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Does Better A1C Control Worsen Osteoarthritis? An Electronic Health Record Cross-Sectional Study

Sarah C. Cattaneo
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Does Better A1C Control Worsen Osteoarthritis? An Electronic Health Record Cross-Sectional Study

by

Sarah C. Cattaneo

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Public Health Department of Occupational Medicine College of Public Health University of South Florida

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Keywords: Diabetes, Obesity, BMI, Metformin, Insulin, Inflammation

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ABSTRACT

Obesity is a major risk factor for osteoarthritis (OA). There is evidence that diabetes also increases risk. Our hypothesis is that A1C is a predictor of OA severity. The aim is to investigate the association between A1C, BMI, and knee and hip OA severity. This is a cross-sectional study within the Veterans Health Administration (VHA) database containing 818 patients with diagnosed diabetes. Patients at one VHA facility with recorded diabetes in fiscal year 2020 were identified. A1C and BMI data was obtained from the electronic health record. Chart reviews were performed to collect data on imaging reports of weight-bearing joints in order to assign an OA severity level. The exposure was BMI and A1C. The outcome was the presence and/or severity of OA in the record. Participants who used nicotine and/or were missing an A1C in the past 12 months, as well as those without weight-bearing imaging, were excluded. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated as a function of A1C and BMI with logistic regression analysis. 220 participants (white, non-Hispanic/Latino males, aged 55-64 years) with weight-bearing imaging were included. Participants with OA did not have a significantly different BMI or A1C than participants without OA. There was no association between BMI and OA severity (OR: 1.00, 95% CI: 0.94-1.07). There was a non-statistically significant inverse association between A1C and OA severity (OR: 0.92, 95% CI: 0.77-1.11). In diabetic patients, BMI does not seem to be predictive of OA severity, whereas better glucose control (lower A1C) is associated with increasing severity of OA, although this was not statistically significant. This is supported by literature that shows the pro-inflammatory nature of insulin and means that tight control of A1C could negatively impact OA. Future research should focus on treating patients with T2DM and OA with exercise and other therapies aimed at improving insulin resistance.
CHAPTER 1:

INTRODUCTION

Osteoarthritis (OA) affects over 30 million people in the United States, which has increased from 21 million in 1990 to 27 million in 2005 (Centers for Disease Control and Prevention [CDC], 2020), and 37% of adults over the age of 60 years are affected by OA (Lawrence et al., 2008). The estimated prevalence of T2DM among individuals aged 45-64 years is 14.3 million (CDC, 2017). According to years lived with disability (YLD) data from 1990 to 2016, diabetes and OA are the two most rapidly rising conditions associated with disability (T. Vos et al., 2012). More than half of people with type 2 diabetes (T2DM) have OA (Arthritis Foundation, 2020). Diabetes costs the United States health care system and employers $237 billion every year (American Diabetes Association, 2018). For arthritis, the estimated total cost was $304 billion in 2013, with nearly $140 billion in medical costs, and $164 billion in indirect costs associated with lost earnings and productivity (CDC, 2020). The increasing burden of both diseases is anticipated to result in significant challenges for health care and public health systems.

T2DM is a complex disease that is influenced by both genetic and environmental factors, to include lifestyle characteristics that result in overweight and obesity. The hallmark of T2DM is insulin resistance in skeletal muscles, the liver, and other tissues (Defronzo, 2009; Stumvoll, Goldstein, & van Haeften, 2008). Resultant prolonged hyperglycemia leads to the generation of advanced glycated end products (AGEs), oxidative stress, and low-grade inflammation. These end-products can damage blood vessels in multiple organs and tissues (King & Rosenthal, 2015). T2DM is managed with lifestyle modification (diet, exercise, weight-loss) as well as medication. While metformin is usually the first line therapy, insulin and insulin secretagogues are also used with the goal of controlling the disease by lowering the hemoglobin A1C (A1C) value to < 8. By definition, A1C values > 8 indicate uncontrolled diabetes (Pantalone et al., 2020). T2DM often coexists with OA in older adults (Piva et al., 2015).
OA is a multifactorial disorder that affects joints of the hand, hip, and knee, and involves all joint tissues to include articular cartilage, subchondral bone, and synovium. The medical community previously held the belief that OA stemmed from age-related wear and tear of cartilage, however, today there is new attention focusing on the role of local and systemic low-grade inflammation on the joints (Arthritis Foundation, 2020; Courties & Sellam, 2016). Articular cartilage houses an extracellular matrix (ECM) generated by chondrocytes that is equipped to absorb mechanical stress between two mobile bone surfaces. In OA, chondrocytes respond to stress by increasing production of pro-inflammatory mediators, to include cytokines (interleukin-1B [IL-1B]), tumor necrosis factor-a (TNF-a), radical oxygen species, AGEs, and prostaglandins. Following this local reaction is increased production of proteolytic enzymes (matrix metalloproteinases [MMPs] and aggrecanases) that can digest the cartilage matrix.

The classification of OA into different phenotypes has been proposed (Bijlsma, Berenbaum, & Lafeber, 2011). These categories include post-traumatic, age-related, genetic, and metabolic-syndrome associated (MetS) (Bijlsma et al., 2011). MetS-associated OA is closely linked to abdominal adiposity, and the mechanical impact of overweight/obesity on joints may easily explain lower limb OA (Louati, Vidal, Berenbaum, & Sellam, 2015). Other MetS components that may impact OA include dysglycemia, hypertension, and dyslipidemia (Alberti, Zimmet, & Shaw, 2005; Puenpatom & Victor, 2009; Zhuo, Yang, Chen, & Wang, 2012). There is significant overlap between T2DM and MetS, with over 75% of patients with T2DM having coexisting MetS (Alberti et al., 2009). To date, the severity of knee OA has been significantly associated with hypertension, dyslipidemia, and the number of MetS factors present, although no association between the severity of radiographic knee OA and MetS factors was identified in the same study (Yasuda et al., 2018).

T2DM and OA have many shared risk factors, including obesity and age (Scheen & Van Gaal, 2014; Visser et al., 2015). There is strong evidence linking obesity and OA via mechanical load, and the majority of patients with T2DM carry the diagnosis of obesity (Scheen & Van Gaal, 2014; Teodoro, Varela, Rolo, & Palmeira, 2014; Visser et al., 2015). Recent studies suggest that T2DM exerts pathologic effects on OA via two routes: chronic hyperglycemia, and insulin resistance (Veronese et al., 2019). The
effects of chronic hyperglycemia include oxidative stress, release of pro-inflammatory cytokines, and AGEs in joint tissues. Insulin resistance affects tissues both locally and through systemic low-grade inflammation (Courties & Sellam, 2016). Leptin is an adipokine secreted mostly by adipose tissue that is capable of promoting chondrocyte apoptosis and increasing cytokine and MMP production by chondrocytes (Courties, Gualillo, Berenbaum, & Sellam, 2015). This hormone helps to regulate energy balance by signaling satiety, which ultimately diminishes fat storage in adipocytes. As a person’s body fat increases, more insulin is required to control blood sugar, a phenomenon known as insulin resistance which leads to T2DM. Insulin resistance increases as a function of body fat, which is thought to be due to leptin (Courties et al., 2015; Simopoulou et al., 2007; Yadav, Kataria, Saini, & Yadav, 2013).

Cartilage relies on subchondral bone and synovial fluid through the joint cavity as the source of its nutrients because it is not vascularized. Chondrocytes express glucose transporters (GLUT) to detect glucose levels and correspondingly adapt GLUT expression (Mobasher, Neama, Bell, Richardson, & Carter, 2002). In OA, chondrocytes lose this ability, which leads to an increased and potentially toxic uptake of glucose (Rosa et al., 2009). Increased uptake of glucose results in impaired differentiation of chondrogenic stem cells, which may exacerbate problems with cartilage regeneration (Courties & Sellam, 2016). Elevated glucose levels cause AGEs to accumulate in cartilage, which increases the stiffness and resistance of this tissue (Eaton et al., 2017; P. A. Vos et al., 2013). Furthermore, hyperglycemia causes chondrocytes to express a pro-inflammatory and pro-catabolic phenotype involved in a signaling pathway that leads to oxidative stress and the release of cytokines by chondrocytes (Chen, Sheu, Tsai, Yang, & Liu, 2013). Other effects of hyperglycemia include upregulated MMP expression and oxidative stress in chondrocytes, as well as enhanced IL-1B cytokine release (Chen et al., 2013).

Hyperglycemia also adversely impacts synovial tissue through a variety of mechanisms. Synovial fibroblasts respond to the oxidative stress of hyperglycemia by expressing pro-angiogenic factors, which turn on synovial angiogenesis and activate pro-inflammatory cells (Tsai et al., 2013). In-vivo models demonstrate this finding (more synovial inflammation in diabetic tissue) as do clinical data that show that diabetic patients have more synovitis in knee OA than patients without diabetes (Ribeiro,
Furthermore, the synovium of T2DM patients with OA had more macrophages and elevated levels of TNF-a than did the synovium of patients without diabetes. Evidence of insulin resistance in synovial tissue is demonstrated by decreased phosphorylation of insulin-dependent insulin receptors (and other components of the intracellular insulin cascade) in cultures of fibroblast-like synoviocytes from patients with T2DM (Hamada et al., 2016).

T2DM may hinder bone remodeling through several mechanisms. In the knee, hyperglycemia is associated with bone marrow lesions that increase the risk of structural damage to bone (Franke et al., 2011). Advanced knee OA in diabetic patients (independent of weight) demonstrates subchondral bone loss characterized by lower bone mineral density and increased porosity (Wen et al., 2013). Diabetic patients are more prone to the accumulation of AGEs in subchondral bone, which may adversely impact the mechanical resistance of this tissue, as well as promote inflammation (Franke et al., 2011). Diabetes adversely impacts the microvasculature, and subchondral bone has multiple arterial inlets and venous outlets. Given that the long bones (such as the hip) are highly vascularized with greater nutrient requirements, the microvascular pathway is another potential route by which T2DM could contribute to joint damage in OA (Findlay, 2007).

An association between the occurrence of T2DM and OA has been demonstrated, but whether T2DM is an independent risk factor for OA is controversial. Louati et al. (2015) performed a meta-analysis of 49 studies involving more than 1 million participants (N = 1,192,518) and found that OA and T2DM were significantly associated (Louati et al., 2015). The odds ratio (OR) of T2DM in the OA population vs. non-OA population was 1.41 (95% CI 1.21, 1.65), and the prevalence of T2DM among patients with OA was 14%. The overall presence of OA in the T2DM population vs. non-T2DM population (OR) was 1.46 (95% CI 1.08, 1.96). In this population (mean age 61 years), the prevalence of OA among patients with T2DM was 30% (38% hand OA, 12% hip OA, and 17% knee OA) (Louati et al., 2015). Nielen et al. (2016) completed a meta-analysis including only studies controlling for weight or body mass index (BMI), and found the presence of OA in patients with T2DM was also high, with an OR of 1.25 vs. non-T2DM population (95% CI 1.05, 1.46) (Nielen et al., 2016). In terms of OA progression,
several studies demonstrate that T2DM may be a risk factor. Eymard et al. (2015) found that T2DM was a significant predictor of joint space narrowing in males with established knee OA (Eymard et al., 2015). They did not, however, examine the impact of glycemic control on disease progression, though they posited that tight glycemic control could reduce the rate of circulating AGE and other downstream inflammatory effects of hyperglycemia, which could help to control OA (Eymard et al., 2015). Schett et al. (2013) found that T2DM predicts the development of severe OA independent of age and BMI, and that it is an independent risk factor for arthroplasty (HR = 2.1; 95% CI 1.1, 3.8; p=0.023) (Schett et al., 2013). In contrast, in a population-based case control study (N = 94,609), Nielen et al. (2016) found no association between DM (almost 20 times more T2DM than type 1 diabetes in this cohort) and total joint replacement (TJR) of either the hip or knee among OA patients with or without DM (Nielen et al., 2016). Dawson et al. (2018) found no evidence for T2DM increasing the risk of incident knee OA, and Khor et al. (2020) presented a comprehensive systemic review and the first meta-analysis to refute an independent association between OA and T2DM (Dawson et al., 2018; Khor, Ma, Hong, Hui, & Leung, 2020). BMI was cited as the most important confounding factor.

There are conflicting reports in the literature about the impact of metformin on OA. Shirinsky et al. (2017) performed an analysis of longitudinal data from the Osteoarthritis Initiative study and reported that medication-treated diabetes has no effect on knee OA incidence (OR = 0.53; 95% CI 0.23, 1.5), but reduces knee OA progression, measured as joint-space narrowing (JSN) or knee replacement therapy (OR = 0.66; 95% CI 0.44, 0.98) (Shirinsky & Shirinsky, 2017). Barnett et al. (2017) conducted a cohort study in the UK using the Consultations in Primary Care Archive. Among 3,217 patients with T2DM, there was no association between metformin prescribed as treatment at baseline and OA as the primary outcome during follow-up (adjusted HR = 1.02; 95% CI 0.91, 1.15) (Barnett, Jordan, Edwards, & van der Windt, 2017). Lu et al. (2018) conducted a case-control study in Taiwan that showed that patients who have OA and T2DM who are prescribed combination NSAIDs and metformin therapy had lower joint replacement surgery rates than those without metformin (adjusted HR = 0.742; 95% CI 0.601, 0.915; p = 0.005) (Lu et al., 2018). It has been suggested that this effect may be due to a reduction in pro-
inflammatory factors associated with combined therapy with metformin (Scheen, Esser, & Paquot, 2015). Wang et al. (2019) studied obese, non-diabetic patients and found that metformin was beneficial. They questioned the accuracy and validity of the method used to identify OA in the study by Barnett et al. (2017), which relied on the general practitioner’s electronic diagnosis of OA (Wang et al., 2019). Amin et al. (2019) presented information on the multiple pathways in which metformin plays a beneficial role, to include antineoplastic effects through inhibition of the mammalian target of rapamycin (mTOR) pathway by activating the AMPK regulator (adenosine monophosphate-activated protein kinase) and p53 (Amin, Lux, & O’Callaghan, 2019). Li et al. (2020) studied mice and found that metformin limits OA progression via AMPK signaling activation (Li et al., 2020).

Similar to metformin, there are conflicting reports in the literature about the impact of insulin on OA. This may be due to the fact that high insulin levels are associated with insulin resistance in T2DM and differentiating between the effects of insulin vs. insulin resistance is not straightforward (Al-Jarallah, Shehab, Abdella, Al Mohamedy, & Abraham, 2016; Askari, Ehrampoush, Homayounfar, Bahramali, & Farjam, 2017). Most recently, Qiao et al. showed that increasing insulin titrations accelerate OA progression based on studies of synovial tissue collected from OA patients (Qiao, Li, & Sun, 2020). This finding is inconsistent with a cross-sectional study by Al-Jarallah et al. (2016) that showed that T2DM patients with knee OA on insulin therapy had fewer radiographic osteophytes compared to T2DM patients not on insulin (Al-Jarallah et al., 2016).

Basic science research may elucidate these discrepancies. Rosa et al. (2011) studied human chondrocytes that express functional insulin receptors that respond to physiologic insulin concentrations. Compared with normal chondrocytes, OA chondrocytes had fewer receptors, and they responded to insulin erratically (Rosa et al., 2011). Ribeiro et al. (2016) examined autophagy, a critical homeostasis mechanism in cartilage that is impaired in T2DM and OA. Immortalized human chondrocytes and cultures of primary human chondrocytes showed decreased autophagy in response to insulin, as well as increased expression of MMP-13 (an enzyme capable of digesting the cartilage matrix) and IL-1B (a pro-inflammatory cytokine) (Ribeiro et al., 2016). Visceral obesity (a progenitor of insulin resistance and
T2DM) is characterized by chronic low-grade systemic inflammation, which may be implicated in joint
damage (Courties & Sellam, 2016; Gregor & Hotamisligil, 2011; Griffin & Huffman, 2016). An
additional source of inflammation is the synovium itself, which has been shown to develop insulin
resistance in obese OA patients with T2DM (Hamada et al., 2016). Insulin plays an important role in
providing negative feedback in the synovial inflammation and catabolism pathway. The development of
insulin resistance in obese individuals, therefore, would impede the ability of insulin to turn off the
signals that promote OA (Griffin & Huffman, 2016). The association of MetS, insulin resistance, and OA
pathophysiology is an area of ongoing research (Courties, Sellam, & Berenbaum, 2017).

Garessus et al. (2016) investigated the association between markers of glucose metabolism and
hand and knee OA with a cross-sectional analysis of baseline measurements of the Netherlands
Epidemiology of Obesity study (Garessus, de Mutsert, Visser, Rosendaal, & Kloppenburg, 2016).
Fasting glucose, insulin, and A1C concentrations were measured. OA was defined following the
American College of Rheumatology (ACR) criteria. After exclusion of participants on glucose-lowering
drugs, odds ratios (ORs) with 95% confidence intervals (CIs) for either hand, knee, or both hand and knee
OA were calculated as a function of each marker of glucose metabolism with logistic regression analysis.
Models were adjusted for age, ethnicity, education, height, weight and total body fat, and stratified by sex.
They found that an impaired glucose metabolism did not seem to be related to OA, however, their study
excluded patients on glucose-lowering drugs. Another limitation of this study is that as a result of its
cross-sectional design, reverse causation could not be excluded (Garessus et al., 2016).

To our knowledge, this type of investigation focused on metabolic markers and OA severity (with
severity category assigned based on radiographic imaging) has not been performed on a population of
T2DM patients. The question of whether T2DM is linked to OA outside of weight overload, and how the
control of T2DM (as evidenced by A1C) relates to OA severity, is the focus of this paper. Given that
insulin is linked to the proinflammatory pathways that cause OA, we hypothesize that better control of
glucose (lower A1C) in diabetics is associated with increasing severity of arthritis. We base this on the
biological mechanism of insulin resistance and high exogenous insulin levels in patients on insulin or
other diabetes medications that increase endogenous insulin levels. We seek to compare the BMI and A1C values of overweight and obese patients with controlled and uncontrolled diabetes in order to further characterize the impact of these variables on osteoarthritis using data from the Veterans Health Administration Support Service Center Capital Assets Database.
CHAPTER 2:
METHODS

This descriptive cross-sectional study utilized the Veterans Health Administration (VHA) Support Service Center Capital Assets Database (VSSC), a web-based project application and tracking database for the VHA. The VHA provides healthcare to a population of veteran service members from the U.S. Army, Navy, Air Force, Marine Corps, and Coast Guard. The Tampa Veteran’s Affairs (VA) hospital system serves over 120,000 beneficiaries. Information on nine variables of interest (diabetes diagnosis and medications, BMI, ethnicity, race, age, gender, A1C, and nicotine use) was ascertained from the VSSC’s Diabetes Cube, which aggregates inpatient and outpatient medical encounter data. Information was collected for fiscal year 2020 on patients assigned to the Tampa VA, of which 26,129 carry the diagnosis of definite diabetes. Search parameters for the sample included a definite diabetes diagnosis, BMI in the overweight and obese range (BMI of 25 to >=30), white race, non-Hispanic/Latino ethnicity, male gender, aged between 55-64 years, non-nicotine users, with an A1C drawn in the past 12 months.

Definite diabetes is assigned to patients in the VSSC Cube if any one of the following three criteria is met: (1) one inpatient diabetes diagnosis, (2) two outpatient diabetes diagnoses, or (3) a prescription for >30 days of diabetes medication. The inpatient diabetes diagnosis is defined as one primary or secondary inpatient diabetes diagnosis where the discharge date (or census discharge date) is within the 24-month window of the selected fiscal year. Two outpatient diagnoses are primary or secondary diabetes diagnoses on two different visit dates where the visit dates are within the 24-month window. These exclude telephone visits, employee health appointments, compensation and pension examinations and other encounters. The diabetes prescription criteria is met with one outpatient fill of a diabetes drug (except Metformin and Liraglutide) with a day supply of 31 or greater, or two outpatient
fills of a diabetes drug (except Metformin and Liraglutide) with a day supply of 30 or less filled within the 24-month window.

The VSSC query captured A1C values for selected individuals. Chart reviews were performed to obtain a list of prescribed diabetes medications and x-ray imaging reports for each patient. Diabetes prescription medications were obtained from the “active medications” tab located in the electronic medical record (EMR). For deceased patients who had no active diabetes medications listed on their EMR cover sheets, the most recent clinical note was reviewed to obtain diabetes medications from the medication reconciliation. The imaging tab of the EMR was reviewed to determine if x-ray reports of weight-bearing joints (knee and/or hip) were present. If so, a severity category was assigned according to a coding system we developed based on the radiology report (no osteoarthritis = level 0, mild OA = level 1, moderate OA = level 2, and severe OA = level 3). Joint replacement was assigned an OA severity level of 3 if it was not due to trauma. Once the OA severity category was extracted from the x-ray report, it was transcribed into a spreadsheet that included corresponding A1C and BMI values for individual patients, as well as prescribed diabetes medications. In this cross-sectional study, participants using nicotine were excluded (because of the pro-inflammatory nature of tobacco products), as were those missing A1C data in the past 12 months.

The selection of participants is shown in Figure 1. A query was run in the VSSC database to identify overweight patients with definite diabetes, which generated 626 unique individuals. 212 of these individuals were excluded because of nicotine use and/or the absence of an A1C in the past 12 months. An additional 8 duplicate names were removed. Of the 406 charts of overweight individuals with definite diabetes, 110 individuals had weight-bearing imaging. Another query was run in the VSSC database to identify obese patients with definite diabetes; this generated 1,272 unique individuals. 365 of these individuals were excluded because of nicotine use and/or the absence of an A1C in the past 12 months. An additional 8 duplicate names were removed, to yield a group of 899 obese individuals with definite diabetes. A random number generator was used to sample this group to obtain a similar number of obese individuals with weight-bearing imaging. During this process 412 individuals were randomly selected, of
whom 110 had weight-bearing imaging and 302 did not have weight-bearing imaging. Overall, 220 overweight and obese participants were included for analysis.

Figure 1: Flowchart for selection of participants

To fit the data to the model, we performed descriptive statistics to investigate the distribution of study variables (BMI and A1C) in relation to Osteoarthritis Severity. P-values for comparison were obtained using the Analysis of variance (ANOVA). Additionally, box plots were produced to investigate the relationships of BMI on levels of OA severity, and A1C on levels of OA severity. As the outcome of this study was ordinal, an ordered logistic regression, also called a cumulative logistic regression or “proportional odds model” was used to obtain predictive probabilities comparing levels of Osteoarthritis Severity. Odds ratios and 95% CI were additionally generated to compare changes in explanatory variables (BMI and A1C) with increasing Osteoarthritis Severity. The SAS software (Version 9.4) was used to perform statistical analysis.
CHAPTER 3:

RESULTS

Information from an exploratory analysis that compared BMI and A1C among the different OA severity categories is shown in table 1. Age was restricted to 55-64 years. The study included only white males who were not Hispanic or Latino. BMI values across OA severity categories are almost constant, although this was not statistically significant. An A1C decrease is noticeable from left to right; as OA severity increases, A1C drops from 7.6 to 6.6. Neither of these findings, however, were statistically significant (p = 0.9506 and p = 0.2666, respectively).

Table 1: Descriptive statistics comparing study variables versus osteoarthritis severity using ANOVA (n = 220)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>None (n = 9)</th>
<th>Mild (n = 141)</th>
<th>Moderate (n = 59)</th>
<th>Severe (n = 11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>32.1 (7.96)</td>
<td>31.5 (3.94)</td>
<td>31.9 (4.14)</td>
<td>31.1 (4.19)</td>
<td>0.9506</td>
</tr>
<tr>
<td>A1C</td>
<td>7.6 (1.48)</td>
<td>7.2 (1.46)</td>
<td>7.2 (1.72)</td>
<td>6.6 (1.13)</td>
<td>0.2666</td>
</tr>
</tbody>
</table>

The information in table 1 is presented with box-whisker plots in figures 2 and 3. In figure 2, there is no visible trend in BMI and OA severity levels.
Figure 2: BMI vs OA Severity

Figure 3 shows an inverse association between A1C and OA; as A1C increases, OA severity decreases.
Table 2 presents the distribution of participants with uncontrolled diabetes (A1C > 8) at each level of OA severity. The greatest proportion of study participants with uncontrolled diabetes were classified in the no OA group (44%), whereas only 9% of these study participants with uncontrolled diabetes were classified in the severe OA group. There is a trend that as OA severity increases from left to right across the table, there is a decrease in uncontrolled diabetes. The p-value for this trend is on the borderline of statistical significance (p = 0.08).

Table 2: Uncontrolled diabetes (A1C >8) by OA severity

<table>
<thead>
<tr>
<th>% (#) of participants with uncontrolled diabetes</th>
<th>No OA</th>
<th>Mild OA</th>
<th>Moderate OA</th>
<th>Severe OA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>44% (4/9)</td>
<td>28% (40/141)</td>
<td>24% (14/59)</td>
<td>9% (1/11)</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 presents parameter estimates from the ordinal logistic model, showing that the predicted probability of osteoarthritis severity category = 3 versus osteoarthritis severity category = 0,1, or 2 is
0.09. The predicted probability of osteoarthritis severity category = 2 versus osteoarthritis severity category = 0, or 1 is 0.78. The predicted probability of osteoarthritis severity category = 1 versus osteoarthritis severity category = 0 is 39.25. For a one unit increase in BMI, we expect a 0.002 increase in the log odds of being in a higher osteoarthritis severity category. For a one unit increase in A1C, we expect a 0.081 decrease in the log odds of being in a higher osteoarthritis severity category. Neither of these log odds achieved statistical significance (p = 0.9479 and p = 0.3802, respectively).

Table 3: Parameter estimates from ordinal logistic regression using osteoarthritis severity status as response with four ordered categories

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity=3</td>
<td>-2.43</td>
<td>1.256</td>
<td>0.0528</td>
</tr>
<tr>
<td>Severity=2</td>
<td>-0.25</td>
<td>1.229</td>
<td>0.8410</td>
</tr>
<tr>
<td>Severity=1</td>
<td>3.67</td>
<td>1.276</td>
<td>0.0039</td>
</tr>
<tr>
<td>BMI</td>
<td>0.002</td>
<td>0.033</td>
<td>0.9479</td>
</tr>
<tr>
<td>A1C</td>
<td>-0.081</td>
<td>0.093</td>
<td>0.3802</td>
</tr>
</tbody>
</table>

Table 4 contains odds ratios transformed from the ordinal logistic regression. For a one unit increase in BMI, the odds of OA severity is not affected because the OR is constant at 1. For a one unit increase in A1C, however, there is a 0.92 decrease in the odds of OA severity. Neither of these odds ratios are statistically significant (p = 0.9479 and p = 0.3802, respectively).

Table 4: Table of odds ratio from ordinal logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.00</td>
<td>0.94-1.07</td>
<td>0.9479</td>
</tr>
<tr>
<td>A1C</td>
<td>0.92</td>
<td>0.77-1.11</td>
<td>0.3802</td>
</tr>
</tbody>
</table>
CHAPTER 4:
DISCUSSION

This population-based study suggests that A1C levels were inversely associated with OA in weight-bearing joints, to include the knee and hip. Lower A1C was associated with more severe OA, though not statistically significant. There was no association between BMI and OA severity. The odds ratio in table 4 demonstrates that for a one unit increase in BMI, the odds of severe osteoarthritis is 1.002 greater when compared to the other osteoarthritis categories (which would be considered clinically insignificant). For a one unit increase in A1C, the odds of severe osteoarthritis is 0.92 lower when compared to the other osteoarthritis categories. BMI does not seem to be predictive of OA severity, whereas better control of diabetes (lower A1C) is associated with increasing severity of arthritis. In fact, using the standard definition of uncontrolled diabetes (A1c >8), table 2 shows the same association.

Although we have a small sample size (N = 220) and did not achieve statistical significance, this result is clinically significant because it suggests that worsening arthritis may be due to prescribed therapies which increase insulin to control glucose and is modulated by insulin resistance. The phenomenon of increased insulin resistance as body fat (BMI) increases has been described in the literature and attributed to the adipokine leptin secreted by fat cells (Courties et al., 2015; Simopoulou et al., 2007; Yadav et al., 2013). This means that as a person’s body fat increases, they produce more leptin, which increases insulin resistance, and therefore requires more insulin to keep their blood sugars under control. For example, if two obese diabetic patients have the same amount of body fat (BMI), the patient with better controlled blood sugars is likely to have more severe arthritis. These data support basic science literature that report that elevated insulin levels activate inflammatory pathways that worsen arthritis. They do not support the concept that worsening arthritis is due to hyperglycemia-derived systemic inflammation or mechanical stress on joints that increases with body weight.
Our study has several limitations that should be considered. As a result of the cross-sectional design, reverse causation cannot be excluded. Furthermore, cross-sectional studies capture one point in time (such as A1C in the past 12 months), but OA is a chronic, dynamic disease process that could be better understood in the context of trended A1C values. The VSSC database cannot generate an average A1C value or lifetime range of values, nor can it supply the date of diagnosis of diabetes and OA. Participants were a homogenous group of white males who were non-Hispanic/Latino. Other races, ethnicities, and genders were excluded, and therefore these findings may not be generalizable to the entire population. Gender was limited to males because female gender is associated with a higher prevalence and severity of OA, and the VHA patient population is predominantly male (Srikanth et al., 2005).

Hypertension is a risk factor for OA, however, we were unable to control for this variable because restricting SBP <150 and DBP <85 resulted in too small of a cohort. Cholesterol-lowering medications (statins) have anti-inflammatory properties which could mitigate OA severity, however, we were unable to control for hyperlipidemia for the same reason as hypertension (Courties et al., 2017; Kadam, Blagojevic, & Belcher, 2013). We are interested in T2DM because of the insulin resistance present in this disease (as compared to the insulin deficit that characterizes T1DM), however, the VSSC database cannot differentiate between T2DM and T1DM. Because T1DM is a disqualifying condition for military service, and T2DM is a disease that presents later in life, we would expect most participants to be T2DM patients.

The absence of weight-bearing joint imaging does not preclude a patient from having OA, and the VSSC Diabetes Cube does not include OA as a searchable diagnosis. This could have underestimated the prevalence of OA among our participants. OA is not an easy diagnosis to capture using ICD codes, which necessitated the need for chart reviews in search of weight-bearing imaging. 818 charts were reviewed to generate 220 study participants, however, time constraints precluded us from including more data that could have increased the power and statistical significance. This is also the reason that diabetes medications were not studied. Long-term use of metformin (which may prevent progression of OA by blunting inflammatory pathways) vs. other therapies (which may speed progression of OA via increase of total insulin load) is a topic which needs further study and may have affected the results of this study.
CHAPTER 5:
CONCLUSION

The results of our study, though non-statistically significant, suggest that better control of diabetes (lower A1C) is associated with an increased severity of OA in a dose-dependent manner. This is best explained by hyperinsulinemia and insulin resistance, assuming that the low A1C values result from insulin resistance that stimulates high endogenous insulin levels or requires exogenous insulin therapy to control blood glucose. This phenomenon is well-described in the basic science literature. Our results do not support hyperglycemia-derived systemic inflammation or mechanical stress on joints from overweight and obesity as important determinants of OA severity in our study population.

Given the detrimental effects of insulin resistance on OA, future research should focus on treating patients with T2DM and OA with exercise and other therapies aimed at improving insulin resistance. Physical activity is known to have a positive impact on glucose homeostasis in terms of improved insulin sensitivity (even in the absence of weight loss) (Dela, Prats, & Helge, 2014). It is also recognized as an important way to manage OA, although involvement of the hip or knee makes this therapy especially challenging (Bruyère et al., 2014).

Based on our results, it is plausible that diabetic patients with OA who are treated with insulin (or other drugs that increase total insulin load) could have worse OA than those who are treated with other therapies. Therefore, it would be good to compare OA phenotypes among T2DM patients on insulin vs. metformin vs. other diabetes drugs. This could help to identify potential disease modifying drugs, such as metformin, which has already shown promise in preliminary studies of its use for this purpose.
REFERENCES


