prevalence according to each age group showed consistent results indicating that T2DM was more prevalent in people with GOA versus LOA. The overall prevalence of T2DM among patients with OA (either GOA or LOA) in the current study was 16.6%. This overall prevalence is consistent with the prevalence of diabetes among people with OA in a recent meta-analysis (14.4%) [5]. However, this study did not report the prevalence of diabetes, specifically in people with GOA and did not distinguish between type 1 or type 2 diabetes. Our study differs from the previous research because we included only patients with OA diagnosis who further categorized as GOA or LOA. Another difference in the current study is the specification of diabetes diagnosis that has not been distinguished in previous studies [5] Our study restricted risk factors (e.g. diabetes) for GOA to patients with diagnoses codes for T2DM and excluded type 1 diabetes. Therefore, the current findings show that the prevalence of T2DM was approximately double in people with GOA compared to LOA in younger and older adults. However, our sample showed that the prevalence of T2DM in people with LOA was less than the reported prevalence in general population [120]. The current study

found the prevalence of diagnosed T2DM in LOA was 7.2% compared to 11.6 in general population in the same age group (45-64 years). Further, the prevalence of diagnosed T2DM in LOA in our sample was 15.7% compared to 21.3% in general population [120]. These differences could be explained by our definition for diabetes as we included only T2DM with at least 2 ICD codes and other factors such as single site and using real world clinical data versus survey data.

This study found that demographic factors, including age, sex, and race, were associated with OA. Aging has a negative impact on many systems and organs and is associated with cellular function decline that has been linked to OA [20, 21]. Although aging is a known risk factor for OA, previous research has focused on LOA (e.g., knee, hip, or hand) [55, 109]. The current study adds to the literature in that increased age was more strongly associated with GOA compared to LOA. Our study showed that females increased the odds of GOA compared to males. A previous meta-analysis has indicated that females have a higher risk of OA after menopause, [66] potentially due to age-associated hormonal changes. Race has also been shown to be associated with OA, with previous research reporting an association between non-Hispanic African Americans and OA using a national health survey in the United States [70]. However, our multivariable analysis did not identify this relationship. This result could be attributed to the single site for our data, resulting in a limited diversity of ethnicity in patients.

A common shared risk factor in OA and T2DM is obesity, which is associated with 90% of diabetes [59] and OA [58]. Obesity might be linked to OA due to the effect of weight

and misalignment on joints [46]. However, previous research has also reported associations between obesity and OA of non-weight bearing joints such as the hands, [13] suggesting a potential systemic dysfunction. In contrast to these studies, our study did not find a statistically significant association between BMI and GOA. The current study utilized multiple imputations method for missing BMI, however, the results were comparable between both datasets. These findings are limited by missing data from BMI in our sample, and the use of BMI data up to one year before or after the index date of OA diagnosis.

Type 2 diabetes, as metabolic syndrome, has been associated with OA. Two meta-analyses were published investigating the association between OA and diabetes, and both showed a significant association between OA and diabetes [5, 6]. Although previous research found an association between diabetes and mainly LOA, our study observed an association with GOA versus LOA that has not been previously. However, in contrast to our findings and previous reports, a third recent meta-analysis found little evidence for an association between diabetes and knee OA, and no evidence to support an association between diabetes and hip or hand OA [37]. This analysis included studies examining only LOA, specifically knee, hip, or hand OA, but GOA was not considered. Given this contradictory evidence, the relationships between diabetes and GOA, which may affect half of people with OA, require further investigation.

Hypertension has also been found to be a risk factor for LOA [117]. Prior research demonstrated that the accumulation of metabolic factors, including hypertension and

diabetes, was associated with the occurrence of knee OA over three years [13]. Hypertension is a systemic disease, and contributes to multiple joint OA through vascular impairments and decreased blood flow that leads to subchondral ischemia [77]. Our study found that people with hypertension are about two times more likely to have GOA compared to those without hypertension, even after controlling for other covariates, including T2DM and hypertension medications.

Dyslipidemia indicates disturbances in serum levels of any form of cholesterol, including high-density lipoprotein, low-density lipoprotein, total cholesterol or triglyceride. Previous studies have demonstrated the association between dyslipidemia, T2DM, and OA [13, 79]. Our study was consistent with this previous research, suggesting that patients with dyslipidemia are about three times more likely to have GOA compared to those without. In contrast, other investigations reported no association between T2DM, dyslipidemia, and OA [38]. This research focused on non-weight bearing OA, included different definitions for dyslipidemia and lacked control for medications and other confounders. This is important because previous studies have shown that antilipemic medications such as statin are associated with a lower incidence and progression of knee OA [84].

This study has limitations to be considered. A retrospective design cannot lead to inferences of causality, and future research should examine the longitudinal impact of T2DM on GOA incidence. In addition, the study used data from a single site, and this may limit the generalizability of the results. Although two ICD-9 or ICD-10 diagnoses

codes were used for each disease to improve accuracy, these codes are prone to potential measurement errors or bias. The sites for OA were not included in the analysis and future research should examine the association within the context of sites and symptoms. Future research should use objective measures of T2DM, such as A1c, and OA, such as X-ray and/or joint space narrowing. GOA diagnosis should be acknowledged as another limitation because of multiple different definitions no universally accepted definition that can be used. Every effort has been made to capture possible confounding variables. However, there may be other factors associated with GOA that have not been included. Missing BMI values in the current study should also be acknowledged as a limitation. Although missing BMI values were imputed using a validated method [119], these imputations were based on data ranging from one year before or after the index date of OA diagnosis. Thus, BMI values used in the study may not reflect the actual BMI values at the time of data collection; BMI may have changed dramatically within a year. Therefore, the results should be interpreted with caution regarding BMI. The duration of OA, T2DM, or other risk factors was not included and could be an important area for future research. Despite these limitations, our study findings add to the current knowledge about diabetes and OA and add new information related to shared risk factors commonly found in each condition, diabetes and OA.

Conclusion

This study found a higher prevalence of T2DM in people with GOA when compared to LOA across all age groups using a real-world clinical data, suggesting an increased

susceptibility to GOA in T2DM. People with chronic diseases including T2DM, hypertension, and dyslipidemia had significantly and independently increased odds of GOA when compared to those without chronic diseases after controlling for other covariates. Future research should longitudinally examine the causality of this association between risk factors and GOA.

Table 3.1: Clinical diagnostic codes using ICD-9 and ICD-10

	ICD-9 codes	ICD-10 codes
Localized OA	715.1	M16, M17, M18, M19
Generalized OA	715.00	M15.xx
T2DM	250.xx	E11
Hypertension	401.xx	I10
Dyslipidemia	272.xx	E78
Neuropathy	356.9, 356.8, 357.2, 356.2, 356.0, 356.4, 250.6	E11.40, E11.41, E11.42, E11.43, G60
Depression	296.2, 296.3	F32, F33
Anxiety	300.00, 300.02	F41.1, F41.8, F41.9
Sleep disorders	307.4 347.xx, 780.5	F51, G47.00, G47.1, G47.30

Table 3.2: Participants' characteristics

	Total sample N= 3855	Generalized OA N= 1265	Localized OA N=2590	*p*-value
Age, years (mean ± SD)	66.43±11.02	71.63± 10.55	63.90 ± 10.32	<0.001
Sex, Female, n (%)	2384 (60.9)	909 (71.9)	1439 (55.6)	<0.001
Race, n (%)				<0.001
Caucasians	3016 (78.2)	955 (75.5)	2061 (79.6)	
African American	500 (13)	222 (17.5)	278 (10.7)	
Others	339 (8.8)	88 (7.0)	251 (9.7)	
Body Mass Index (mean± SE)	31.08±7.10	30.50±0.15	31.36±0.35	0.04
Type 2 diabetes, n (%)	639 (16.6)	327 (25.8)	312 (12.0)	<0.001
Hypertension, n (%)	1769 (45.9)	898 (71.0)	871 (33.6)	<0.001
Dyslipidemia, n (%)	1442 (37.4)	839 (66.3)	603 (23.3)	<0.001
Neuropathy, n (%)	172 (4.5)	99 (7.8)	73 (2.8)	<0.001
Depression, n (%)	490 (12.7)	284 (22.5)	206 (8.0)	<0.001
Anxiety, n (%)	441 (11.4)	275 (21.7)	166 (6.4)	<0.001
Sleep disorders, n (%)	405 (10.5)	285 (22.5)	120 (4.6)	<0.001
Medications				
Insulin, n (%)	164 (4.3)	38 (3.0)	126 (4.9)	0.007
Hypoglycemic, n (%)	326 (8.5)	48 (3.8)	278 (10.7)	<0.001

Antihypertensive, n (%)	444 (11.5)	70 (5.5)	374 (14.4)	<0.001
Antilipemic, n (%)	1046 (27.1)	164 (13.0)	882 (34.1)	<0.001
Antidepressants, n (%)	737 (19.1)	124 (9.8)	613 (23.7)	<0.001

Table 3.3: Prevalence of diabetes in people with generalized and localized OA

Age groups	Type 2 diabetes	Generalized OA N= 1265	Localized OA N=2590
45-64 years	YES, n (%)	60 (17.8)	126 (7.2)
	Standardized residuals	4.0	-2.0
	NO, n (%)	277 (82.2)	1282 (91.1)
	Standardized residuals	-1.4	0.7
65 years or older	YES, n (%)	267 (28.8)	186 (15.7)
	Standardized residuals	4.8	-4.3
	NO, n (%)	661 (71.2)	996 (84.3)
	Standardized residuals	-2.5	2.2
All age groups	YES, n (%)	327 (25.8)	312 (12.0)
	Standardized residuals	8.1	-5.7
	NO, n (%)	938 (74.2)	2278 (88.0)
	Standardized residuals	-3.6	2.5

Table 3.4: Logistic regression for the association of each risk factor with generalized OA

	Unadjusted OR [95% CI]	p-value	Adjusted OR [95% CI]	p-value
Age	1.07 [1.06-1.08]	<0.001	NA	
Sex	2.04 [1.77-2.36]	<0.001	NA	
Race	1.04 [0.93-1.15]	0.53	NA	
Type 2 diabetes	2.55 [2.14-3.03]	<0.001	2.21 [1.84-2.66]	<0.001
Hypertension	4.83 [4.17-5.59]	<0.001	3.68 [3.15-4.30]	<0.001
Dyslipidemia	6.49 [5.60-7.53]	<0.001	5.13 [4.39-5.99]	<0.001
Neuropathy	2.93 [2.15-3.99]	<0.001	2.58 [1.85-3.59]	<0.001
Body Mass Index	0.98 [0.96-1.00]	0.06	1.006 [0.98-1.03]	0.44
Adjusted OR: adjusted for age, gender, and race				

Table 3.5: Multiple logistic regression for the association of type 2 DM, hypertension, dyslipidemia, neuropathy and body mass index with generalized OA

	Adjusted OR [95% CI]	p-value
Age	1.05 [1.04-1.06]	<0.001
Sex	1.69 [1.41-2.02]	<0.001
Race	0.97 [0.84-1.11]	0.61
Type 2 DM	1.37 [1.05-1.78]	0.02
Hypertension	1.99 [1.63-2.43]	<0.001
Dyslipidemia	3.46 [2.86-4.19]	<0.001
Neuropathy	1.36 [0.91-2.05]	0.13
Body Mass Index	0.99 [0.97-1.01]	0.22
Adjusted OR: adjusted for age, gender, race, depression, anxiety, sleep disorders, medications (antidiabetics, antihypertensives, antilipemic, and antidepressants), risk factors (diabetes, hypertension, dyslipidemia, neuropathy, and body mass index)		

Chapter 4: Type 2 Diabetes Affects Joint Pain Severity in People with Localized Osteoarthritis: A Retrospective Study

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 A1c 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, 54.3% women) were used.

Methods: Patients were grouped to localized OA only (n=671) and localized OA+T2D (n=148) based on diagnoses 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. Hemoglobin A1c values were obtained for patients with T2D within six months of the index date. Multiple linear regression was used.

Results: After controlling for age, sex, BMI; diagnoses for 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) 0.64-21.51, p=0.014). For patients with T2D and localized OA with available data for A1c (n=87), the results showed that increased A1c value was significantly associated with higher pain severity (B=0.36, 95% CI 0.036-0.67, 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 A1c 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 are coexisted 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 [89]. Metabolic syndrome has been shown to be associated with increased pain severity in people with knee OA [16, 50]. Hypertension, dyslipidemia, diabetes, or obesity were also associated with increased pain severity in people with knee OA [16, 50]. However, limited research has examined the association between T2D and pain in people with OA.

Recent evidence has shown that diabetes was associated with increased pain severity in people with knee OA [12, 16-18]. However, these reports were focused on the knee or hip joint that could be affected by many factors such as obesity, other metabolic components, and their medications. T2D may affect any joint due to the impact of hyperglycemia and low-grade inflammation [29, 30]. Thus, glycemic control, measured by A1c, could potentially affect pain severity in people with OA; however, this has yet to be explored. 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 knee, hip, ankle, hand, or shoulder.

Previous evidence concerning the impact of diabetes on pain severity in people with OA was limited due to a 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 [51, 52]. Therefore, this study aimed to examine the association between T2D and pain severity in people with localized OA and to explore the association between A1c 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 increased levels of A1c would be associated with increased pain severity in people with localized OA and T2D.

Methods

Design and setting

This research is a retrospective study design of de-identified data using the Healthcare Enterprise Repository for Ontological Narration (HERON) database at a tertiary medical center [112]. 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 contains demographic data (age, sex, and race), service use, clinical data (diagnoses codes, flowsheet data, laboratory data, and patients' vitals) and pharmacy data.

Approval for using this dataset was obtained from the Data Request Oversight Committee.

Study Cohort

Participants for this study were selected using i2b2 query and analysis tool [113] for HERON [112]. Participants who were seen between 2011 and 2017 were included if they had at least two diagnoses codes of localized OA. These codes must be separated by at least one day using either International Classification of Disease 9th revision (ICD-9) or International Classification of Disease 10th 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 codes 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 sex (males or females) were obtained for all participants. OA locations included 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 diagnoses 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 have at least two diagnostic codes or using 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 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 was obtained from the flow sheet and linked to the index date for localized OA. Data for hemoglobin A1c for participants with T2D and localized OA were obtained from the flow sheet. Due to missing values for A1c within three months of the index date, A1c 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 diagnoses codes separated by one day using ICD-9 or ICD-10. List 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 type was searched. 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, non-opioids, and benzodiazepine), antidiabetics (insulin or hypoglycemic), antihypertensives, antilipemic, and antidepressants. Use of medications was further categorized as yes or no. Table 1 shows the ICD-9 and ICD-10 codes for all variables.

Statistical analysis

Descriptive analyses included frequencies and percentages for categorical variables, or means and standard deviations for continuous variables. For comparing people with localized OA and T2D to people with localized OA only, variables were analyzed using the Chi-square test for categorical variables and independent t-test for continuous variables. Further, independent t-test was conducted to compare pain severity between people with and without T2DM at each OA location.

Linear regression analyses were performed to examine the association between T2D and joint pain severity. Two models were created with unstandardized coefficients (B) and 95% confidence intervals (95% CIs). T2D was entered to 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, non-opioids, and benzodiazepine; antidiabetics; antihypertensive; antilipemic; antidepressants) within 90 days of the index date.

To examine the association between A1c and joint pain severity in people with localized OA and T2D, linear regression analyses were performed. Two models were created with the associated unstandardized coefficient (B) and 95% confidence intervals (95%

CIs). A1c was entered to the model as a predictor variable and pain severity as the dependent variable. Model 1 was univariable or unadjusted because of the small sample size with A1c value. Model 2 was a multivariable linear regression with adjustment for age, gender, BMI, OA locations, and taking medications (pain medications including opioids, non-opioids, and benzodiazepine; antihypertensive; antilipemic) within 90 days of the index date.

Excluding cases affects results and could create biased estimation [118]. Therefore, missing values for BMI (n=50, 6.11%) were imputed using a multiple imputations method. The imputation model included age, sex, BMI, T2D, hypertension, dyslipidemia, depression, OA locations, A1c value, and medications (antidiabetics, antihypertensives, antilipemic and antidepressants). This Imputation created five complete datasets according to Rubin's method [119]. Pooled results were used for data analysis. We conducted a sensitivity analysis comparing the results from the imputed data to the original dataset, and the results were similar. Therefore, we chose to report the multivariable results based on the imputed model. All analyses performed using SPSS 25 for mac (Chicago, IL). All analyses conducted at a 0.05 alpha level.

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 all sample, localized OA, and localized

OA with T2D subsample. To summarize, people with localized OA+T2D (n=148) were older and had higher values of BMI and pain severity when compared to people with localized OA only (n=671). People with localized OA+T2D had a higher prevalence of hypertension, dyslipidemia, depression, and medication usage (for T2D, hypertension, dyslipidemia) when compared to individuals with localized OA only. However, people with localized OA+T2D had a lower prevalence of using opioids compared to people with localized OA only. Participants with localized OA+T2D had higher pain severity when compared to participants with localized OA only at 3 locations (i.e., shoulder, hand or elbow, and knee or lower leg). Hip or pelvis and ankle or foot locations showed no significant difference in pain severity when compared to localized OA+T2D. A total of 37 (42.53%) participants within T2D group who had available A1c value (n=87) had poor glycemic control (A1c $\geq$ 7). Table 3 shows the summary of pain severity across OA locations and T2D status.

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 3 with associated 95% confidence interval (CI). Model 2 shows that T2D was significantly associated with increased joint pain severity (B = 1.07; 95% CI: 0.64-1.51, p=0.014) after adjustments for covariates including age, gender, OA locations, BMI, depression, hypertension, dyslipidemia, and medication usage (pain medications including opioids, non-opioids, and benzodiazepine; antidiabetics; antihypertensives; antilipemic; antidepressants) within 90 days of index date.

For the impact of A1c level on joint pain severity in people with localized OA+T2D, the results of the linear regression are listed in Table 5. Model 2 shows that an increase in A1c value was significantly associated with increased joint pain severity (B = 0.36; 95% CI: 0.036-0.67, p=0.029) after adjustments for age, gender, BMI, OA locations and pain medications (opioids, non-opioids, 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 A1c 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, independent from using medications such as pain and antidiabetics. Poor glycemic control measured by A1c was associated with increased pain severity in people with localized OA and T2D 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 [16-18]. The findings from the current study were consistent with these previous studies examining the association between

diabetes and knee pain severity in people with knee OA [12, 16-18]. Additionally, the current study found higher pain severity in people with T2D at different locations, including 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**.** Eitner et al. found that people with end-stage knee OA and diabetes had higher pain severity when compared to those without diabetes [17]. 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 [18]. However, the amount of pain increase due to diabetes was below clinically important difference (>1 score) in this study (B= 0.4) [18]. Our study found that T2D was associated with higher pain severity using a numeric rating scale that exceeded clinically significant difference (B=1.16) [98].

All of the previous reports were focused on weight-bearing joints (i.e., knee or hip OA) regardless of other parts that might be affected by OA such as hands and ankles. 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.

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[12, 16-18]. Especially when pain severity is an outcome, pain medications such as opioids and non-opioids 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 [51, 52, 82, 83, 121]. Thus, the present study can 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 A1c and pain severity was 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 A1c and pain severity. Only one study showed a significant correlation between A1c and knee pain score in people with end-stage knee OA [17]. 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 [122]. Under 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 [29, 30, 123]. Previous evidence showed a higher concentration of interleukin-6 in the synovial fluid and higher synovitis scores among patients with diabetes and end-stage knee OA when compared to patients with knee OA only [17].

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 2 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. Missing some values for BMI and excluding those from analyses for model 2 should be considered as another limitation. Although every possible effort was made to capture pain severity data by linking pain to OA diagnostic codes, there is a possibility for including pain data not related to OA. A1c value was obtained within six months of the index date to increase the sample size for this subgroup analyses. However, the A1c is usually a measure for three months of glycemic control. Therefore, the results regarding A1c should be interpreted with caution. This study is limited due to 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 versus oral) may show another spectrum of this association and should be considered in future research. Some possible unknown factors that cannot be captured in HERON database may influence the results.

Conclusion

This study found that T2D was a significant factor for increased pain severity in people with localized OA after controlling for medications and other chronic diseases. participants with T2D had higher pain severity at any localized OA location including weight-bearing and non-weight bearing joints (i.e. knee, hand, shoulder) except hip and ankle locations. Increased A1c level was not significantly associated with increased pain severity in people with localized OA and T2D. However, after controlling for medications including pain medications, antilipemic, antihypertensives, and antidiabetics, A1c was a significant factor for increased pain severity in this population. T2D as a systemic disease results in chronic hyperglycemia that 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 A1c control might help with pain management in people with T2D and OA. Since increased A1c 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 medications adherence to minimize the level of pain in people with localized OA and hyperglycemia.

Table 4.1: 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

Table 4.2: Participants' characteristics

	Total sample N= 819	localized OA+T2D N= 148	localized OA only N=671	p-value
Age, years (mean ± SD)	66.08±10.00	66.38± 9.42	63.58 ± 10.32	0.002
Sex, Female, n (%)	374(54.3)	81 (54.7)	364 (54.2)	0.49
Body Mass Index (mean± SE)	33.67±.79	33.90±.70	31.21±.41	0.003
Hypertension, n (%)	401 (49.0)	115 (77.7)	286 (42.6)	< 0.001
Dyslipidemia, n (%)	251 (30.6)	82 (55.4)	169 (25.2)	<0.001
Depression, n (%)	84 (10.3)	28 (18.9)	56 (8.3)	<0.001
Medications				
Insulin, n (%)	91 (11.1)	91 (61.5)	-	-
Hypoglycemic, n (%)	99 (12.1)	77 (52.0)	22 (3.3)	<0.001
Antihypertensive, n (%)	186 (22.7)	57 (38.5)	129 (19.2)	<0.001
Antilipemic, n (%)	366 (44.7)	92 (62.2)	274 (40.8)	<0.001
Antidepressants, n (%)	230 (28.1)	49 (33.1)	181 (27.0)	0.08
Opioid, n (%)	759 (92.7)	127 (85.8)	632 (94.2)	0.001
Non-Opioid, n (%)	624(76.2)	114 (77.0)	510 (76.0)	0.44
Benzo, n (%)	670 (81.8)	114 (77.0)	556 (82.9)	0.06
A1c (mean ± SD)	87 (10.62)	7.03±2.01	-	-
Pain Intensity (mean ± SD)	5.81±2.79	6.22±2.85	5.17±2.80	<0.001

Table 4.3: Descriptive for pain severity across each OA location and groups

OA Locations	No T2D		T2D		p-value
	n	Pain severity ± SD	n	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	0.016
Ankle or foot	110	5.29±3.08	19	6.26±2.98	0.20
Knee or lower leg	258	5.01±2.80	63	5.92±2.88	0.02
Hip or pelvis	95	5.80±2.85	15	5.13±2.95	0.40

T2D: type 2 diabetes

OA: Osteoarthritis

SD: Standard deviation

Table 4.4: Linear regression analyses for the association between T2D and joint pain severity

Dependent variable		n	B	SE	95% CI	p-value
Pain severity	Model 1	819	1.025	0.26	0.52-1.53	<0.001
	Model 2	819	1.07	0.43	0.64-1.51	0.014

n = number of patients; SE = standard error; CI = confidence interval

Model 1 =adjusted for age and gender

Model 2 = adjusted for model 1 and BMI, depression, hypertension, dyslipidemia, and taking medications (pain meds, antidiabetics, antihypertensive, antilipemic, and antidepressants within 90 days of index date)

Table 4.5: Linear regression analyses for the association between A1c and joint pain severity in people with T2D and localized OA

Dependent variable		n	B	SE	95% CI	p-value
Pain severity	Model 1	87	0.25	0.15	-0.044-0.55	0.095
	Model 2	87	0.36	0.16	0.036-0.67	0.029

n = number of patients; SE = standard error; CI = confidence interval

Model 1 = unadjusted

Model 2 = adjusted for age, gender BMI, OA locations, and taking medications within 90 days of index date (pain meds, antihypertensive, antilipemic, insulin, and hypoglycemic)

Chapter 5: The Association Between Diabetes, Knee Pain Locations, Pain During Walk and Walking Speed

Abstract

Background: Osteoarthritis (OA) and diabetes mellitus (DM) are coexisted and may result in negative outcomes. DM may affect pain and walking speed in people with knee OA. However, the DM impact on knee OA is insufficiently studied.

Objectives: To investigate the association of diabetes with knee pain locations, pain severity during walk and walking speed in people with knee osteoarthritis (OA).

Design: A cross-sectional analysis was used

Methods: Data from 1,790 individuals from the osteoarthritis initiative (mean age: 69. (8.77)) with knee pain were included and grouped into knee OA and diabetes (n=236) or knee OA only (n=1,554). Knee pain locations were categorized to no pain, localized, regional, or diffused pain. Knee pain during a 20-meter walk test was categorized as: no pain, mild, moderate, and severe knee pain. Walking speed was measured using a 20 m walk test. Multinomial and linear regression analyses were performed.

Results: After controlling for covariates including age, gender, OA composite grade, body mass index, and depression symptoms, diabetes was associated with only regional knee pain (Odds Ratio (OR) 1.77; 95% Confidence Interval (95% CI) 1.01, 3.11). Diabetes was also associated with only moderate (OR 1.78; 95% CI 1.02, 3.10) and severe pain during walk (OR 2.52; 95% CI 1.01, 6.28). Diabetes was associated with decreased walking speed (B -0.064; 95% CI -0.09, -0.03).

Limitations: The degree and direction of causality cannot be determined because of the observational nature of this study.

Conclusions: Diabetes was associated with regional knee pain but not localized or diffused knee pain and was associated with moderate to severe knee pain during walk and slower walking speed in people with knee OA.

Keywords: elderly, knee pain map, gait speed

Introduction

Osteoarthritis (OA) and diabetes mellitus (DM) are common chronic diseases affecting approximately 14% and 10% of the general population, respectively [1-4]. OA is characterized by joint pain that is one of the leading causes of disability, and the main reason for seeking medical intervention [4]. Many factors such as age and comorbidities, such as DM affect pain and are associated with increased knee pain severity [17, 89].

DM is characterized by high blood glucose due to a disturbance in insulin metabolism leading to hyperglycemia, which often leads to systemic changes in body organs, including joints [29]. Another consequence of hyperglycemia is the production of advanced glycation end products (AGEs) that can accumulate in any part of the body, including joints, and may increase cartilage stiffness and bone fragility [30]. DM and OA shared some risk factors that may explain their coexisting prevalence [6], but the pathophysiological relationship is still unclear. Several studies have shown a significant association between DM and OA incidence and progression [5, 6, 10, 14, 124]. Further, DM has been shown to be an independent risk factor for hip or knee OA progression and associated with negative outcomes following joint replacement [12-14, 42-44]. Previous evidence suggests that systemic metabolic syndrome such as obesity and DM may play a role in the pathophysiology of OA at any joint.

Pain is considered the fifth vital sign that has many components, including pain severity and pain location during daily activities [125]. Examining the association between DM and OA in people with OA is necessary to identify specific pain pattern to establish the appropriate intervention. Comorbidities such as DM may influence the ability to identify pain location. Hyperglycemia or high glucose concentration is associated with the pro-inflammatory and pro-degradative effect of OA. Under 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 [29, 30, 123]. These changes due to DM might affect the ability to identify pain locations. Previous studies have found that diffuse knee pain is associated with physical dysfunction compared to localized pain in people with knee OA [87, 126-129]. Clinicians will benefit from knee pain locations because it will help in targeting the optimal intervention. A traditional target for physical therapy is the anterior medial knee location. However, when the pain is diffused, clinicians should consider broader areas, including posterior knee pain [87]. Few studies have reported higher pain severity in adults with DM and OA [9, 12, 17]. However, these studies examined a subgroup of individuals with OA such as end stage-knee OA before arthroplasty [12, 17] or erosive form of hand OA [9] that is considered a severe form of OA [130]. There is a lack of evidence examining pain during daily activities such as walking that may have a negative impact on walking speed and functionality.

Walking speed is considered as a sixth vital sign [131] and an important predictor for disability [132] and mortality [133] in older adults. Previous research has shown that a

decline in walking speed is associated with poor health outcomes [134], and associated separately with knee OA or diabetes. People with hip or knee OA walk slower than others with healthy joints [135, 136]. Furthermore, adults with DM showed slower walking speed when compared to healthy individuals [137, 138]. Although knee OA or DM are associated with slower walking speed, the impact of diabetes on walking speed in people with knee OA remains unknown. Therefore, it is necessary to consider all factors that may affect walking speed in order to implement an effective treatment.

Understanding the impact of diabetes on pain experience and walking speed in people with knee OA is valuable because it will help in establishing an interdisciplinary approach for this population. Therefore, the aims of this study were 1) to examine the association between diabetes and knee pain locations, 2) to investigate the impact of diabetes on knee pain during walking and walking speed in individuals with knee OA who had knee pain. We hypothesized that diabetes will be associated with diffused knee pain, higher pain severity during 20 Meter Walk Test, and decreased walking speed in people with knee OA.

Methods

Study design

This study is a cross-sectional analysis from the Osteoarthritis Initiative (OAI) at 96 months follow up. OAI is an ongoing multisite longitudinal study in the United States that

enrolled 4,796 participants with or at risk of knee OA to investigate the impact of knee OA over time to understand the prevention and treatment strategies better. This study was approved by the Institutional Review Board (IRB) for the University of California, San Francisco (UCSF) and its affiliates (approval number: FWA00000068). The IRB approval was also obtained from all the four clinical sites located at Brown University in Rhode Island, Ohio State University in Columbus, Ohio, University of Maryland/Johns Hopkins University joint center in Baltimore, Maryland, and at the University of Pittsburgh in Pennsylvania. All participants provided their informed consent before the screening and/or recruitment. For this study, we used data for patients with knee OA from OAI https://data-archive.nimh.nih.gov/oai/.

Participants

The protocol of OAI contains diverse groups of individuals ages from 45 to 79. Participants are divided into three cohorts; progression cohort (n=1,389 participants) who have symptomatic knee OA with presence of both osteophytes and frequent knee symptoms in at least one knee, incidence cohort (n=3,285 participants) who have no symptomatic knee OA but are at increased risk for symptomatic OA in at least one knee, and control cohort (n=122 participants) who have no symptomatic or radiographic knee OA and who have no risk for OA. In this study, we used data for participants with knee OA at baseline measured by X-ray composite OA grade (≥ 2) and reported having knee pain in at least one knee over 12 months using the following question: “During the past 12 months, have you had this pain, aching, or stiffness in your right/left knee”.

Previous longitudinal studies have utilized these questions [94, 95]. Figure 1 shows the flow of the included participants (n=1,790). Participants were further grouped based on the presence or absence of DM without missing DM status into knee OA and DM group (n=236) or knee OA only without DM (n=1,554).

Measures

Self-reported diabetes from the Charlson Comorbidity Index was utilized to categorize participants with and without diabetes. Participants were asked whether they have been diagnosed with diabetes with yes/no answers. Previous research has reported validity and reliability of self-reported diabetes using the Charlson Comorbidity Index [92, 93].

Knee pain map was administered at 24 and 96-months follow-up, and we selected 96 months since it has less dropout. Knee pain map is an interviewer-administered survey to identify painful areas of the knee. The area is defined as localized when the participants point into an area that hurt using one or two fingers, regional when participants point into an area that hurt using their hand over a region, or diffuse pain when participants say it hurts everywhere. This procedure was performed when the participant sits at the edge of the exam table with their legs bent over the edge. Trained interviewers identified and recorded the locations using an artist's drawing knee divided into specific locations utilized in a previous study [139]. This study reported, "The pain was recorded as being in one of seven local areas (superior medial, medial joint line, inferior medial, patella, superior lateral, lateral joint line, inferior lateral), one of four

regional areas (medial, patella, lateral, back) or as diffuse pain that cannot be localized or regionalized. If participants reported more than four local areas of pain or more than two regions of pain in a knee, their pain in that knee was classified as “diffuse.” Participants were also allowed to identify one location and one non-overlapping region of pain” [139]. These locations were further categorized into four categories including no pain, localized pain, regional pain or diffuse pain if the participant reported knee pain location in both knees, the most symptomatic knee was included for analysis.

Knee pain during 20-m walk test was measured immediately after performing 20-m walk test by asking this question for each knee: “Please, rate your maximum amount of pain experienced during walk from 0 no pain to 10 severe pain”. The most symptomatic knee was selected for this analysis. Further, knee pain during walk was categorized as follows: no pain, mild pain (1-3), moderate pain (4-6), and severe pain (7-10) [140].

Usual pace walking speed was measured during a 20-m walk test using the average of two trials. Walking speed was computed by dividing the distance (20 m) by the time (s) needed to complete the test. Participants were instructed to wear their usual footwear and used the assistive device if they need it.

Age, gender, and BMI were included as covariates as previous research has shown their association with knee pain severity and knee pain locations [126, 127]. Participants were classified as having depression symptoms when their scores on center for epidemiologic studies disease (CES-D) ≥16, and it was included as a covariate [141].

Radiographic evidence at baseline for tibiofemoral knee OA using OAI composite OA grade was included as a covariate.

Statistical analyses

The data and descriptive statistics were presented as means for continuous variables and percentages for categorical variables. All analyses were performed using SPSS for Macintosh, version 25.0 (SPSS Inc, Chicago, IL). Significance level was set at an alpha of 0.05.

Two multinomial logistic regression analyses were used. One was utilized to examine the impact of diabetes on knee pain locations and the other was utilized to examine the impact of diabetes on knee pain during a 20-m walk test. Knee pain locations included four categories; no pain, localized, regional, and diffused knee pain, and knee pain during 20-m walk test included four pain categories; no pain, mild pain, moderate pain, and severe pain. Two models were created with diabetes as the independent factor and knee pain during walk as well as knee pain locations as the outcome variables. These models include model 1 (adjusted for age, gender, and radiographic OAI composite OA grade) and model 2 (adjusted for model 1 in addition to BMI and depression symptoms). These covariates have shown association with knee pain and/or locations in people with knee OA [142-144]. Odds ratios (OR) with an associated confidence interval (CI) were calculated for each model and each category of the outcome variable. The reference

category for both outcome variables was set as no pain location and no pain during walk, respectively.

Multiple linear regression analyses were utilized to examine the impact of diabetes on walking speed during the 20-m walk test. Two models were created with diabetes as the independent factor and walking speed (m/s) as the outcome variable. These models include model 1 (adjusted for age, gender, and radiographic OAI composite OA grade) and model 2 (adjusted for model 1 in addition to pain during the walk, BMI, and depression symptoms).

Results

This study included a total of 1,790 participants as summarized in Figure 1, of those 236 (13.18%) participants had self-reported diabetes. Of participants with diabetes, 60.2% were female, 20.5% had depression symptoms, and the mean BMI was 32.30. Table 1 shows participants' characteristics for all sample and diabetes subsample.

Results from the multinomial logistic regression analyses are presented in Table 2, including two models. The final adjusted model 2 (n=1,300) showed that diabetes remained significantly associated with regional knee pain (OR 1.77; 95% CI 1.01, 3.11) when compared to no diabetes and no pain after controlling for age, gender, BMI, depression symptoms, and OA grade. Diffused and localized knee pain were not significantly associated with diabetes in both models.

Results for knee pain during walk using the multinomial logistic regression analyses are presented in Table 3 including two models. The final adjusted model 2 (n=1,316) showed that diabetes remained significantly associated with only moderate (OR 1.78; 95% CI 1.02, 3.10) and severe pain during walk (OR 2.52; 95% CI 1.01, 6.28) when compared to no diabetes and no pain during walk after controlling for age, gender, BMI, depression symptoms, and OA grade.

The results of the linear regression analyses examining the association of diabetes with walking speed are presented in Table 4 including two models. The final adjusted model 2 (n=1,316) showed that participants with diabetes were significantly ($p < 0.001$) had decreased walking speed (B [95% CI]): -0.064 [-0.09, -0.03]) after controlling for age, gender, knee pain during walk, BMI, depression symptoms, and OA grade.

Discussion

This study examined the impact of diabetes on knee pain locations, knee pain during walk and walking speed in individuals with knee OA. This study found that diabetes was associated with specific knee pain location, including regional knee pain, moderate and severe knee pain during walk and decreased walking speed in this population.

The most frequent knee pain location in the current study was localized knee pain, followed by regional and diffused knee pain. These findings were consistent with a

previous study [126] but contradictory to others [87, 145]. The consistency with Thompson et al. could be attributed to the same sample retrieved from the OAI database but at a different time point; 24 months follow up versus 96 months follow up. In contrast to the previous studies, other studies found that diffused knee pain was the most frequent knee pain location [87, 145]. The discrepancy in the current study with previous evidence may be due to the use of different knee pain location definitions or different knee pain map positions (sitting versus standing). Further, patients who referred to a large hospital may have a greater degree of OA severity and pain that may result in central diffused knee pain [145].

Contradictory to our hypothesis, DM was associated with different knee pain locations, including regional knee pain, but not diffused knee pain. The current study found that DM was related to regional knee pain after controlling for other covariates such as BMI and depression. The lack of association between DM and diffused knee pain requires further research to understand the possible mechanisms. Diffused knee pain might be associated with chronic comorbidities, including metabolic syndrome [126], but our study did not find such association. In this study, adults with DM are about 1.77 times more likely to have regional pain when compared to non-diabetes and no knee pain. Only a few studies examined risk factors associated with knee pain locations using knee pain map [126, 128]. Although Thompson et al. reported an association between higher BMI and all knee pain locations, this association was greater for diffused knee pain [126]. This study did not examine the risk of DM, and the only link between this study and the current study is the metabolic syndrome for obesity and DM. However, there is

additional confounder with obesity, which is a weight-bearing component. Another confounder is taking pain medications that may affect the results and was not measured. Regional knee pain might be associated with specific pain triggers. Multiple sources of joint pain are richly innervated tissues such as periosteum, synovium, muscle spasm, joints capsules and particular ligaments [146]. These components may be affected by DM and chronic hyperglycemia.

Moderate and severe knee pain during walk was associated with DM in the current study. Adults with DM are about 1.77 to 2.5 times more likely to have moderate or severe pain when compared to individuals without DM and without knee pain during walk. Little is known about pain during walk in people with knee OA. Only one study examined the association between pain during walk and dynamic knee load. This study found a strong association between medial knee load and pain during walk [147]. Current study findings were consistent with previous research that found higher pain severity in people with DM and knee OA compared to knee OA only [28]. However, this study measured pain severity without walking, unlike our study. This study found a higher concentration of inflammatory markers, including interleukin-6 (IL-6) in the synovial fluid in patients with DM and knee OA [17]. Also, this study reported higher synovitis scores in patients with DM and knee OA when compared to patients with knee OA only [17]. Whether DM added inflammatory changes to the knee joint or biomechanical loading require further research.

In the current study, walking speed was significantly slower in people with DM, independent of knee pain during walk. Mean walking speed was 1.12 m/s in people with DM and knee OA compared to 1.24 m/s in people with knee OA only. Therefore, the mean difference exceeds 0.1 m/s for a clinically meaningful difference in walking speed [148]. The current study showed that DM was associated with decreased walking speed after controlling for other covariates (B [95% CI]): -0.064 [-0.09 to -0.03]). These findings were consistent with a previous report among adults with DM [137]. Volpato et al. found that individuals with DM had decreased walking speed using a 400 m walk test when compared to those without DM (B: -.053 m/s). Another study by Kera et al. reported similar findings except the mean walking speed was higher than our study for people with DM (1.32 m/s) [149]. Previous research on walking speed and knee OA could not control for knee pain during performing walking speed test. However, our study was able to control for knee pain during walk to examine the influence of DM on walking speed independent of pain. Recent research on walking speed in individuals with knee OA showed that women had decreased walking speed compared to men in the Japanese population [150]. In our study, age and gender were included as covariates in the analyses, and the association remained significant between DM and walking speed.

Limitations

This study has potential limitations that should be considered. First, the self-reported diabetes is a key variable in this study, and there is a chance of inaccurate or underestimated answers due to the presence of undiagnosed diabetes, prediabetes,

denial, or lack of awareness. Also, self-reported diabetes did not have a specific type of diabetes, such as type 1 or type 2. However, the majority of diabetes (about 95%) is classified as type 2. Second, the cross-sectional design of this study may limit the interpretation of the results and the causal relationship between diabetes and knee pain locations, pain during walk or walking speed cannot be drawn from this study. Finally, other confounders cannot be considered such as pain medications, hemoglobin A1c, and diabetes duration.

Conclusion

Diabetes was associated with regional knee pain but not diffused or localized knee pain in people with knee pain during the past 12 months who had knee OA. Diabetes was associated with moderate to severe knee pain during walk and slower walking speed in people with knee OA. Diabetes can cause damage to the musculoskeletal system and might affect pain locations and walking performance. Identification of the impact of diabetes on knee pain locations, pain during walk, and walking speed may help clinicians in developing the appropriate intervention. Based on the known risk factors such as fall risk that is associated with slower gait speed, we suggest that clinicians should include walking speed assessment for patients with diabetes and knee OA to rule out any future risk. Future research should investigate whether good versus poor glycemic control affects the association between diabetes and knee pain and walking speed.

FIGURE 1 FLOW CHART OF PARTICIPANTS SELECTION

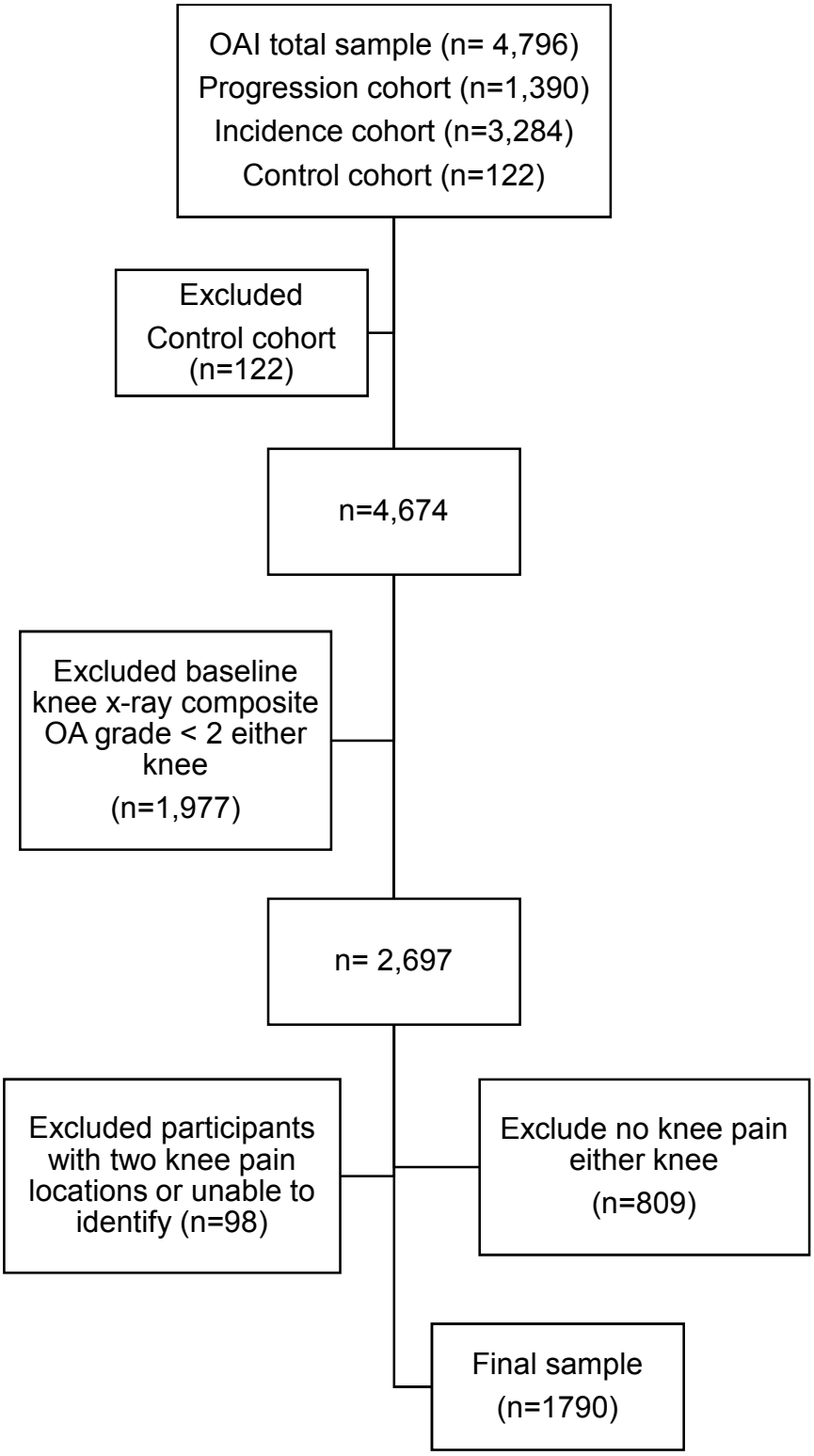

Table 5.1: Participants' demographics and clinical characteristics

	Total sample (n=1790)	Diabetes subsample (n=236)
Mean Age, years (SD)	69.65 (8.77)	69.93 (8.43)
Female, n (%)	967 (59.3)	142 (60.2)
BMI*, kg/m^2	29.81 (5.23)	32.30 (5.09)
Depression symptoms*, yes, n (%)	215 (13.6)	46 (20.5)
Knee pain locations, n (%)	1333 (74.47)	197 (83.47)
No pain	207 (15.5)	23 (11.7)
Localized	432 (32.4)	68 (34.5)
Regional	366 (27.5)	61 (31.0)
Diffused	328 (24.6)	45 (22.8)
Mean walking speed*, m/s (SD)	1.23 (0.22)	1.12 (0.21)
knee pain during walking*, n (%)	1350 (75.42)	191 (80.93)
No pain	902 (66.8)	111 (58.1)
Mild pain	331 (24.5)	48 (25.1)
Moderate pain	89 (6.6)	23 (12.0)
Severe pain	28 (2.1)	9 (4.7)

*Indicate statistically significant at 0.05 level using Chi-square or independent t-test

Table 5.2: Multinomial logistic regression for the association between diabetes and knee pain locations

	Model 1 (n=1317)	*p-value*	Model 2 (n=1300)	*p-value*
Localized	1.64 [.97-2.80]	0.067	1.65 [.95-2.87]	0.077
Regional	1.76 [1.03-3.01]	0.040	1.77 [1.01-3.11]	0.047
Diffused	1.37 [.78-2.40]	0.27	1.15 [.64-2.07]	0.65

Model 1: adjusted for age, gender and knee composite grade

Model 2: adjusted for age, gender, knee composite grade, BMI, and depression symptoms

Reference category set as no pain

Table 5.3: Multinomial regression for the association between diabetes and the maximum amount of pain experienced in the worst knee during the 20-meter walk

	Model 1 (n=1331)	*p-value*	Model 2 (n=1316)	*p-value*
Mild knee pain	1.26 [.87-1.84]	0.22	1.08 [.73-1.60]	0.70
Moderate knee pain	2.52 [1.49-4.24]	0.001	1.78 [1.02-3.10]	0.043
Severe knee pain	3.50 [1.45-8.44]	0.005	2.52 [1.01-6.28]	0.048

Model 1: adjusted for age, gender and knee composite grade

Model 2: adjusted for age, gender, knee composite grade, BMI, and depression symptoms

Reference category set as no pain

Table 5.4: Linear regression analyses for the association between diabetes and walking speed measured by 20-meter walk test

	Model 1 (n= 1331)			Model 2 (n= 1316)		
Diabetes vs	B	SE	*p-value*	B	SE	*p-value*
no diabetes	-0.12	0.016	<0.0001	-0.064	0.015	<0.0001
R^2	0.17			0.30		

Model 1: adjusted for age, gender and knee composite grade

Model 2: adjusted for age, gender, knee composite grade, BMI, depression symptoms, and pain during walk

SE: Standard Error

Chapter 6: discussion and conclusion

Summary of findings

This body of work represents the association of diabetes mellitus (DM) with osteoarthritis (OA) in a comprehensive work, including prevalence, association, and pain. The overall results of this work demonstrated the negative impact of DM on OA. Specifically, DM was associated with higher pain severity and bilateral knee pain distribution in people with knee OA. DM had a higher prevalence among people with generalized OA compared to localized OA. DM was associated with generalized OA in addition to age, sex, hypertension, and dyslipidemia. In terms of pain, DM was associated with higher pain severity in people with knee OA and localized OA, and DM was associated with specific knee pain pattern in people with knee OA. This work added to the literature the relationship between DM and OA in multiple ways and multiple definitions of OA (e.g., generalized OA, localized OA and knee OA) and pain (pain severity, distribution, and locations).

Summary of Chapter 2: The Association of Diabetes with Knee Pain Severity and Knee Pain Distribution in People with Knee Osteoarthritis

In the second chapter of this dissertation, we conducted a preliminary study using the Osteoarthritis Initiative (OAI) database. This database is a multisite observational study included 96 months follow up for individuals who have or at high risk of knee OA. The aims of our secondary analysis were 1) to examine the association between DM and knee pain severity, 2) to examine the association between DM and bilateral knee,

unilateral knee pain versus no knee pain among people with knee OA. Data at baseline were analyzed for 1,319 participants. The linear regression results showed that DM (n=148) was associated with higher pain severity over seven and 30 days. Multinomial regression results showed that people with DM were about three times more likely to have unilateral knee pain and about 3.5 times more likely to have bilateral knee pain. Clinicians should consider DM as a risk factor during pain management for people with knee OA, whether bilateral or unilateral. Proper management of DM using either pharmacological option such as DM control by medications or non-pharmacological intervention such as exercise may help in pain management for those with knee OA.

Summary of Chapter 3: The Prevalence of Type 2 Diabetes and Associated Risk Factors with Generalized Osteoarthritis: A Retrospective Study Using a Clinical Data Repository System

The third chapter of this dissertation was conducted using the Healthcare Enterprise Repository for Ontological Narration (HERON) [112] at the University of Kansas Medical Center. This database included de-identified data for participants who visited the University health system or affiliated clinics. The aims of this retrospective study were 1) to examine the prevalence of type 2 DM (T2DM) in people with generalized OA compared to localized OA, 2) to examine the association between age, gender, race, body mass index (BMI), T2DM, hypertension, dyslipidemia and neuropathy with generalized OA versus localized OA. This study examined 2,590 participants with localized OA and 1,265 participants with generalized OA. The results of this study found

that the prevalence of T2DM was higher in people with generalized OA (25.8%) compared to the prevalence of T2DM in people with localized OA (12.0%). The logistic regression analyses demonstrated that age, sex, T2DM, hypertension, and dyslipidemia were associated with generalized OA compared to localized OA. However, race, BMI, and neuropathy were not significantly associated with generalized OA in the final adjusted model. These factors could be considered by clinicians as risk factors for generalized OA during the management of people with OA. Because people with T2DM, hypertension, and dyslipidemia appear to be at higher risk of GOA, they may benefit from screening and an interventional approach to manage arthritis in multiple parts of the body. These factors could be screened for and deliberated in the management approach. This holistic approach includes appropriate medications, diet, exercise, and behavioral intervention. Improving the awareness of the risk of T2DM may help patients with LOA from developing multiple joints OA. Finally, people at the early stage of T2DM need to improve their glycemic control to avoid developing complications related to diabetes, such as GOA for the long term.

Summary of Chapter 4: Type 2 Diabetes Affects Joint Pain Severity in People with Localized Osteoarthritis: A Retrospective Study

In this chapter, we consider focusing on one of the most important symptoms of OA, pain severity, to understand its association with T2DM using a retrospective design and HERON database. The aims of this study were 1) to investigate the association between T2DM and pain severity in people with localized OA, and 2) to explore the

association between glycemic control A1c and pain severity in people with T2DM and localized OA. This study included data for 819 participants with localized OA and further data for 87 participants with T2DM and localized OA with A1c data. The results of linear regression showed that T2DM was associated with higher pain severity in people with localized OA, and A1c value was associated with higher pain severity in people with T2DM and localized OA. This association was consistent at any localized OA location including weight-bearing and non-weight bearing joints (i.e., knee, hand and shoulder) except hip and ankle locations. These results were independent of using medications such as pain medications. T2DM was associated with clinically important difference score for pain severity. Clinicians should consider T2DM as a risk factor for pain severity in people with localized OA. Therefore, health care providers should emphasize that better A1C control might help with pain management in people with T2D and OA. Since increased A1C 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 LOA and T2D. Clinicians may need to reinforce the importance of medications adherence to minimize the level of pain in people with LOA and hyperglycemia.

Summary of Chapter 5: The Association Between Diabetes, Knee Pain Locations, Pain During Walk and Walking Speed

In this chapter, our interest is to look deep to pain and to understand whether DM is associated with these pain parameters. Exploratory work has emerged from this study

to look at the association of DM and gait speed in people with knee OA. To summarize, the aims of this study were 1) to examine the association between DM knee pain locations (localized, regional or diffused knee pain), 2) to explore the association between DM and knee pain during walking, and 3) to explore the association between DM and gait speed in people with knee OA. This study used data at 96th month follow up from the OAI database (n=1,790). The results of multinomial regression showed that DM was associated with regional knee pain, but not diffused or localized pain. DM was also associated with moderate and severe knee pain during a 20-meter walk test. Finally, DM was associated with slower gait speed compared to people with knee OA only. Identification of the impact of DM on previously mentioned outcomes will help clinicians in developing an appropriate intervention for this population. Based on the known risk factors such as fall risk that is associated with slower gait speed, we suggest that clinicians should include walking speed assessments for patients with diabetes and knee OA to rule out any future risk. Future research should investigate whether good versus poor glycemic control affects the association between diabetes and knee pain and walking speed.

Potential mechanisms

This work was mainly focused on a retrospective analysis of existing data from electronic health records and other large databases, and direct measurement of the pathophysiological mechanisms between DM and OA was beyond the scope of this project. Osteoarthritis is known as a degenerative and complex disease affects joint

tissue, cartilage, subchondral bone and synovium, and metabolic syndromes such as DM may accelerate OA incidence and progression. OA is associated with low-grade inflammation locally and systemically [122]. Potential mechanisms have been studied mainly in animal models [29, 151-153], and some on humans [17, 154, 155]. Pathophysiological research has linked metabolic syndrome, including DM to OA.

Diabetes is associated with OA pathophysiology through the impact of hyperglycemia and insulin resistance [122]. Chronic hyperglycemia is associated with increased production of oxidative stress, advanced glycation end products (AGEs), and pro-inflammatory cytokines in the joints [156]. Insulin resistance affects joints locally and systemically by low-grade systemic inflammation. Fatty acids are associated with insulin resistance as well as obesity that may facilitate OA progression [157]. Some fatty acids can accumulate inside joints negatively affecting chondrocytes and synovial fluid [158, 159].

Chondrocytes are responsible for the synthesis of the extracellular matrix that is the basis for articular cartilage and can be affected by DM. The basic function of the cartilage is the absorb mechanical stress. However, in cases of OA, the stress absorption occurs with production and increase of pro-inflammatory mediator by chondrocytes that could be exacerbated by DM [153]. These pro-inflammatory mediators include cytokines, tumor necrosis factor radical oxygen species, AGEs, and prostaglandins [160]. In a state of local high glucose, the chondrocytes lost their capacity to adapt during OA, and in turns, high glucose uptake occurs ending up with

possible glucose toxicity [161]. Hyperglycemia also affects the ability of chondrocytes to differentiate, leading to a decrease in potential regeneration of cartilage [122]. In addition to the OA effect on chondrocytes, DM might add a negative impact that leads to disturbance in chondrocyte metabolism.

Cartilage is affected through the dysfunction of chondrocytes metabolism due to high glucose concentration. Hyperglycemia or high glucose concentration is associated with pro-inflammatory and pro-degradative effect OA. Under 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 in humans [162, 163]. Previous research has shown that AGEs level was 32% higher in bone and 21% higher in cartilage from participants with DM and OA when compared to bone and cartilage from people without DM [162].

Furthermore, increased levels of AGEs was associated with decreased levels of local synovial fluid in joints with OA [162]. Another study has reported that the cartilage from diabetic ankles was softer and associated with lower stiffness when compared with the cartilage from non-diabetic ankles [163]. These studies indicated a negative impact of DM on joint properties.

In addition to the effect of DM on cartilage, the impact of hyperglycemia or DM has been studied on bone properties. Research on the impact of DM on subchondral bone has revealed a negative impact of DM or hyperglycemia on bone characteristics affecting

bone marrow and mineral density [154, 164]. A previous study has linked high glucose concentration to bone marrow lesions in knee OA [164]. Another report has shown that the loss of subchondral bone was associated with lower bone mineral density and higher porosity in people with knee OA and DM [154]. AGEs accumulation in the subchondral bone could impact the mechanical resistance. A recent study has found that AGEs accumulate in subchondral bone in people with DM more than those without DM [165]. Because past studies found a negative impact of DM on subchondral bone in people with OA, DM effect might be extended to other joints parts such as synovium.

The impact of hyperglycemia on synovium was reported in a few studies. Hyperglycemia was associated with increased pro-angiogenic factor expression via oxidative stress in the synovial fibroblasts [166]. Previous research has shown that DM induces more synovitis in animal models [167]. These observations have been confirmed in humans and showed that patients with DM and knee OA had more synovitis compared to patients with knee OA only [17]. Synovium from patients with DM and knee OA involved more macrophages and inflammatory markers than patients without DM. Although previous reports have mainly investigated the possible potential mechanisms of DM and OA, little is known about whether inflammatory pathways affect pain perception in humans.

Lack of research examined the impact of DM on pain in individuals with OA within the context of potential mechanisms. Eitner et al. [17] have examined the association between DM and pain in people knee OA. This study found that pain severity was

higher in people with DM and knee OA compared to those with knee OA only. Also, people with higher synovitis score had higher pain severity. The positive association between pain severity and inflammatory markers was dependent on DM and /or synovitis [17]. Further research is needed in human subjects with DM and OA to understand potential mechanism with pain. Specific pathological markers could explain the association between DM and OA including fatty acids, advanced glycation end products (AGEs) and oxidative stress that may affect joints cartilage, subchondral bone and synovium [51, 160]. Future research should address the association of these inflammatory markers with pain and symptoms in a multidimensional approach including severity, location, frequency (constant vs. intermittent), and pain during activities.

Limitations

Study designs

In this dissertation, two designs were utilized: retrospective studies using electronic health records from HERON and cross-sectional studies using research data from OAI. Both databases have their limitations. Overall, these databases were suitable for our research questions and feasible to use. However, the retrospective design is not of favor for observational research as prospective design for many reasons such as missing data, missing variables of interest, unstandardized data collection, or inability to define baseline data. Retrospective design cannot establish causality between factors.

Variables of interest

For chapter 2 and 5, OAI was used to answer two different research questions; knee pain severity and knee pain locations. Data from the OAI was utilized at different time points because an outcome of interest for knee pain locations was administered only two times during the 96th months follow up. Knee pain map data were collected at 24th months follow up and at 96th months follow up. We selected the latter because of the smaller amount of missing data for DM and knee pain map. This database has another major limitation that could affect our results. DM was defined as self-reported, and this was one of the major outcomes in this dissertation and these chapters. Although DM is highly prevalent in people with OA, this definition may omit people with unknown DM or unaware of the disease, and this might affect the results. Another limitation of the OAI is that DM was not specified either type 1 or type 2, although the majority of DM is type 2. The mechanism and treatment could be different from disease to the other. Other factors related to DM were not measured, such as glycemic control A1c or fasting plasma glucose. The duration of DM was not measured or reported in the OAI database, and this may affect the interaction with knee OA.

For chapter 3 and 4, HERON database was used to answer different research questions; the prevalence of DM among people with generalized OA and the associated risk factors with generalized OA versus localized OA. HERON is a database using real-world clinical data that could have many potential limitations. The diagnostic codes for

key variables DM and OA are one of the main limitations. Although every possible effort has been made to improve the accuracy of diagnoses, such as using two codes, there is still a possibility for errors in these diagnoses. Further, the clinicians (primary care versus specialty visit) assigning the codes have not been considered in this study, and this could affect the results. Other important factors were captured in HERON including education, socioeconomic status, diet, and physical activity level that might be potential confounders for these studies. Medications were extracted from pharmacy data based on filling the prescriptions, and this cannot guarantee using these medications by patients. Although every effort has been made to capture medication usage within 90 days of the index date, some medications could be missed because they have not been filled within 90 days or potentially be filled at another pharmacy out of the network. An important factor that can affect the association between DM and OA is obesity or BMI. In HERON, it was difficult to obtain BMI value that is close to the index date (first date of OA diagnosis). Therefore, we linked BMI value to be within one year of the index date. Even using this approach with a relatively long period, missing data for BMI was 32.1%. Multiple imputations have been utilized to impute missing values for BMI using all possible factors including age, sex, race, DM, hypertension, dyslipidemia, neuropathy, depression, anxiety, sleep disorders, and medications (antidiabetics, antihypertensives, antilipemic, and antidepressants). In our analysis, we reported the results using imputed and non-imputed data. The main findings remain similar for this sensitivity analysis. Although this approach can impute BMI values that are missing, these imputations were based on one-year data within the index date. This approach may result in imputed values that do not reflect the real BMI values that may change within a year. In general,

missing values for measurements can lead to bias in the estimation of the parameters and reduce the representativeness of the samples. Using multiple imputations cannot generate the accurate imputation for the missing value because imputation depends on prediction model that predicts the missing value. The prediction is prone to errors and in some cases is far from the actual missing values. Therefore, the results should be interpreted with caution regarding BMI.

Future directions

This dissertation work has attempted to answer multiple questions about the impact of DM on OA prevalence and pain. However, other areas of research still need to be considered in future research.

Identifying causality in observational studies is difficult because a prospective longitudinal design may not be feasible. Identifying whether DM causes OA or vice versa is an essential step to be taken by future research to understand this association. A temporal association could be identified by a retrospective design using electronic health records with at least ten years of longitudinal data. This study can involve two cohorts; one should include patients with DM without OA for at least two years before the index data (the first date of the longitudinal follow up), and the other cohort should include patients with OA without DM for at least two years before the index date. Then, both cohorts will be retrospectively followed up until the end of the 10^{th} year, lost to follow up or death. This study will eventually help in understanding the direction of the

relationship between DM and OA. Another logical next study should examine the association between metabolic syndromes, including DM and pain severity among people with GOA. This study could be a retrospective design for people with GOA. Pain severity can be measured by a numeric rating scale from 0 to 10. Most importantly, the covariates should be included especially metabolic syndrome medications and pain medications at least three months before the pain severity index date. Other factors that may affect the association between DM and OA should be considered including physical activity level and diet. Proper management for identified risk factors such as DM, hypertension, and dyslipidemia should be examined in future research. Also, whether proper management of these factors is associated with decreased risk for OA or influence pain. A recent report has found that the incidence of DM among OA population was mediated by walking difficulty. However, walking difficulty was a binary variable with having or not having difficulty. Future studies may quantify walking difficulty (e.g., gait speed) over time and its association with DM incidence in people with OA.

Using real-world clinical data, such as HERON, has some challenges that should be considered in future research. The data and observations are captured from many sources (i.e., inpatient, outpatient, emergency room visits…etc). Therefore, it is essential to specify the source of data to improve the generalizability and replicability of the research questions using similar database. Future research should examine whether the diagnosis codes differ depending on the encounter types (inpatient or outpatient), type of visit (specialty versus primary care), or emergency room visits. Also,

examining the prevalence and association of diabetes and OA with consideration to the codes source is another area of research.

In the current study using HERON, missing BMI data was a limitation that needs to be considered in future analysis. BMI value could be measured consistently in recent years and encounters. Future research using HERON database can consider selecting cohorts from recent years that could have more consistent data about BMI.

Mechanisms for how DM affects OA is beyond the scope of this dissertation. However, this scope will be an interesting future direction for this work. Future research should extensively examine possible pathways for this association and possible inflammatory markers that could affect both DM and OA symptoms such as pain. Only one study has examined the impact of DM on inflammatory markers in people with end-stage knee OA. Future research should further examine these associations in people with OA in other joints such as hands or other forms of OA such as generalized OA.

Parts of this dissertation has been focused on the impact of DM on pain in people with OA. Although this dissertation found that DM was associated with pain severity in people with localized OA and with specific knee pain pattern in people with knee OA, pain is a multidimensional outcome. This dissertation focused on only a few aspects of pain (e.g., pain severity, pain locations, and pain during walking). Future research should extensively focus on other subjective parts of pain, such as pain description, neuropathic pain, intermittent, or constant pain. Other aspects that could be associated

with pain might be considered in future research such as fear-avoidance beliefs and biopsychosocial model and the impact of DM on these measures in individuals with OA.

This dissertation explored the impact of DM on pain during walk and gait speed in people with knee OA. DM was associated with moderate to severe knee pain in people with knee OA. Further research should shift the focus to pain during activities such as walking since walking is an essential function for people with either DM or OA. There was a clinically meaningful negative association between DM and gait speed, and it was evident even after controlling for other covariates. Future research can explore this association in-depth and look at the association in the general population. For example, future studies may explore the impact of combined DM and OA, DM only, OA only, and none of these on gait speed in the general population and older adults.

Conclusion

This body of work has found a higher prevalence and stronger association of DM among people with GOA, and DM was associated with pain severity and specific pain locations in individuals with OA.

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