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Risk optimization of periprosthetic joint infection in the diabetic patient

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Thesis

**RISK OPTIMIZATION OF PERIPROSTHETIC JOINT INFECTION IN THE
DIABETIC PATIENT**

By

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ABSTRACT

Background

The lifespan of the US population is increasing with many people remaining active throughout their extended years. Often, when burdened with osteoarthritis, people will eventually look to a total joint arthroplasty (TJA) for relief of their symptoms and as a way to remain active. While it is a relatively routine operation, it has associated risks, especially in those who are diabetic. Diabetic patients are at an increased risk of developing periprosthetic joint infections (PJI), a costly complication with high morbidity and mortality.

Literature Review

Those with diabetes have a higher incidence of PJI after a TJA. The combination of a hyperglycemic state in the perioperative period and the ideal habitat for infection with the prosthesis harbors the increased risk. Often studies have been conducted retrospectively to gain a better understanding of the glycemic control required to reduce the risk but none have identified a definitive threshold. A clear threshold of glycemic control must be established through a prospective study that can strategically collect data to then minimize the risk of PJI in diabetic patients.

Methods

This proposed study is a longitudinal cohort study that will track participants from their preoperative planning appointment for their TJA through two postoperative years. It will analyze two groups, one with known type 2 diabetes and one without diabetes. After analysis of the set time points at which both hemoglobin A1c and blood glucose are measured, a clear and safe threshold for glycemic control will be able to be defined for diabetic patients.

Conclusion

If a clear threshold can be identified from the proposed study that was deemed safe for those with diabetes to stay within in order to minimize risk of PJIs, then the results may be applied to a secondary study. This next study would test the identified threshold of glycemic control. This study aims to help decrease the economic and physical burden of PJIs.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS.....	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	vii
LIST OF TABLES.....	ix
LIST OF FIGURES.....	x
LIST OF ABBREVIATIONS.....	xi
INTRODUCTION.....	1
Background.....	1
Statement of the Problem.....	2
Hypothesis.....	3
Objectives and Specific Aims.....	3
REVIEW OF THE LITERATURE.....	4
Overview.....	4
Existing Research.....	13
METHODS.....	19
Project Design.....	19
Project Population and Sampling.....	19

Exposure Groups.....	21
Project Variables and Measurement Tools	21
Recruitment.....	22
Data Collection	22
Analysis.....	23
Timeline and Resources	23
Institutional Review Board	24
CONCLUSION.....	25
Discussion.....	25
Summary	26
Clinical and/or Public Health Significance.....	27
REFERENCES	28
CURRICULUM VITAE.....	33

LIST OF TABLES

Table 1. Risk factors for PJI 18–20	6
Table 2. BMI Classifications	7
Table 3. Participant Criteria for the Diabetic Group.....	20
Table 4. Participant Criteria for the Non-Diabetic Group	20

LIST OF FIGURES

Figure 1. MSIS 2018 PJI Criteria ³¹	10
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LIST OF ABBREVIATIONS

AAOS.....	American Academy of Orthopedic Surgeons
ADA.....	American Diabetes Association
BMI.....	Body Mass Index
BUMC.....	Boston University Medical Center
CDC.....	Centers for Disease Control
CGM.....	Continuous Glucose Monitor
CRP.....	C-Reactive Protein
DM.....	Diabetes Mellitus
ESR.....	Erythrocyte Sedimentation Rate
FBG.....	Fasting Blood Glucose
HbA1c.....	Hemoglobin A1c
HR.....	Hazard Ratio
INSPIR II.....	Integrated Network for Subject Protection In Research
IRB.....	Institutional Review Board
LE.....	Leukocyte Esterase
MSIS.....	Musculoskeletal Infection Society
NSAID.....	Non-steroidal Anti-inflammatory Drug
OA.....	Osteoarthritis
OGTT.....	Oral Glucose Tolerance Test
PJI.....	Periprosthetic Joint Infection
POD.....	Postoperative Day

RA.....Rheumatoid Arthritis
RBC.....Red Blood Cell
THA.....Total Hip Arthroplasty
TJA.....Total Joint Arthroplasty
TKA.....Total Knee Arthroplasty
US.....United States

INTRODUCTION

Background

The incidence of total joint arthroplasty (TJA) is increasing due to the continually aging population in the United States (US).^{1,2} Along with the rise in the number of procedures is also an increase in complications with periprosthetic joint infection (PJI) having the highest morbidity and mortality.³ PJI is an infection at or around the implanted prosthesis onto which microorganisms adhere to and flourish, sometimes utilizing biofilms or collections of microorganisms that utilize a protective matrix which serve to protect them from environmental stresses such as the host immune response, antibiotics, or disinfectants.

People undergo TJA for many reasons but the most common by far is osteoarthritis which is complicated by obesity, due to the increased stress on the joints. Obesity is also a risk factor for diabetes mellitus (DM), which is itself associated with many complications. DM is due to the loss of function of the β -cell located in the pancreas which impacts glucose regulation in the body. DM not only predisposes someone to poor wound healing but is also associated with increased risk of infection due to the resultant hyperglycemic state. Surgery commonly induces a hypermetabolic stress response, characterized by a period of hyperglycemia. This increase in blood glucose makes a patient more susceptible to developing an infection.^{4,5} The presence of a prosthesis due to a TJA also facilitates the development of an infection, as it is an optimal spot for an infection to prosper; as the prosthesis lacks circulation and thus, host defense.⁶

The diagnosis of PJI follows the musculoskeletal infection society (MSIS) criteria and includes a history and physical, synovial and serum assays, imaging, and possible intraoperative cultures. Infections of a TJA prosthesis can be classified in various ways, however, typically they will be distinguished as acute/early, delayed, or late, depending on the timing of the infection. The postoperative period at which these infections occur can typically be linked to a certain group of organisms responsible and help guide treatment options.⁷

Statement of the Problem

Patients with DM and who have had previous joint replacements are at an increased risk of developing PJI.⁸⁻¹² Spikes of blood glucose levels after surgery and poorly controlled DM predispose patients to PJI and thus, revision surgery. This leads to increased morbidity, total costs, and the combined economic burden of TJA and DM. Thus far, a particular blood glucose level has not been outlined as a recommended threshold for DM patients maintain in order to reduce risk of PJI development. Thresholds of hemoglobin A1c have been outlined but are controversial, as this measurement reflects the previous 3 months of glycemic control rather than the patient's current glycemic status.

Previous studies observing an association between PJI and blood glucose levels have been limited by retrospective data and inflexibility in choosing when and how frequent blood glucose checks are being conducted. As the number of TJA is expected to rise significantly, it is vital to ensure each patient is properly assessed and managed to

minimize risk. For DM patients, that means outlining a safe window of blood glucose levels that reduces their increased risk of developing a PJI.

Hypothesis

A definitive threshold of glycemic control can be established in diabetic patients undergoing a total joint arthroplasty by closely monitoring multiple variables including hemoglobin A1c, blood glucose, and incidence of periprosthetic joint infections.

Objectives and Specific Aims

The goal of this study is to track perioperative blood glucose levels of both diabetic and non-diabetic TJA patients and record the incidence of PJI. By doing this, the data can then be stratified to outline an optimal blood glucose level for diabetic patients to maintain in order to minimize the risk of PJI. HbA1c and blood glucose will both be monitored to create a more encompassing picture of the patient's glycemic status and ability to manage their condition. The information gathered from this study will then ideally be applied to observe if the defined blood glucose level does optimize risk of PJI.

Specific aims:

1. Accurately assess glycemic status of diabetic and non-diabetic patients in the perioperative period of a TJA.
2. Identify if there is a blood glucose threshold level that decreases risk of PJI in patients with DM.

REVIEW OF THE LITERATURE

Overview

Joint replacements were initially implemented for older patients (>65 years old) who had low activity levels related to joint pain and immobility. However, in recent years, the incidence of joint replacement among younger patients (<65 years old) is increasing.¹³ The average age of patients undergoing total knee arthroplasties (TKA) and total hip arthroplasties (THA) is 66 years old with the majority being of non-Hispanic white ethnicity.¹⁴ These procedures are being used more frequently in active patients of various lifestyles to preserve and/or improve quality of life. Projections show that from 2005 to 2030 there will be a 174% increase in demand for THA as well as a 673% increase in TKA.¹ This increase in demand corresponds to the aging population. The United States (US) Census Bureau estimates that by 2030, one in five people will be 65 years old or older.²

Osteoarthritis (OA) is a common condition that necessitates a joint replacement when conservative management is unsuccessful in controlling the patient's pain or disability. Conservative management may consist of weight loss, use of non-steroidal anti-inflammatory drugs (NSAID), joint injections, or bracing. OA is a degenerative arthritis that commonly affects the hip, knee, and wrist joints as a person ages. This disease wears down the cartilage within the joint spaces and elicits pain and discomfort. Common risk factors for OA outlined by the Centers for Disease Control (CDC) are obesity, female gender, advancing age, and joint injury or overuse.¹⁵ Total joint arthroplasties (TJA) are not limited to patients with OA, but are performed in patients

with other conditions such as rheumatoid arthritis (RA) and posttraumatic arthritis as well. RA is an autoimmune disease characterized by an inflamed synovium, or joint space, which then causes damage to the surrounding cartilage. Although RA is commonly seen in smaller joints, it can attack larger joints and cause significant pain which may require a TJA to provide relief. Posttraumatic arthritis occurs after injury to the joint such as ligament tears, bone fractures, or joint dislocations. If severe enough, treatment options may include TJA. These classifications of arthritis are common conditions for why patients present to their orthopedic surgeon when conservative management fails.

Accompanying the increase in TJA is an increased risk of peri- and post-operative complications such as prosthetic joint infection (PJI), hardware failure, thromboembolism, cardiovascular events, fracture, and/or nerve or ligament injury. Prosthetic joint infection is by far associated with the highest morbidity and mortality amongst TJA patients. There is a 6x higher risk of mortality after revision of a TKA due to PJI than aseptic complications.³ PJI is an extremely costly complication for the hospital and is projected to amount to \$1.85 billion in annual hospital costs by 2030 between THA and TKA.¹⁶ TJA revisions in the setting of PJI are more costly than revisions due to aseptic complications as they are often associated with long hospital stays and more frequent outpatient visits.¹⁷ There have been numerous risk factors outlined that are closely associated with PJI as demonstrated in table 1.¹⁸⁻²⁰ Proper management of these risk factors pre-, intra-, and post-operatively can greatly reduce morbidity and risk of PJI.

Table 1. Risk factors for PJI 18–20

Diabetes Mellitus
Obesity
Immunosuppression
Tobacco Use
Steroid Use
Depression
Frailty
Male Gender
Alcohol Abuse
Urinary Tract Infections
Rheumatoid Arthritis

Obesity is a common comorbid condition of patients undergoing TJA and is often objectified using body mass index (BMI), outlined in table 2. A high BMI is a significant risk factor for TJA as extra weight increases the load on joints and thus, leads to the development of OA. According to the American Academy of Orthopedic Surgeons (AAOS), each pound of body weight is calculated to place about 4-6 pounds of weight on a joint. The AAOS also argues that obese patients are at a 20x increased risk of needing a TKA than a patient with a healthy level BMI.¹¹ Coggon et al. found that people with a BMI ≥ 30 are 6.8x more likely to need a TKA and its been observed that if these patients are able to decrease their weight by 5kg or to within healthy limits, then about 24% of

TKA could be avoided.²¹ Increased BMI not only contributes to the need for TJA but also predisposes patients to diabetes mellitus (DM) and risk of revision of their arthroplasty. Hussein et al showed that obese and morbidly obese patients are more likely to experience adverse events associated with their procedures including PJI, likely from their diabetic status and malnourished state.²² More specifically, a BMI ≥ 30 is associated with an increased risk of infection.²³ Malinzak et al. identified the average BMI of those with recorded infections after TJA in their study was 32.8kg/m².¹²

Table 2. BMI Classifications

Body Mass Index (kg/m²)	Weight Status
<18.5	Underweight
18.5-24.9	Healthy weight range
25.0-29.9	Overweight
30.0-34.9	Class 1 obesity
35.0-39.9	Class 2 obesity
≥ 40.0	Class 3 obesity

DM is a condition with increasing prevalence amongst the US population and is accompanied by an increasing economic burden. It is often a comorbid condition that complicates not only people's daily lives but the procedures they endure. According to the CDC's national diabetes statistics report, there are about 37.3 million people with diabetes in the US which accounts for about 11.3% of the population.²⁴ Within the US, there is an average increase of about 1.4 million cases per year.²⁴ By 2050, the incidence

of DM is projected to increase from 1 in 10 adults to somewhere between 1 in 5 and 1 in 3 adults.²⁵ The increase in prevalence also contributes to the increasing economic burden of DM in the US. As of 2017, the cost of diagnosed diabetes and its associated complications in the US is estimated at \$327 billion.²⁴

The American Diabetes Association (ADA) utilizes fasting blood glucose (FBG) levels to aid in diagnosing diabetes. Generally, they state a FBG <100 mg/dl is within normal limits, 100-125 mg/dl is prediabetic, and ≥ 126 mg/dl is indicative of DM.²⁶ The concentration of blood glucose varies widely throughout the day so optimizing the time at which it is tested when trying to associate it with adverse outcomes of TJA is important. About 40% of patients will have some degree of post-operative hyperglycemia and typically, patients have their blood glucose sugars tested pre-operatively and on postoperative day (POD) 1.²⁷ In both non-diabetic and diabetic patients, 9pm on the day of surgery was observed to be the most sensitive for hyperglycemia levels when compared to multiple day of surgery time points as well as POD 1.²⁸ Hemoglobin A1c (HbA1c) is another measurement used to diagnose DM as well as assess glycemic control in a patient. It is a reflection of the previous 3 months of a person's glycemic status as it measures the amount of glucose attached to the hemoglobin on the red blood cells (RBC). The ADA defines an HbA1c of <5.7% as normal, 5.7-6.4% as prediabetic, and $\geq 6.5\%$ as diabetic.²⁶

Numerous complications accompany DM and without proper management of the disease, these can cause significant morbidity and mortality. DM is characterized by the dysfunction of the β -cell within the pancreas which leads to impaired insulin secretion

and thus, inadequate control of appropriate blood glucose levels. So, as the pancreatic β -cells continue to fail, resistance to insulin increases. Common complications of DM affect all major body systems such as renal, musculoskeletal, cardiovascular, ocular, and neurologic. Patients with DM are predisposed to nephropathy, retinopathy, atherosclerosis, poorly healing wounds, and neuropathy, amongst others. In diabetic patients undergoing surgery, there is increased concern for hyperglycemia. After surgery there is a chance for stress hyperglycemia in all types of patients, with or without diagnosed DM, as a body's natural response to the procedure. It is a hypermetabolic stress response which further impairs the body's ability to produce insulin to control blood sugars. This physiologic response greatly increases the risk of adverse outcomes in post-operative patients.⁴ Not only does the hyperglycemic state itself predispose patients to infections, but it has also been discovered that it impairs the phagocytic action of leukocytes.⁵

Proper classification while considering the timing of infection is also important in the diagnosis and treatment of PJI. Tsukayama et al. defines infection in his study of diagnosing TKA infection in four classifications. Type I involves a positive, yet unsuspected, culture during the operation, type II is an infection within the first postoperative month and is either superficial or deep, type III is a delayed infection from hematogenous spread, and type IV is late infection present for at least 4 weeks.²⁹ Another well-established classification system for PJI recommended by the musculoskeletal infection society criteria (MSIS) is the McPherson Classification of Periprosthetic Infection. This system considers the infection type, the systemic host grade, and the local

extremity grade while classifying infections within 4 weeks as acute and after 4 weeks as chronic. This classification system also further distinguishes acute infections as postoperative or hematogenous.³⁰ Hematogenous spread may arise from dental procedures or bacteremia within the respiratory system, skin, or urinary tract. In a simpler manner, infection can also be referred to as acute/early, or within 3 months, delayed, or 3-24 months postoperative, or late, after 24 months postoperative.

Major criteria (at least one of the following)		Decision	
Two positive cultures of the same organism		Infected	
Sinus tract with evidence of communication to the joint or visualization of the prosthesis			

Preoperative Diagnosis	Minor Criteria		Score	Decision	
	Serum	Elevated CRP <i>or</i> D-Dimer	2		≥6 Infected 2-5 Possibly Infected ^a 0-1 Not Infected
		Elevated ESR	1		
	Synovial	Elevated synovial WBC count <i>or</i> LE	3		
		Positive alpha-defensin	3		
		Elevated synovial PMN (%)	2		
		Elevated synovial CRP	1		

Intraoperative Diagnosis	Inconclusive pre-op score <i>or</i> dry tap ^a		Score	Decision	
	Preoperative score		-		≥6 Infected 4-5 Inconclusive ^b ≤3 Not Infected
	Positive histology		3		
	Positive purulence		3		
	Single positive culture		2		

Figure 1. MSIS 2018 PJI Criteria³¹

Diagnosis of PJI has been standardized using the MSIS and its major and minor criteria (Figure 1).³¹ The use of various biomarkers and assays are useful in detection of infection prior to surgery. However, the diagnosis is typically made clinically beginning with a detailed history and physical exam, specifically looking for signs of infection. Acute infection is typically characterized by effusion, erythema, increased pain, fever, warmth of the area, and presence of exudate or cellulitis. More delayed type infections can present in a more subtle fashion with prosthesis loosening or persistent pain. Known

risk factors may also increase one's suspicion for a PJI. Assays that can help determine the diagnosis often include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These tests have high sensitivity and negative results of both ESR and CRP are associated with a low chance of PJI.³² Testing for ESR and CRP levels is relatively inexpensive and, thus, recommended in patients with a painful TJA.

The diagnosis of PJI can be further evaluated with joint aspiration and a synovial fluid analysis. A white blood cell (WBC) count of $>3,000$ cells/ μL and neutrophil count of $\geq 80\%$ is consistent with the diagnosis of a PJI.³³ Joint aspirate can further be cultured, however, there is low sensitivity with this method and antibiotic regimens prior to aspiration can impact this result, potentially inhibiting the yield of some organisms for weeks to months.³⁴ Another inexpensive and quick method to aid in the diagnosis of PJI is leukocyte esterase (LE) test strips. A positive LE test and elevated joint WBC count are highly diagnostic and specific for PJI.³⁵ The diagnosis may also include use of a bone scan. It can be utilized in numerous ways, typically as a triple phase scan which includes radionucleotide imaging tagging for Technetium-99, Indium-111, and sulfur colloid or a WBC scan.^{34,36} If the diagnosis of PJI is uncertain, methods may turn to intraoperative techniques via cultures and gram stains.³⁴

Once diagnosed, treatment typically will involve debridement, antibiotic suppression, and implant retention, or DAIR, in acute and subacute infections. If unsuccessful or complicated by a deep, chronic infection, treatment options may include one or two stage reimplantation or even amputation. At this time, two stage revision arthroplasty is considered the gold standard for treatment of PJI which have failed

DAIR. The first stage includes removal of all hardware in the joint, debridement of the area, and replacing it with an antibiotic spacer while the patient undergoes 4-6 weeks of systemic antibiotic therapy. The second stage typically involves the removal of the spacer and replacement with a new prosthesis

PJI are complicated infections as the organisms that are typically responsible thrive using biofilms. Biofilms, a polymeric matrix that encompass the colonies of organisms, shields them from antimicrobials and increases the risk of resistance.³⁷ PJI are further complicated by a myriad of microorganisms including staphylococcus species, streptococci species, gram negative bacteria, and fungi which utilize the prosthesis as a growth medium.¹⁸ Prosthetics serve as an optimal spot for infection due to their lack of circulation and lack of host defense. In two thirds of cases, gram positive bacteria are the primary cause of infection.¹⁸ Often, early infections are caused by *Staphylococcus aureus* and/or gram-negative bacilli. Delayed infections are often caused by coagulase-negative staphylococci and/or *Propionibacterium acnes*.⁶ The type of microorganism can predict the response to certain treatment options. Microorganisms of low virulence, mainly non-staphylococcus species, in an otherwise healthy patient have typically respond adequately to more conservative treatment like DAIR.⁷ Others may progress to needing two stage revision.

Existing Research

Proper management of one's DM is vital to minimize the numerous complications associated with DM as well as minimizing the risk of adverse events with procedures. Multiple sources have demonstrated that DM increases the risk of PJI and that increasing blood glucose levels correlates with an upward linear progression of infection risk, however, a clear threshold value of blood glucose levels that patients should remain under when undergoing a TJA has not been established.⁸⁻¹²

Blood glucose screening is an important perioperative assessment to optimize the patient's recovery; 58.9% of the total TJA patients have been found to have DM or prediabetes.³⁸ It is not uncommon for patients to be found as having undiagnosed DM with Shohat et al. finding that 8.4% of patients had undiagnosed diabetes preoperatively. It should be noted that the rate of incidence of PJI in both patients with known DM and those with undiagnosed DM were similar at 1.6-1.7%.³⁸ Despite demonstrating the need for more utilization of broad DM screening in TJA patients, this study was conducted at a single institution and is not generalizable to the US population. It also lacked the data to show if diagnosing these previously undiagnosed DM patients had any correlation to risk reduction in their postoperative recovery.

Duensing et al. performed a large cohort study with an adequate follow-up period of ≥ 2 years which observed PJI risk in those with type 1 and type 2 DM. They noted an increased rate of PJI in those with diagnosed DM at 4.3% versus non-DM patients at 2.6%.⁸ When comparing the two DM groups to each other, their data demonstrated an almost doubled increased rate of PJI in those with type 1 DM at 7% versus 4% in those

with type 2 DM. When incorporating body habitus as a factor, obese patients with type 2 DM and underweight patients with type 1 DM were noted to be at a higher risk of PJI. Strengths of this study included its population size and stratification by type of diabetes diagnosis. Duensing et al. limited their data to a Utah-specific database and did not encompass a more generalizable population.

A different approach to deciphering patients with DM and their risk of PJI was conducted by Godshaw et al. who stratified by insulin-dependent diabetics and non-insulin-dependent diabetics.³⁹ To compare the two groups, two endpoints were used, a blood glucose of >200 mg/dL and occurrence of a PJI within one year of surgery. Insulin-dependent DM patients were observed to have postoperative blood glucose levels 70 mg/dL greater on average than their non-insulin-dependent counterparts. This also correlated to the higher prevalence of postoperative glucose levels of >200 mg/dL which included 63.84% of the insulin-dependent group compared to 20.83% of the non-insulin dependent group, putting the insulin-dependent group at a 5.2x higher risk of experiencing postoperative hyperglycemia. However, this included patients with poorly controlled DM, so when considering HbA1c and only comparing those with moderately controlled DM from the insulin-dependent group to the non-insulin-dependent group, their risk was only 4.5x greater. If stratifying by poorly controlled DM via HbA1c levels, the risk was 13.3x greater. They also noted a HbA1c threshold correlated with increased risk of hyperglycemia was 6.59% for the insulin-dependent group and 6.60% for the non-insulin-dependent group.³⁹ The data from this study further solidified that poorly controlled DM is associated with greater risk of postoperative hyperglycemia despite not

being able to correlate it with incidence of PJI. This study was limited by being a retrospective, chart reviewed study out of a single institution which limits its ability to be translated into the greater population.

The presence of both obesity and DM are established risk factors for the development of PJI. Jansen et al. studied 7181 TJA cases at an institution in Finland better establish correlation between obesity, DM, and PJI.⁹ They noted that preoperative blood glucose levels had no correlation with risk of PJI in any of their patients. When comparing risk associated with body habitus, morbidly obese patients had a 4.66% risk of PJI compared to 0.37% in those of a healthy weight, with over 50% of morbidly obese patients being male, a previously outlined risk factor. And aside from weight class, DM has been observed to double the risk of PJI with the greatest risk in those who are both morbidly obese and diabetic with a risk of about 9.8%, observed more in THA patients than TKA patients.⁹ Of note, patients with DM and a BMI of <25 had no incidence of PJI in this study. Patients who were diagnosed with DM after their TJA were demonstrated to not be at an increased risk of PJI. Of the patients without diagnosed DM, they were observed to have a greater risk of PJI when they recorded a postoperative blood glucose of 115-124 mg/dL or greater.

This study also focused more specifically on the infections. The authors noted that 52% of the PJI recorded amongst their patients occurred within 1 year postoperative.⁹ Of these infections, Staphylococcus aureus was responsible for 33% and coagulase-negative staphylococci as the second most common cause at 21%. Unfortunately, this study was conducted at a single institution in Finland and lacks generalizability to the US

population. It was also only able to outline a threshold range of blood glucose levels for non-diabetic patients. Their results may also have been complicated by patients with undiagnosed DM at the time of surgery as they did not perform FBG and oral glucose tolerance tests on all patients prior to surgery. Some of the postoperative glucose results were also noted to be performed at outside labs which resulted in excluded data.

Maradit Kremers et al. also demonstrated that hyperglycemia and DM increases one's risk of PJI after TKA.⁴⁰ However, they defined hyperglycemia as a blood glucose >180 mg/dL within 1 week of surgery whether that was pre or postoperative. Their data lacked consistency in set time points as postoperative blood glucose levels on POD 1 were only available for 22% of cases and only 45% of cases had a blood glucose value from within 1 week of surgery. Their analyses demonstrated that between DM patients and non-DM patients, hyperglycemia and its effect on the rate of PJI did not significantly differ. HbA1c levels and rate of PJI also did not have any significant correlation in this study. Of the 23% of patients who had a preoperative blood glucose level measured, those without diagnosed DM who were hyperglycemic preoperative day one were at an increased risk of PJI with a hazard ratio (HR) of 1.86 compared to those with DM who were hyperglycemic on preoperative day one with a HR of 0.09. Due to its limited access to data since it was a retrospective study, a number of patients lacked proper blood glucose monitoring or it was inadequately reported for use in the study which meant a small percentage of the patient's included in the study had adequate data points. The study was also limited to one institution despite it incorporating a large cohort. However,

they were able to assess more than one assessment of glycemic status with both blood glucose measurements as well as HbA1c.

Issues regarding HbA1c relate to its status as a reflection of the previous 3 months of glycemic control and not the patient's current glycemic status. However, it is still a useful measurement for gauging a patient's glycemic status, ability to manage their DM, and in the initial diagnosis of DM. A HbA1c of 7.5-7.7% or higher has been linked to a higher occurrence of PJI within one year of surgery.^{41,42} Of the complications observed in the Tarabichi et al. study, PJI was the only one noted to have a correlation with a higher HbA1c level.⁴¹ They determined a threshold level of 7.7% was the most significant in determining occurrence of PJI versus the previously thought of 7%. When they utilized a HbA1c of 7.7%, incidence of PJI was shown to increase from 0.8% to 5.4%. Tarabichi et al. included 1645 diabetic patients in their study who averaged a HbA1c level within 3 months of surgery of 6.6%.⁴¹ This study excelled in collecting data from multiple institutions, however, it was retrospective in nature which limited its ability to collect specific and unique data points, lacking more supportive data on glycemic status aside from HbA1c levels such as FBG.

Kheir et al. conducted a retrospective study which included almost 25,000 arthroplasty cases in order to determine if blood glucose levels had a correlation to infection risk. However, only a little over 13,000 cases had a substantial follow-up period of ≥ 1 year. They determined a positive linear trend between blood glucose levels ≥ 115 mg/dL and rate of infection.¹⁰ They defined a threshold blood glucose of 137 mg/dL for decreasing risk of PJI at one year postoperative using the Youden index. Importantly it showed a

relative risk of PJI of 2.39% in diabetics versus 1.46% in non-diabetics.¹⁰ Although this study was able to set a blood glucose threshold for perioperative patients, it was limited by being a retrospective study and lacked generalizability as it only analyzed patients from one institution. Since it was retrospective, it also lacked the ability to monitor blood glucose levels at multiple, specific time points throughout the patients' perioperative period and wasn't able to fully ensure it was using fasting blood glucose levels.

The existing studies fail to outline a clear threshold of blood glucose level within which patients with DM should strive to fall within to minimize their postoperative risk. Each study illustrates the heightened risk of infection in diabetics and even further delineates higher risk among those with DM. However, multiple studies have been limited due to their retrospective viewpoint, lack of multi-institutional analysis, and limited access to the proper data to define this threshold. The Endocrine society guidelines strongly recommend all patients undergoing surgery be assessed using FBG and HbA1c despite whether or not they already have a pre-existing DM diagnosis.⁴³

METHODS

Project Design

This prospective project will be a longitudinal cohort study to assess diabetic and non-diabetic patients undergoing a total joint arthroplasty (TJA). Throughout the perioperative phase, hemoglobin A1c (HbA1c), blood glucose levels, and incidence of PJI will be recorded.

Project Population and Sampling

Participants will be recruited from the Boston Medical Center orthopedic clinic which currently has three surgeons performing TJAs. The participants will be prospective TJA patients either undergoing a THA or TKA between ages 40 and 70 years old as the average age of patients undergoing TJA is currently 66 years old but the incidence of younger patients undergoing TJA is increasing.^{13,14} The population will include participants of varying race, ethnicity, socioeconomic status, and gender. Participants will then be split into the DM group and non-DM group. Those with DM must be formally diagnosed based on the ADA's guidelines which include a HbA1c $\geq 6.5\%$, a FBG $\geq 126\text{mg/dl}$, or an oral glucose tolerance test (OGTT) $\geq 200\text{mg/dl}$.²⁶ Exclusion criteria include prediabetes, a previous TJA, BMI $>40\text{kg/m}^2$, type 1 DM, and other metabolic conditions that may alter glucose metabolism (Tables 3 and 4).

Table 3. Participant Criteria for the Diabetic Group

Inclusion Criteria for DM Group:	Exclusion from DM group:
<ul style="list-style-type: none"> • DM diagnosis based on ADA criteria: <ul style="list-style-type: none"> • HbA1c \geq6.5% • FBG \geq126 mg/dl • OGTT \geq200 mg/dl • Age 40-70 years old 	<ul style="list-style-type: none"> • History of a TJA • Type 1 DM • BMI $>$40 kg/m²

Table 4. Participant Criteria for the Non-Diabetic Group

Inclusion Criteria for non-DM Group:	Exclusion Criteria for non-DM Group:
<ul style="list-style-type: none"> • Age 40-70 years old 	<ul style="list-style-type: none"> • Prediabetes • Other metabolic conditions • History of a TJA • BMI $>$40 kg/m²

Once participants meet the inclusion criteria, a sample of 679 total participants will be recruited. The DM group will include 136 patients while the non-DM group will include 543 patients. This will account for 80% power and an alpha of 0.05, knowing that the literature has demonstrated a prevalence of PJI in non-DM patients to be roughly 0.5 - 2% compared to those with DM with a prevalence of 1.6 - 4.7%.^{9,44} It also assumes that about 20% of patients undergoing a TJA have DM.³⁸

Exposure Groups

In this observational, prospective study, two groups of participants who meet the study's inclusion criteria will be closely followed throughout their TJA perioperative period. The first group will be participants with diagnosed type 2 DM and the second group will be those without diagnosed DM. Participants with DM will continue to control their DM with lifestyle measures or medications throughout the study as recommended by their primary care provider or endocrinologist.

During the study both groups will have their HbA1c measured at their pre-operative appointment and then post-operatively at set points. Blood glucose will also be measured pre- and postoperatively at set timepoints. Glucose measurements will be monitored using a continuous glucose monitor (CGM) so it can provide real time measurements as well as averages of glycemic control between appointments.

Project Variables and Measurement Tools

Throughout this study, three key variables will be monitored: HbA1c, blood glucose, and incidence of PJI. HbA1c will be assessed at the pre-operative appointment and then post-operatively at the 90 day, 6 month, 12 month, and 24 month appointments. Blood glucose levels will be assessed at the pre-operative appointment, the morning of surgery, 9pm on the day of surgery, and post-operative days 1 thru 7 at 7am and 9pm. Following the initial postoperative week, CGMs will be utilized to track and record blood glucose level averages between appointments. Participants will attend follow up appointments post-operatively at 90 days, 6 months, 12 months, and 24 months.

Throughout the 24 month course of the participant's recovery, incidence of PJI will be recorded directly from the clinicians.

Recruitment

Participants will be enrolled from the orthopedic clinic at Boston Medical Center which currently has three surgeons performing TJAs. These surgeons and their physician assistants who work with TJA patients will be advised regarding the new study and will enroll their patients as patients are willing to do so and fit the study's participant criteria. Participants will be given a handout that explains the study and outlines the expectations for their perioperative period as a participant. Given the large sample size, it is anticipated that recruitment will be carried out over several years.

Data Collection

As new patients are enrolled into the study via their providers, they will be coded into the system so their data can be filed. The data will file into a secured system that will allow the research team to access all variables. Providers may update the participants' profiles in the system as they are seen for their TJA visits. To ensure updates on the participant's status, a reminder will be placed on the electronic medical record of each participant to prompt the providers to enter the required information. If a PJI is diagnosed during the two year post-operative period, it will flag in the EMR for collection by the research team. All information will remain confidential and the data will be backed up using a cloud system.

Analysis

The main outcome of this study will be the incidence of PJI in participants. In order to assess for an increased incidence of PJI in those with DM as seen in other studies, we will conduct a chi-square test between incidence of PJI and participants with DM.^{9,44} The occurrence of those with PJI in each group after 24 months postoperative will also be stratified and compared.

Mean and standard deviations will be conducted for blood glucose and HbA1c at each timepoint for both study groups. A t-test will then be utilized to see if there is a significant difference in blood glucose levels in those with a reported PJI versus those without.

Further analysis will assess for ranges of blood glucose measurements that may be associated with an increased incidence of PJI. This would include a chi-squared test looking at incidence of PJI and blood glucose levels in various increments: 100-139 mg/dl, 140-179 mg/dl, 180-219 mg/dl, and ≥ 220 mg/dl.

Timeline and Resources

Patients will be approached and informed about the study during their surgical planning appointment. If the patient meets the participant criteria and expresses willingness to participate, they will be followed from the time of their surgical planning appointment through a two-year postoperative period. This study window has been chosen as most PJI occur within the first two postoperative years, usually in the early and delayed timeframes.^{45,46} It is anticipated that the study will take place over the course of a

few years to allow time for ample participant recruitment with the understanding that all participants are followed for two years.

Each participant will be equipped with a CGM. CGMs are wearable devices with sensors beneath the skin that track and record real time glucose measurements. They have the ability to connect to smart devices and allow for providers to better analyze their patients' glycemic control.

To execute this study, the required team would include clinical and research staff. The clinicians would be comprised of the total joint surgeons as well as their advanced practice providers who will play a vital role in patient care and data collection. The research team would consist of a primary investigator, study coordinator, statistician, and research assistants who will all work collaboratively facilitating the study and analyzing the data.

Institutional Review Board

This study will require approval from the Boston University Medical Campus (BUMC) Institutional Review Board (IRB) prior to enrolling participants. Through the BUMC IRB, an application will be submitted to the Integrated Network for Subject Protection In Research, or INSPIR II. This project will be proposed for expedited review under category 2 in section 10.2.2.4.1.2 for necessary blood draws such as HbA1c and blood glucose analysis as well as category 11 in section 10.2.2.4.1.3 for any joint aspirations needed to help diagnose PJI. Once approval is granted, total joint providers may start recruiting their patients into the study.

CONCLUSION

Discussion

This study is aimed to promote a safer procedure for diabetic patients who are striving to maintain an active and healthy lifestyle rather than being burdened by PJI's. There are advantages that come with this proposed study when comparing it to the previous literature that evaluated PJI's in diabetic patients. This study is designed in a longitudinal cohort fashion that allows for a prospective study. With this design, it can be tailored to encompass all of the necessary data required to support the hypothesis that a safe, definitive threshold of glycemic control can be accurately established. This will include a myriad of timepoints both pre- and postoperatively through a 2 year postoperative period. It will consider both blood glucose and HbA1c for a more encapsulating glycemic picture.

Another advantage is its incorporation of CGMs. These devices will standardize the way blood glucose is measured. They will also allow for a better picture of glycemic control between appointments. CGMs have the ability to remotely connect to various devices and will provide ease of access to data. This study design is advantageous as some previous studies have had participants using various labs for testing which can potentially skew data.

Like many studies, this design does come with its limitations that are important to note. Through its design, the study only considers patients of Boston Medical Center's orthopedic clinic. This single institution, although with a diverse patient population, will lack generalizability to the entire population. Another limitation of the study is its large

sample size. Due to this, it may take longer to recruit participants. Other special considerations to note are the compliance of participants. It is recognized that the study period of over two years is a long duration which may result in some loss to follow up participants or dropouts. Contrarily, it is also possible that simple participation in the study may yield lower rates of PJI due to participants better managing their blood glucose secondary to the monitoring associated with the study.

Summary

The number of people undergoing TJAs is increasing, especially with the aging population. People are remaining more active for longer and TJAs can help improve their quality of life while retaining their activity levels. The increase in TJAs comes with a concurrent increase in adverse outcomes with PJI having the highest morbidity and mortality. PJIs can be complicated by numerous factors with DM being one of the most significant factors. DM is also on the rise in the population, accounting for just over 10% of people in the US.²⁴

It is imperative that efforts are made to counteract the adverse outcomes of TJAs to promote a healthier patient population. Previous research has often been limited by the use of retrospective data. It prevents them from developing a study design that thoroughly encapsulates the glycemic picture of these patients. This study will assess glycemic control as a whole, considering both blood glucose measurements and HbA1c at numerous, set time points throughout the perioperative period. Through the use of CGMs, glycemic control can be monitored at any time and give the providers a sense of their

patient's status between appointments. It controls how blood glucose is monitored amongst participants. This study has the ability to inform a secondary study that will test and confirm the outlined glucose threshold that minimizes risk of PJIs.

Clinical and/or Public Health Significance

As the population is extending its longevity and people are remaining more active for longer, it is important that the medical field helps maintain quality of life in the population. People are having TJA operations younger and more frequently while the rates of DM are also increasing within the population.^{1,13,24} So ensuring the influx of TJAs continues on a safe trajectory while limiting adverse outcomes is imperative.

The economic burden of PJI is large and often due to longer hospital stays and more frequent outpatient follow-up. This complication of TJAs is often associated with DM and can be painful and disabling. Outlining a safe glycemic threshold could, in turn, lower the incidence of PJI and reduce the costs associated with these patients while promoting active lifestyles. The safe glycemic window outlined in this study can be able to further be applied to an additional study in which the proposed glycemic window is directly tested.

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CURRICULUM VITAE



