A Thesis

entitled

Increased Complications and Healing Time in Diabetics with Distal Tibial Fractures

by

Isabel Robinson

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the

Master of Science Degree in

Biomedical Science

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An Abstract of

Increased Complications and Healing Time in Diabetics with Distal Tibial Fractures

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This is a case series study looking at the surgical outcomes and healing times of distal tibial fractures in diabetic patients. There were 31 diabetic patients reviewed and 161 non-diabetic patients set as the control group. The complications, outcomes, and BMI were examined in this study. It was seen that diabetics had more complications with the healing of their distal tibial fractures and lesser positive outcomes. Within the diabetic patient group, about 50% of them were obese according to BMI. This information should be further investigated. Diabetes is a disease that affects bone healing and slows and/or complicates the process. The results of this study reveal that new approaches should be taken for treating diabetic patients with distal tibial bone fractures. This study provides information that should be used for further research.
Table of Contents

Abstract ...................................................................................................................... iv

Table of Contents ...................................................................................................... v

List of Tables .............................................................................................................. vii

List of Figures .......................................................................................................... viii

List of Abbreviations .............................................................................................. ix

List of Symbols ........................................................................................................ x

1 Introduction .............................................................................................................. 1

2 Methods .................................................................................................................. 3

2.1 How the Subjects were selected ........................................................................... 3

2.2 Study Procedure ................................................................................................. 6

2.3 An Explanation of the Parameters ...................................................................... 8

2.4 Data Analysis ...................................................................................................... 8

3 Results ..................................................................................................................... 10

3.1 Incidence ............................................................................................................. 10

3.2 Fracture Types Seen ......................................................................................... 11

3.3 Outcome of Fractures ....................................................................................... 12

3.4 Complications During Healing ......................................................................... 13

3.5 BMI ................................................................................................................... 13

3.6 Medications and Comorbidities ....................................................................... 17

4 Discussion .............................................................................................................. 20

5 Conclusion ........................................................................................................... 25
References ........................................................................................................................................... 26

A Diagnosing Diabetes ......................................................................................................................... 28
List of Tables

Table 1. A list of the demographic factors for the diabetic and non-diabetic group .......7

Table 2. The fracture type distribution for the diabetic and non-diabetic group as well as
the number of open and closed fractures seen ........................................11

Table 3. A list of Anti-Diabetic drugs how many patients from each group were
on each drug........................................................................................................18

Table 4. A list of Anti-osteoporotic drugs and how many patients from each group were
on each drug........................................................................................................18

Table 5. A list of the comorbidities seen amongst the patients and how many patients
from each group had the comorbidities listed......................................................19
List of Figures

Figure 1. AO Orthopaedic Surgery Reference Classification for distal tibial fractures ...4

Figure 2. AO Orthopaedic Surgery Reference Classification for distal shaft tibial fractures............................................................................................................................................................................................5

Figure 3. Incidence rate depicting the number of diabetic patients and non-diabetic patients with a distal tibial fracture...........................................................................................................................................10

Figure 4. Outcome distribution for both the diabetic group and the non-diabetic group........................................................................................................................................................................................................12

Figure 5. Complication distribution for both the diabetic group and the non-diabetic group........................................................................................................................................................................................................13

Figure 6. BMI distribution for both the diabetic group and the non-diabetic group.......14

Figure 7. Complication distribution for the non-diabetic group based on BMI...............................................................................................................................15

Figure 8. Complication distribution for the diabetic group based on BMI......................15

Figure 9. Outcome distribution for the diabetic group based on BMI.........................16

Figure 10. Outcome distribution for the non-diabetic group based on BMI..................17
List of Abbreviations

HbA1c .......................Hemoglobin A1c
FPG ..........................Fasting Plasma Glucose

BMI ..........................Body Mass Index

UTMC ......................University of Toledo Medical Center

ADM .........................Anti-Diabetic Medications
AOM .........................Anti-Osteoporotic Medications
List of Symbols

mg ........................................... milligrams

dL ........................................... deciliters

% ........................................... Percent
Chapter 1

Introduction

In 2014, over 29 million people (9.3% of the population) were documented as diagnosed diabetics in America.\textsuperscript{1} Individuals with diabetes have an increased risk of fracture due to diabetic symptoms and the effect that their medications have on their bone health.\textsuperscript{2} Diabetic symptoms like blurry vision, numbness in the limbs, fatigue and increased risk for comorbidities like hypertension can increase the fracture risk.\textsuperscript{3} Diabetes has an association with collagen defects, like decreased collagen concentration, defective crosslinking in the collagen leading to wrongly structured and incorrectly organized bone that decreases bone quality.\textsuperscript{4}

In this study, I examine the outcomes and complications that occur in distal tibial fracture healing of diabetics and non-diabetics treated at the University of Toledo Medical Center. I suggest that there are greater complications and lesser progressive outcomes for the diabetic group. I also thought it would be interesting to look at BMI for each group and the outcomes and complications that occurred in each BMI group for both the diabetics and the non-diabetics. I propose that this study will show that the individuals with a more complicated healing process were obese diabetic individuals. This information can be used for future studies.

There are three stages of the bone healing process: Inflammation, Repair, and Remodeling.\textsuperscript{5}
During inflammation the nearby blood vessels rupture and a hematoma around the fracture forms. There is also necrosis of the ends of the bone that are fragmented due to a lack of blood supply. This causes the release of cytokines, which initiate an inflammatory response. Inflammatory cells are called to the fracture site: Polymorphonuclear neutrophils, macrophages, lymphocytes, and monocytes. Fibroblasts also infiltrate the area and this begins the process of tissue granulation, micro-vascularization, and migration of mesenchymal stem cells, which will differentiate into osteoblasts via direction from osteoinductive growth factors like BMP-2 and TGF-β1.\(^5\) During the reparative stage, fibroblasts form a periosteal callus (soft callus) along the edge of the fracture site. Endochondral ossification transforms the soft callus into a hard callus (woven bone). This, as well as calcification, help to stabilize the fracture site. The last stage is remodeling, which converts the woven bone (hard callus) that has been laid down to lamellar bone, which is much more organized. The medullary cavity is reorganized/rebuilt, and the bone is restructured in response to the stress and strain placed on it.\(^5\)

Other studies have shown that there are greater complications for diabetics with healing fractures in other bones (i.e. ankles and hips).\(^6,7\) However, the effect that diabetes has on healing of distal tibial fractures has not been presented. Currently the long bone that has the greatest fracture incidence is the tibia.\(^8\) This study indicates that patients with diabetes have a greater chance of complications during their fracture healing process and either experience delayed unions or mal-unions more often than non-diabetic individuals. There currently is no protocol designed for treating diabetic patients with distal tibial fractures. Therefore, the approaches taken to achieve union of their fracture should be tailored to their diabetic condition.
Chapter 2

Methods

2.1 How the subjects were selected

A list of patients who were treated by the University of Toledo Medical Center was provided. These patients had experienced Orthopaedic issues in their distal tibia between the years of 2008 and 2015. All patients were reviewed and of the 553 patients, there were 161 non-diabetic patients and 31 diabetic patients who had experienced a distal tibial fracture. Distal tibial fractures were determined using the AO Orthopaedic Surgery Reference. Figure 1. depicts the classification for distal tibial fractures. The fractures are different based on whether the fracture occurs outside of articular space (in the metaphysis), partially within, or completely within the articular space. Also the shape and complexity of the fractures are differentiated as well. Included in this study are distal-shaft fractures that occurred in the distal end of the shaft, but extended into the extra-articular region of the distal tibia. Figure 2. depicts the classification for shaft fractures.
Figure 1. Classification for Distal Tibial Fractures. Going down a column reveals the location of the fracture. Going across a row reveals the complexity of the fracture: simple/pure split, two line fracture (wedge) or more than one fragment, and many fracture lines or multiple fragments.  

\[\text{Figure 1. Classification for Distal Tibial Fractures. Going down a column reveals the location of the fracture. Going across a row reveals the complexity of the fracture: simple/pure split, two line fracture (wedge) or more than one fragment, and many fracture lines or multiple fragments.}^{16}\]
Figure 2. Classification of Distal Shaft Fractures. Going down a column reveals the complexity of a specific type of split/fracture: whether the fracture had a simple split, a two line split or multiple lines creating a fragmented fracture.\textsuperscript{16}

Another key difference between fractures is whether the fracture was open or closed. An open fracture occurs when the bone fragment(s) breaks through the skin and other soft
tissues. A closed fracture is when the bone is fractured, but the fragments do not break through skin or soft tissue.

The non-diabetic patients were set as the control group. To determine if an individual was diabetic, I looked at the transcriptions from the patient’s visits, which sometimes stated very clearly if the individual had diabetes. I confirmed this by looking at the HbA1c levels. I went with the criteria used by the American Diabetes Association, which is a percentage equal to or greater than 6.5%. I also looked at Fasting Plasma Glucose levels to further confirm. UTMC’s standard was set at any amount over 100mg/dL was an indication of diabetes. Any individual who had a HbA1c level lower than that or had transcriptions that clearly stated they were a non-diabetic were added to the list of non-diabetic patients in the control group. To determine the fracture type, I consulted the operative report as well as the x-rays to determine whether it was distal, proximal, or a shaft fracture. I also used this to determine whether it was open, closed, and what type (i.e. 43 A1 or 43 B2, etc.).

2.2 Study Procedure

In order to get a complete understanding of each patient’s case, I gathered different factors from their time as a patient at UTMC. The factors were date of the incident, cause of fracture, age, gender, race, BMI, medications used, smoker or not a smoker, comorbidities, HbA1c percentages, FPG levels, location and type of fracture, the type of fixation used, the outcome (non-union, mal-union, delayed union, or normal union), if infections were developed (osteomyelitis or soft tissue, whether a bone graft was done, “other complications (i.e. development of arthritis), and revisions.
This was done for both the diabetic group and the non-diabetic control group.

Table 1 shows the demographics for both groups that were documented. There were 11 diabetic males, 20 diabetic females, 88 non-diabetic males, and 73 non-diabetic females. The age range for the diabetic group was 13 to 96. For the non-diabetic group, the ages ranged from 12 to 91. There were 7 African American diabetics, 11 African American non-diabetics, 1 Asian non-diabetic, 13 Caucasian diabetics, 95 Caucasian non-diabetics, and 2 Hispanic non-diabetic patients. In the Diabetic group there were 8 smokers, 16 non-smokers and 7 former smokers. In the non-diabetic group there were 45 smokers, 56 non-smokers, and 9 former smokers.

Table 1. Factors recorded for both Diabetics and Non-diabetics. This table reflects the demographics of both populations: Gender, Age, and Race. Also shows the number of patients who smoke, do not smoke, and used to smoke.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Diabetics</th>
<th>Non-Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>11</td>
<td>88</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>73</td>
</tr>
<tr>
<td>Age: 0-12yrs</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Age: 13-19yrs</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Age: 20-29yrs</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Age: 30-39yrs</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>Age: 40-49yrs</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>Age: 50-59yrs</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Age: 60-69yrs</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Age: 70-79yrs</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Age: 80-89yrs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Age: 90 or older</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>African American</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Caucasian</td>
<td>13</td>
<td>95</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Smoker</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>16</td>
<td>56</td>
</tr>
<tr>
<td>Former Smoker</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>
2.3 An Explanation of the Factors

Cause of the fracture refers to how the fracture occurred.

BMI is the Body mass index. Underweight is any BMI under 18.5, normal is 18.5-24.9, overweight is 25-29.9, obese is over 30.10

Medications used refers to Anti-osteoporotic medications (AOM) and Anti-diabetic medications (ADM)

Comorbidities are any relevant conditions that the individual has along with their fracture that would affect their healing process. This could be the condition itself or medications taken for it.

The type of fixation used refers to the hardware and technique for stabilizing the fracture (i.e. intramedullary rod or external fixator)

Non-union is for a fracture that has not healed, delayed union is for a fracture that is healing very slowly, union is a fracture that has correctly healed in a healthy time frame, and mal union is for fracture that have healed in an incorrect alignment.9

Osteomyelitis is an infection of the bone and soft tissue infections refer to infections occurring in the muscle, fascia, skin, etc.

Revision refers to whether the patient had to come back in for an adjustment or replacement of their hardware with a different option.

2.4 Data Analysis

This study was done to determine incidence rate and to compare the outcomes and complications that came up in both groups. In order to make relevant comparisons, I wanted to display specific findings between the diabetics and non-diabetics. I compared incidence, outcome (union, non-
union, mal-union, and delayed union), complications (infections, revisions, other conditions that developed), BMI, BMI for the complications, BMI for the outcomes, and medications. Only descriptive statistical analysis was done for this study.
Chapter 3.

Results

3.1 Incidence

The incidence rate reveals that of the 192 patients with distal tibial fractures, 16% of them were diabetic and 84% were non-Diabetic. This can be seen in figure 3. below.

Figure 3. Incidence rate: Depicts the percentage of diabetic patients and the percentage of non-diabetic patients who experienced a distal tibial fracture and were treated at UTMC. There were 31 diabetic patients (blue), which is 16% of the total distal tibial fracture patients. There were 161 non-diabetic patients (red), which is 84% of the total.
3.2 Fracture types Seen

In Table 2, depicted are the fracture types that were seen amongst both populations. Most common for both the Diabetics and non-diabetics was 42 A2: Oblique fracture of the distal end of the shaft that reached into the metaphysis. There were 9 open fractures and 20 closed fractures reported in the Diabetic group and 40 open and 74 closed fractures in the non-diabetic group, which can also be seen in Table 2.

Table 2. Fracture type seen in both groups. This table shows, which fracture types were present in both the diabetic and non-diabetic groups. Also seen is how many patients sustained an open or closed fracture.

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Diabetics</th>
<th>Non-Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>42 A1</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>42 A2</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>42 A3</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>42 B1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>42 B2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>42 B3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>42 C1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>42 C2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>42 C3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>43 A1</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>43 A2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>43 A3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43 B1</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>43 B2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>43 B3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>43 C1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>43 C2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>43 C3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Open</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>Closed</td>
<td>20</td>
<td>74</td>
</tr>
</tbody>
</table>
3.3 Outcome of Fractures

Next, I looked at the outcome of fracture healing for both groups. Seen in figure 4. is the distribution of the outcomes. Revealed is that in the diabetic group, the most common outcome was a non-union of the fracture. There were diabetic patients who were treated for up to 3 or 4 years for their fracture. However, for the control group (non-diabetics), the most common outcome was continued healing for the fracture. This means that the latest report in the patient records was done when the patient’s fracture was demonstrating a healthy pace for healing, but a follow up had not been done to see if their was a healed fracture. “Undocumented” is referring to the patients who did not have a reported outcome.

![Outcome Distribution: Diabetics vs. Non-Diabetics](image)

Figure 4. Outcome Distribution: Diabetics vs. Non-Diabetics. This graph depicts what percentage of patients in each group (diabetic and non-diabetic) that experienced each of the outcomes: mal-union, delayed union, non-union, continued healing, and union.
3.4 Complications during Healing

I then compared the complications that occurred in each group. In figure 5, the percentage of diabetics who experienced each complication is shown as well as for the non-diabetic group. The complication that occurred the most for the diabetic patients was revisions followed by soft tissue infections. The most common complication for non-diabetics was a development of osteopenia or osteoporosis. Very few diabetic patients experienced sclerosis of the tissue and bone grafting. The least common complication amongst the non-diabetic patients was sclerosis as well and also osteomyelitis.

![Complication Distribution: Diabetics vs. Non-Diabetics](image)

Figure 5. Complication Distribution: Diabetics vs. Non-diabetics. This graph is a depiction of the occurrence (in percentages) of each complication in both groups.

3.5 BMI

Additionally, I thought examining the BMI for each group would reveal interesting results. Figure 6 shows the BMI distribution for both the diabetic group and the non-diabetic group as well. It can be seen that over 50% of the diabetic patients were obese.
Close to 20% of non-diabetic patients were in the normal BMI while fewer than 10% of diabetics fell into the that category.

![BMI Distribution: Diabetics vs Non-Diabetics](image)

Figure 6. BMI Distribution: Diabetics vs. Non-Diabetics. This graph depicts the distribution of BMI in diabetic patients and non-diabetic patients. Over 50% of diabetic patients were obese.

Figures 7 and 8 show how many non-diabetics and diabetics of each BMI group experienced each of the complications. It can be seen that the patients that experienced each of the complications the most in the diabetic group were the obese individuals. In the non-diabetic group, it varied: the greatest number of revisions and occurrence of osteopenia/osteoporosis was with the obese patients, but normal needed bone grafts more often tied with the patients who’s BMIs were not documented.
Figure 7. Complication Distribution for Non-diabetics based on BMI. Each column represents a BMI group. The graph shows how many non-diabetics in each BMI group experienced each of the complications.

Figure 8. Complication Distribution for diabetics based on BMI. Each column represents a BMI group. The graph shows how many diabetics in each BMI group experienced each of the complications.
Figures 9 and 10 show that obese diabetic patients experienced non-unions the most and equal percentages of normal, obese, and undocumented patients experienced unions in their tibial fractures. As with the non-diabetics, there were more undocumented BMI groups that experienced non-union, continued healing, and union. However, the second greatest percentage for non-unions was seen in obese patients, overweight patients for continued healing, and obese patients for unions.

Figure 9. Outcome Distribution for diabetics based on BMI. Each column represents a BMI group. The graph shows how many diabetics in each BMI group experienced each of the outcomes.
Figure 10. Outcome Distribution for Non-diabetics based on BMI. Each column represents a BMI group. The graph shows how many non-diabetics in each BMI group experienced each of the outcomes.

3.6 Medications and Comorbidities

It is worth mentioning the medications that are being taken by the patients as well as their comorbidities because they may affect the bone health and fracture healing process. In Table 3, listed are the Anti-diabetic medication drug classes from the medical history for the diabetic patients: Biguanides, Sulfonylureas, Insulin, DPP-4 Inhibitors, GLP-1 receptor agonists, and Metglitinides.
Table 3. Anti-Diabetic Medications. There are 6 Anti-Diabetic drug classes listed as well as how many of both groups were taking them. Also noted is how many patients from both groups were not taking drugs for Anti-diabetes at all.

<table>
<thead>
<tr>
<th>Anti-Diabetic Medications</th>
<th>Diabetics</th>
<th>Non-Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Insulin</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metglitinides</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>5</td>
<td>155</td>
</tr>
</tbody>
</table>

I also documented the AOM that were being taken. The main Anti-Osteoporosis drugs that were seen were SERMS (Selective Estrogen-Receptor Modulators), Calcitonin, Vitamin D supplements, and Calcium supplements.

Table 4. Anti-Osteoporosis Medication. This table shows a list of Anti-Osteoporosis medications and the number of diabetics and non-diabetics that are taking each of them. You can also see the quantity from each group that is not taking any anti-osteoporosis medications.

<table>
<thead>
<tr>
<th>Anti-Osteoporosis Medications</th>
<th>Diabetics</th>
<th>Non-Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERMS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Calcium</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>24</td>
<td>119</td>
</tr>
</tbody>
</table>

Many of the patients in this study had one or more comorbidities along with their Diabetes. The non-diabetics also had comorbidities that are noted in Table 5. The comorbidities that were seen were Hypertension, Arthritis, Cancer, Multiple Sclerosis, Neuropathy, Guillain Barre Syndrome, Hyperlipidemia, Osteoporosis, Anemia, and Osteogenesis Imperfecta.
Table 5. Comorbidities. This table lists the comorbidities that were seen in the records of the patients who were diabetic and non-diabetic. Also seen are how many of each group have one or more of the comorbidities listed in the table.

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Diabetics</th>
<th>Non-Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Cancer</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Guillain Barre Syndrome</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Osteogenesis Imperfecta</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>4</td>
<td>75</td>
</tr>
</tbody>
</table>
Chapter 4.

Discussion

In this study, I explored the outcomes and complications that occurred in the fracture healing process of distal tibial fractures in Diabetic patients and non-diabetic patients (the control group). I also provided data on BMI’s affect on outcomes and healing time for both diabetics and non-diabetics as well as identified factors that could possibly contribute to outcome and healing time. The outcome for diabetic patients revealed that more experienced negative outcomes that lead to more revisions. There was a high percentage, about 52%, of diabetics who were obese in this study. Discovering that the diabetic group had greater negative outcomes than the non-diabetic group is seen in the percentages of non-unions and delayed unions that occurred in both groups: 50% of diabetics and 25% of non-diabetics had non-unions while 10% of diabetics and 3% of non-diabetics had delayed unions. The results of this study also show that there were a greater percentage of patients in the diabetic group who developed osteomyelitis, soft tissue infections, and compartment syndrome and had revisions than in the non-diabetic group. It should be noted that about 84% of the diabetic patients were using some type of ADM, which could potentially have an effect on the results. The results of this study are consistent with similar studies that have been done. In one study by Gehling et. al., diabetes had a negative impact on hip fractures leading to an
increase in complications and greater occurrence of surgical site infections.\textsuperscript{11} In the same study, discussed were the reasons for increased complications of ankle fractures. The authors stated that the issues arise from increased peripheral neuropathy and problems with the micro-vascularity around the fracture site.\textsuperscript{11} Another study concluded that there is increased delayed healing incidences in diabetic patients with closed fractures of the lower extremities.\textsuperscript{12}

Diabetes affects the bone fracture healing process in many different ways. Hyperglycemia leads to the formation of advanced glycation end products (AGEs). These glycosylated proteins cause damage to the nerves (neuropathy).\textsuperscript{13} With neuropathy there can be an increase in osteoclastic activity and thus cause osteopenia.\textsuperscript{13} Along with the glycosylated proteins, there is an increase in atherosclerotic plaque due to the hyperglycemic blood.\textsuperscript{13} This decreases vascularization to the periphery of the bones and therefore, there is a decrease in nutrients and oxygen leading to complications and delayed healing of fractures. This, in turn, can impair the ability for immune response cells to migrate into the fracture site and be able to clean up debris and bacteria and thus, infection can occur.\textsuperscript{13} In fracture healing, this information suggests that the initial stage of inflammation is impaired due to hyperglycemia. Literature shows that Diabetics have increased TNF levels.\textsuperscript{14} TNF is an inflammatory mediator that inhibits the differentiation of mesenchymal stem cells into Osteoblasts.\textsuperscript{14} One study proposed that during the soft and hard tissue formation, in diabetics, TGF-β1 and BMP-2 are not as strongly expressed.\textsuperscript{15} This could mean that the remodeling stage is impaired as well due to a lack of osteoblast differentiation thus a decrease in osteoblastic activity.
The effect that BMI has on the fractures has been explored in other studies. In one study, BMI was seen to affect the increased incidence of fractures in the lower leg. The authors concluded that due to the type of fall that occurs in obese individuals (backwards or sideways), there is twisting of the ankle leading to fractures in the ankle or distal tibia.\(^{16}\) In another study BMI and radiological and clinical outcome for tibial pilon fractures were not correlated. BMI did not affect the outcome of the fracture healing process except for the increase in superficial infection, operation and hospital time.\(^{17}\) This does still prove to be relevant because it is consistent with the results of the present study that show that there is an increase in infection and revisions, which could translate to increased hospital time. Another study states that obese diabetics did have increased markers for adipocytes, irregular bone marrow fat levels, and increased sclerostin (a protein that down regulates osteoblast activity). However, this was also seen in obese individuals who did not have diabetes.\(^ {18}\)

Taking medications into account is important because of the information that other studies have provided about their effect on bone. The results of the present study show that the majority of the patients used Biguanides (i.e. Metformin) and insulin. Stated in an article by Meier et al., Biguanides decrease the risk of fracture in diabetics.\(^ {2}\) With that being said, those patients’ results do not take away from the conclusion. Insulin is the second most common medication used in the diabetic population of this study. There is not a clear effect of insulin on fractures and bone health. In a paper from 2015, there were contradictions seen in how insulin affects bone mass and density.\(^ {19}\) Therefore there should be further investigation into this matter. The third most common drug used was sulfonylureas. Sulfonylureas do not have a negative or positive effect on fractures, but are
more so neutral and therefore do not create an issue in concluding the results of this study.\textsuperscript{2} Thiazolidinediones are the ADM that increase the risk of fractures in diabetics. However, there were no patients documented as users of this drug and therefore there is no need for analysis in this study.

The results show that only vitamin D and calcium supplements were used for the diabetic patients. Vitamin D does have an affect on bone health: it is needed for bone mineralization and maintaining bone health.\textsuperscript{20} Only 1 non-diabetic used SERMS and 1 used calcitonin. However, due to these very low numbers, anti-osteoporotic medications were not a focus in this study.

The most common comorbidity seen was hypertension amongst both groups. The diabetic group had a much greater prevalence of patients with hypertension (22 of 31) than the non-diabetic group (35 of 161). Diuretics are the drug class used for hypertension and result in excretion of calcium through the urine and greater osteoclastic activity.\textsuperscript{21} Greater osteoclastic activity leads to more resorption than formation. Excretion of calcium results in weakening of bone. However, comorbidities and the drugs used to treat them should be discussed in a separate paper, as that was not the focus of the present study. The data has been presented in the results section for future use.

The incidence rate of tibial fractures that occurred in diabetics is 16\% of the total distal tibial fractures that occurred in patients who visited UTMC. This percentage is high enough that it warrants attention. The focus for this population should be on the changes that can be made to protocols for distal tibial fracture treatment. Taking this into account and modifying how diabetics with distal tibial fractures are treated could help improve this process for diabetics altogether. Firstly, the medical costs could decrease by
decreasing the number of visits and revisions/surgeries to be done. Another aspect that could change is the overall experience for the patients: decrease inconveniences, decrease the number of complications that arise, thus decreasing the number of revisions, and possibly increasing the number of unions and decreasing the time to union.

This study reveals information that can be used in the future, however, since this is a retrospective cohort study with limitations there are factors that cannot be assessed. Though age, gender, race, and smoking status were all recorded, they were not the focus of this study and were therefore not analyzed to determine their role in the results. These variables could potentially affect the outcomes and complications that present themselves during the fracture healing process. Along with those, comorbidities and the medications taken for them could also determine the course of the healing process, but were not the emphasis of this study. The patients used for this study are those who visited UTMC between 2008 and 2016 and this contributes to the small sample size for the diabetic group. Another limitation is that there was information that was not documented for many of the patients and therefore those patients could not be included in some of the analyses. There were also inconsistencies in some of the administrative notes used to document patient records. Lastly, some patients did not have an X-ray to view and therefore their specific fracture location and type could not be documented.
Chapter 5.

Conclusion

Results indicated that the diabetic patients with distal tibial fractures had greater complications and increased healing times. This could be due to the effect that diabetes has on bone healing: increase in osteoclastic activity, decrease in osteoblastic activity, as well as neuropathy causing a decrease in vascularization to the fracture site. Though there are studies producing information on fracture healing for diabetics in with fractures in different bones of the body, this is the first study to provide information on the fracture healing outcomes for the distal tibial fracture in diabetics. This information could be used with future research to develop a protocol for treating distal tibial fractures obtained by diabetics.
References


Appendix A

Diagnosing Diabetes

There are two types of Diabetes: Type 1 and Type 2. Type 1 Diabetes results from the pancreas’ inability to produce insulin, which would normally work to remove the glucose from the blood stream. Type 2 Diabetes occurs when the body is unable to use insulin to remove the glucose from the bloodstream. According to the American Diabetes Association, in order to diagnose Diabetes, three tests should be done: Hemoglobin A1c (HbA1c) levels test, Fasting Plasma Glucose (FPG) levels test, and Oral Glucose Tolerance Test (OGTT). However, for this study, only HbA1c and FPG were examined. HbA1c is a measurement of blood glucose levels for the past 2-3 months. It looks at the amount of glycosylated hemoglobin in the bloodstream. A high percentage of glycosylated hemoglobin, over 6.5%, indicates a Diabetic condition. It gives an indication of how the body has been able to metabolize glucose and whether it has happened efficiently or not. This test in more recent years has become the gold standard for diagnosing Diabetes. FPG is a test done to determine the level of glucose in your bloodstream after 8 hours of fasting. A score of 126 mg/dl or higher indicates an individual with diabetes. This test is normally done more than once because the patient can alter the results: if the patient ate within the 8-hour timeframe. Additionally, if an
individual has gone to the hospital due to trauma or if they are simply an anxious person, their blood can show high blood glucose levels due to stress.\textsuperscript{3}