THE EFFICACY OF MAGGOT DEBRIDEMENT THERAPY COMPARED TO NON-SURGICAL CONVENTIONAL DEBRIDEMENT METHOD

BY

PIREHMA MARIMUTHU

A thesis submitted in fulfilment of the requirement for the degree of Master of Biobehavioral Health Sciences

Kulliyyah of Nursing
International Islamic University Malaysia

JULY 2020

ABSTRACT

Diabetic foot ulcer or DFU is a hard to heal chronic wound, quite resistant to conventional methods and mainly associated with foot complications such as infection, gangrene and lower limb amputations. Maggot debridement therapy, commonly known as MDT has been widely used for decades as an alternative tool in the debridement of chronic wounds to remove slough, necrotic tissue from the wound bed. However, comparison studies between MDT and conventional method in the treatment of DFU remained limited and inconclusive. The aim of the study was to evaluate the effectiveness of MDT using *Lucilia cuprina* in the treatment of DFU as compared to non-surgical conventional method based on slough percentage and size of ulcer on day 3, 6 ,9. The study was conducted in University Malaya Medical Centre (UMMC) on 110 adult diabetics with sloughy foot ulcer, less than 2cm deep and ankle brachial index (ABI) of 0.8 or higher. The patients were divided into 2 group whereby 55 in MDT group and 55 in conventional group. Slough percentage and size of ulcer were measured using the wound monitoring application, NDKare^{TM}. Data analysis with descriptive inferential statistics (Rm-ANCOVA) was performed using the Statistical Package for the Social Sciences Version 23. The result showed significant difference in slough percentage on day 3, 6 and 9 between both groups ($p<0.001$). Rapid reduction of slough on day 3, complete debridement achieved on day 6, 9 was observed with MDT whereas there was still 67.31% of slough on day 9 in the ulcers treated with conventional method. However, size reduction was not significantly different between both groups. Site of ulcer was shown to have significant relationship with slough percentage in the study. Due to the shorter time to debridement with MDT, it is highly recommended MDT to be integrated into the treatment protocol of DFU in the debridement of DFU to improve wound healing outcomes and prevent foot complications.

خلاصة البحث

قرحة القدم السكرية أو DFU يصعب شفاء الجروح المزمنة، وهي مقاومة تمامًا للطرق التقليدية وترتبط بشكل أساسي بمضاعفات القدم مثل العدوى والغرغرينا وبتر الأطراف السفلية. وتم استخدام علاج إنضار باليرقات، والمعروف باسم ايم. دي. تي. على نطاق واسع لعقود كأداة بديلة في تنضير الجروح المزمنة لإزالة الأنسجة الميتة والنيتروجينية من طبقة الجرح. ومع ذلك، ظلت دراسات المقارنة بين ايم. دي. تي. والطريقة التقليدية في علاج قرحة القدم السكرية (دي. ايف. يو) محدودة وغير حاسمة. وكان الهدف من الدراسة هو تقييم فعالية (ايم. دي. تي) باستخدام لوسيليا كوفرتينا في علاج قرحة القدم السكرية (دي. ايف. يو) مقارنة بالطريقة التقليدية غير الجراحية على أساس النسبة المئوية للقرحة وحجم القرحة في الأيام 3 و6 و9. وأجريت الدراسة في المركز الطبي بجامعة مالايا (UMMC) على 110 مريضًا سكريًا بالغًا مصابًا بقرحة القدم المتسللة، وعمق أقل من 2 سم ومؤشر الكاحل العضدي (ABI) يبلغ 0.8 أو أعلى. وتم تقسيم المرضى إلى مجموعتين حيث 55 في المجموعة ايم. دي. تي. و 55 في المجموعة التقليدية. وتم قياس النسبة المئوية للقرحة وحجمها باستخدام تطبيق مراقبة الجرح، NDKare™. وتم إجراء تحليل البيانات باستخدام الإحصائيات الاستدلالية الوصفية (Rm-ANCOVA) باستخدام الحزمة الإحصائية للإصدار 23 من العلوم الاجتماعية. وأظهرت النتائج فرقا معنويا في نسبة الانحدار في الأيام 3 و 6 و 9 بين المجموعتين (P <0.001). ولوحظ انخفاض سريع في المستنقع في اليوم 3، تم تحقيق التنضير الكامل في اليوم 6 ، 9 مع MDT في حين لا يزال هناك 67.31 ٪ من المستنقع في اليوم 9 في القرحات المعالجة بالطريقة التقليدية. ومع ذلك، لم يكن اختلاف الحجم مختلفًا بشكل كبير بين المجموعتين. وقد تبين أن موقع القرحة له علاقة معنوية بالنسبة المئوية في الدراسة. ونظرًا لوقت أقصر للتنضير باستخدام MDT، يوصى بشدة أن يتم دمج MDT في بروتوكول علاج DFU في تنضير DFU لتحسين نتائج التئام الجروح ومنع مضاعفات القدم.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Biobehavioral Health Sciences.

..……
Asst. Prof. Dr.Aniawanis Makhtar
Supervisor

..…….
Asst. Prof. Dr. Wan Mohd Azizi Wan Sulaiman
Co-Supervisor

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Biobehavioral Health Sciences.

……...
Asst. Prof. Dr. Norlinda Abd Rashid
Internal Examiner

……..….
Dr. Shams Amir Shamsul Bahar
External Examiner

This thesis was submitted to the Kulliyyah of Nursing and is accepted as a fulfilment of the requirement for the degree of Master of Biobehavioral Health Sciences.

……...
Assoc. Prof. Dr. Salizar Mohamed Ludin
Dean, Kulliyyah of Nursing

DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Pirehma Marimuthu

Signature ..... Date .....

INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

DECLARATION OF COPYRIGHT AND AFFIRMATION OF FAIR USE OF UNPUBLISHED RESEARCH

THE IMPACT OF MOBILE INTERFACE DESIGN ON INFORMATION QUALITY OF M-GOVERNMENT SITES

I declare that the copyright holders of this dissertation are jointly owned by the student and IIUM.

By signing this form, I acknowledged that I have read and understand the IIUM Intellectual Property Right and Commercialization policy.

Affirmed by Pirehma Marimuthu

…..…..……. ……
Signature Date

ACKNOWLEDGEMENTS

My utmost gratitude to God Almighty for giving me the strength, knowledge and ability to pursue and complete my postgraduate studies in IIUM, Kuantan. Without God's blessing, this research would not have been completed successfully.

I would like to take this opportunity to thank Kulliyyah of Nursing for providing the avenue to pursue my postgraduate study. I would like to extend my gratitude to my supervisor Dr Aniawanis and co-supervisor Dr Wan Azizi for their precious time, encouragement and guidance towards the completion of the research.

My heartfelt gratitude also goes to the study team in UMMC which was initiated by DrKantan, headed by Dr NikAizah and her orthopaedic team in Ward 8U & 9U. Also, my appreciation to the diabetic patients who participated in the study. Without the team and patients, it would have been impossible to conclude the research on time.

Last but not least, I would like to dedicate the research work to my parents Mr Marimuthu and Mrs Mariammah and my brother Mr Anbalagan for whom I owe my resilience and success in pursuing my education. To my dear husband, Mr Kunasegar and kids (Rohil & Maansi), there is no words to describe your love, patience, continuous support in granting me the space and time to pursue my postgraduate study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABI	Ankle-brachial index
ADA	American Diabetes Association
DFU	Diabetic foot ulcer
EWMA	European Wound Management Association
GCP	Good Clinical Practice
IDF	International Diabetes Federation
IIUM	International Islamic University Malaysia
KON	Kulliyyah of Nursing
MDT	Maggot debridement therapy
MREC	Medical Research Ethics Committee
NHMS	National Health and Morbidity Survey
T.I.M.E	Tissue, Inflammation/Infection, Moisture balance, Epithelial advancement framework
UMMC	University Malaya Medical Centre

CHAPTER ONE

INTRODUCTION

1.1 INTRODUCTION

This chapter describes mainly the background of the study and problem statement. This is followed by an elaboration on study objectives, research questions, and the significance of the study.

1.2 BACKGROUND OF THE STUDY

Incidences of diabetic foot ulcers or DFU had been on an upward trend due to the increase of diabetes prevalence worldwide. The global estimate for the prevalence of diabetes has increased from 151 million in the year 2000 to 451 million in 2017 and expected to rise to 691 million by 2045 as reported in the International Diabetes Federation (IDF) (Cho et al., 2018). The IDF report has estimated the risk for developing foot ulcers in their lifetime is 25% with one lower limb amputation occurring every 30 seconds across the globe. Complications of DFU have been the major indication for infection, gangrene, and lower limb amputation. Thus, DFU has become a major healthcare burden for developing countries and negatively affected the patients' economic standpoint and quality of life (Raghav et al., 2018). Management of DFU is expected to be costly, mostly include a long period of hospital admissions and surgical interventions (Coffey, Mahon, & Gallagher, 2019). Therefore, a comprehensive treatment strategy is urgently required to offset the impact and devastating complication of DFU (Bus et al, 2016).

Wound bed preparation has been the main component of chronic wound management as described in the structured framework for wound bed preparation, T.I.M.E (T=tissue management, I=infection/inflammation, M=Moisture imbalance, E=

advancing edge). Tissue management via debridement is a crucial process in wound bed preparation to remove slough, necrotic, non-viable tissue, promote granulation, and eventually epithelialization (Panuncialman & Falanga, 2009). Moreover, debridement also plays a pivotal role in controlling an infection (Pritchard et al., 2016). Thus, the benefits of debridement are irrefutable in the management of chronic wounds especially in DFU (Lavery et al., 2016).

Due to the chronicity of DFU, the usage of the century-old MDT had gained momentum and been advocated for debridement purposes in healthcare settings (Stadler, Shaban, & Tatham, 2015). MDT had been effective in debriding chronic and infected wounds, DFUs, venous ulcers, and pressure ulcers since its inception in the 19th century. Initial investigations had revealed that the healing of chronic wounds was expedited due to the debridement effect of sterile maggots in removing 25mg of slough and necrotic tissue within 24 hours (Sherman, 2014). Pursuing from the debridement effect, MDT was also utilized in DFUs with antibiotic resistance due to its mode of action in disinfection (Choudhary, Choudhary, Pandey, Chauhan, & Hasnani, 2016). Ultimately, MDT had been explored in chronic wound debridement when the conventional method failed to achieve the targeted outcomes. Nevertheless, MDT is mostly utilized as a last option for limb salvaging in actual clinical settings as demonstrated in a majority of clinical observations with MDT (Davies et al., 2015; Rosen et al., 2014; Davydov, 2011).

MDT had been prescribed as bio-surgery, larval therapy, maggot debridement therapy, or maggot therapy referring to the application of medical-grade sterile larvae on chronic wounds. Chronic wounds included pressure ulcers, venous stasis ulcer, DFU, and even osteomyelitis (Baer, 1931; Sherman, 2002; Steenvoorde et al., 2007; Zarchi & Jemec, 2012). MDT using sterile maggots of *Lucilia sericata,* with limited studies using *Lucilia cuprina* had shown promising outcomes in removing slough and necrotic tissue

as revealed in previous studies (Bazaliński, Kózka, Karnas, & Więch, 2019). However, comparison studies between MDT and conventional methods (surgical and non-surgical) in the treatment of DFUs remain sparse (Wang et al., 2016; Edwards & Stapley, 2010).

Despite advancements in technology, MDT had stood the test of time and emerged as a promising tool for debridement in chronic wounds (Nigam., 2006). However, not all species of flies were safe and effective for wound debridement. The sterile larvae of greenbottle blowflies, *Lucilia sericata*, and *Lucilia cuprina* (Diptera: Calliphoridae) have been used for the debridement of chronic wounds (Williams, Richards, & Villet, 2014). However, most of the MDT studies were conducted with *Lucilia sericata* which is abundantly present in Europe. Very few studies had been published with *Luclia cuprina* which is mainly found in Asia and Africa (Paul et al., 2009; Tantawi, Williams, & Villet, 2010). When conventional debridement methods failed to yield positive outcomes, MDT had been an alternative debridement modality for limb salvaging used by clinicians mainly in Europe and the USA (Wilasrusmee et al., 2014). The striking effect of MDT was based on its three major modes of action which include debridement, disinfection, and stimulation of wound healing (Gottrup & Apelqvist, 2012; Shi & Shofler, 2014).

Recent findings have shown that chronic wounds achieved faster healing when debrided with MDT as compared to conventional methods (Petherick et al., 2006; Spilsbury et al., 2008). Lack of significant findings in previous studies supporting the beneficial effect of MDT as compared to conventional methods is a matter of concern. Nevertheless, clinical experiences with MDT were abundant and had been effective in saving limbs (Davydov, 2011; Steenvoorde, Jacobi, Van Doorn, & Oskam, 2007). The efficacy of MDT in the treatment of DFU had been encouraging but inconclusive.

Although abundant promising reports and small-scaled studies on MDT were evidently present, MDT is still yet to be integrated into the treatment protocol of chronic wounds and remain under-used (Gottrup & Jørgensen, 2011) Despite the devastating effect of DFU complications, the exploration into the comparison studies between MDT and conventional therapy in the management of DFUs globally were less in common (Opletalová et al., 2012). Therefore, conclusive findings are required to demonstrate the superior effect of MDT as compared to conventional methods for MDT to be integrated into the treatment protocol of DFU in healthcare settings (Elraiyah et al., 2016; Pritchard & Nigam, 2013).

It was reported that wound closure in venous or DFU with conventional therapy only accounted for 25- 50% in 6-7 months; mainly due to antibiotic resistance (Masiero & Thyssen, 2016; Gould et al., 2015; Margolis et al., 2005). Thus, delayed wound healing in chronic wounds increases the risk of foot complications in diabetics (Sweitzer, Fann, Borg, Baynes, & Yost, 2006). Chronic wounds such as DFU became a challenge for clinicians since conventional methods were not able to achieve optimal debridement effect and improve wound healing outcomes (Nishijima et al., 2017a; Pritchard et al., 2016; Shahbazian, Yazdanpanah, & Latifi, 2013). Historical data had shown that MDT re-emerged during the era of antibiotic resistance in 1990 (Plessis & Pretorius, 2011) with successful outcomes in treating infected wounds infected with multi-drug resistant Staphylococcus aureus (Dumville et al., 2009). Therefore, utilization of MDT is crucial to accelerate healing in long-standing DFUs and improve wound healing outcomes (Beasley & Hirst, 2004; Chan, Fong, Leung, Patil, & Leung, 2007; Falch, de Weerd, & Sundsfjord, 2009; Čičková, Čambal, Kozánek, & Takáč, 2013; Bohova, Majtan, Majtan, & Takac, 2014).

In Malaysia, the prevalence of diabetes and incidences of DFU is not appealing either. Diabetes has become a major concern and healthcare burden in Malaysia (Hussein, Taher, Singh, & Chee, 2015). As reported in the 5th Malaysian National Health and Morbidity Survey (NHMS) (2015), the prevalence of Type II diabetes among the adult population is 17.2 % as compared to 11.6% reported in the 3rd NHMS report (2006). It was estimated 15-25% of diabetics with poor control of glucose suffer from foot ulceration, 4% underwent lower limb amputation (Letchuman et al., 2010). Thus, an alternative method such as MDT is critically needed to shorten the wound healing process and prevent foot complications among diabetics (Ahmed Hassan Fawzi El-Tawdy., 2016; Ousey et al., 2018). Hence, the present study is undertaken to evaluate the effectiveness of MDT using local species *Lucilia cuprina* in the treatment of DFU.

1.3 STATEMENT OF THE PROBLEM

The risk of a patient developing DFU throughout his life is estimated to be 25% and recent findings had demonstrated that DFU is the main cause for foot complications leading to infection, gangrene and in worst case lower limb amputation (Pedras, Carvalho, Da, & Pereira, 2016). About 85% of lower limb amputation was preceded by diabetes-based foot ulcers. It was reported that a person with diabetes has a 10–30 times greater risk of undergoing lower limb amputation as compared to non-diabetic (Ogurtsova et al., 2017; Cho et al., 2018). Thus, the prevalence of foot complications including lower limb amputations continues to be a healthcare burden to a developing country such as Malaysia (Lam, Zaim, Helmy, & Ramdhan, 2014) and contributing factor to morbidity and mortality (Lavery et al., 2016). Since the number of diabetes is increasing globally, incidences of DFU and its complications will see an upward trend

too (Hussein et al., 2015; Tallis et al., 2013). Consequently, non-healing DFUs had become a common causal pathway for lower limb amputations which could contribute to an unnecessary financial burden to the patient and country (Nube et al., 2016).

Managing DFU also considered to be costly due to the need for prolonged care of antibiotics, hospital admissions, wound dressings, surgical intervention, and rehabilitation (Fife, Horn, Smout, Barrett, & Thomson, 2016; Uccioli et al., 2015). In a study by Lam et al. (2014), managing DFU in one the major state hospital was estimated at USD 11,000 per year in Malaysia (May 2012-April 2013) and forecasted to be much more if outpatient rehabilitation was taken into consideration. The resistance of DFU towards conventional methods contributes greatly to massive foot complications, amputations, and mortality. The impact of managing DFU could affect the patients' lives and also the economy of the country (Arifin et al., 2017). The majority of the massive consequences of non- healing DFU can be prevented if DFU is treated with an efficient wound healing strategy since the chronicity of DFU delays wound healing. Delay in debridement could result in delayed wound closure (Cazander, Gottrup, & Jukema, 2009). In one meta-analysis conducted by Wilasrusmee et al. (2013) on more than 35 retrospective studies, usage of MDT in chronic wounds showed significantly better outcomes in wound healing with an average improved healing rate of 15.9 days as compared to the conventional method. Also, treatment with MDT was more cost-effective (40% less) compared to conventional methods. Thus, consideration of MDT as a frontline debridement tool in managing chronic wounds such as DFU could be potentially useful (Musa & Ahmed, 2012; Raposio, Director, Bortolini, Maistrello, & Grasso, 2017). Based on recent publications, MDT is one of the alternative biological debridement methods which has been gaining momentum for the past decades in improving wound healing outcomes (Sun et al., 2014; Jordan, Khiyani, Bowers,

Lukaszczyk, & Stawicki, 2018). However, most of the promising findings on the beneficial effect of MDT in chronic wounds were suboptimal and inconclusive (Abela, 2017; Shi & Shofler, 2014). In Malaysia, the pioneer study with MDT using *Lucilia cuprina* on DFU was conducted by Paul et al. (2009) and followed by Azad et al. (2016). However, the outcome in both studies did not achieve statistical significance. MDT was not indicated to be more effective than the conventional debridement method in the treatment of DFU. Therefore, continuous research is required to conclusively confirm the findings and maximize the beneficial effect of MDT to prevent foot complications and lower limb amputations.

1.4 STUDY OBJECTIVES

The main objective of this study is to evaluate the effectiveness of MDT with *Lucilia cuprina* for the treatment of DFU.

Specific objectives of the study are stated below:

1. To compare the efficacy of MDT and non-surgical conventional debridement method in the treatment of DFU based on slough percentage and size of ulcer at baseline, 3rd, 6th, 9th day.

2. To determine if there is any relationship between participants' demography (age, gender) and clinical characteristics (type of diabetes, duration of diabetes, HbA1c, grade of ulcer, size, site of ulcer, duration of ulcer, and percentage of slough.

1.5 RESEARCH QUESTIONS

The research questions are developed based on the objective of the study to provide a focus for the study and assist in the study design and methodology. Research questions

for the present study are stated as follows:

1. How is the efficacy of MDT compare with non-surgical conventional debridement method based on slough percentage and wound size at baseline, 3rd, 6th & 9th day?

2. Is there any relationship between participants' demographic data, clinical characteristics, and slough percentage in the study population?

1.6 ALTERNATIVE HYPOTHESIS

Alternative Hypothesis 1, H_a1:

There will be a significant difference between MDT and non-surgical conventional method in relation to slough percentage and wound size in the treatment of DFUs from baseline to day 3, day 6, and day 9.

Alternative Hypothesis 2, H_a2:

There will be a significant relationship between age, gender, type of diabetes, duration of diabetes, HbA1c, grade of ulcer, size, site, duration of ulcer, and percentage of slough.

1.7 SIGNIFICANCE OF THE STUDY

Despite technological advancements, the number of diabetics developing ulcers, foot complications, and amputations are still on the rise (Mavrogenis et al., 2018). To a certain extent, the non-surgical conventional debridement method was successful in producing positive debridement outcomes (O'Loughlin, McIntosh, Dinneen, & O'Brien, 2010). However, there was still a large population of diabetics suffering from hard-to-heal ulcers when non-surgical and even surgical debridement methods fail to produce targeted wound healing outcomes (Naves, 2016). Therefore, MDT can provide an alternative

debridement platform for clinicians to address the challenging and prolonged management of DFU (Abela, 2017). Based on previous clinical observations and studies, MDT had great potential to produce positive outcomes in the debridement of DFU (Vilcinskas, 2011). Thus, increasing the evidence base of MDT with *Lucilia cuprina* in Malaysia could increase the window of usage for MDT to treat DFUs, improve wound healing outcomes, and reduce foot complications. Consequently, significant evidence could bring MDT a step closer to be integrated into the debridement protocol of DFU in healthcare settings.

1.8 CHAPTER SUMMARY

Healing of DFU is very much dependent on efficient wound bed preparation to stimulate the wound healing process. Wound bed preparation cannot be optimized without an effective debridement strategy to remove slough, necrotic tissue, and non-viable tissue. MDT had stood the test of time and shown promising outcomes in the debridement of chronic wounds at large. However, the lack of significant clinical findings on the effectiveness of MDT compared to the non-surgical conventional debridement method has created a limited window of usage for MDT as the last option especially in the treatment of DFU. Therefore, the undertaken study could establish a strong evidence base for MDT using *Lucilia cuprina* as a frontline debridement tool in the treatment of DFU as compared to non-surgical conventional debridement method. Hence, MDT could be utilized to the best of medical advantage to reduce foot complications and prevent amputations.

CHAPTER TWO

LITERATURE REVIEW

2.1 OVERVIEW

The role of maggots in the debridement of chronic wounds is very promising and irrefutable. Hence, the most appropriate approach to consider the positioning of maggots in the treatment of DFU is to elaborate on the chronic wound healing process in general. Therefore, the first section of this chapter includes a brief discussion on DFU, factors related to wound healing outcomes, wound bed preparation, and debridement methods. The second section focuses on MDT, MDT's historical perspective, its mode of action, and side effects. The third section presents the literature search strategy to locate relevant clinical studies and discussion of the literature focusing on the comparison studies between MDT and conventional methods in the treatment of DFU.

2.2 DIABETIC FOOT ULCER (DFU)

The prevalence of diabetes had increased worldwide, and so did diabetes-based foot ulcers. Based on a global report by the International Diabetes Federation 9th Edition (2019), there are more than 400 million diabetics as compared to 171 million in the year 2000 worldwide and the numbers are expected to double in 2030 (Wild et al., 2004). It was reported that 25% of diabetics had DFU in their lifetime and more than a million diabetics suffered lower limb amputation (4-7%) across the globe. The upward trend is expected to prevail due to the aging population and obesity (Hingorani et al., 2016). It was estimated that 80% of lower limb amputations were due to the complication of prolonged uncontrolled diabetes and foot ulceration (Boulton et al., 2018). In Malaysia, the prevalence of diabetes among the adult population had increased from 15.2% in 2011

to 17.2% in 2015 based on the NHMS (2015). It was estimated that 15-25% of foot ulcers were diabetes-based and lower limb amputation was reported to be 4.3% which had contributed to massive healthcare burden in developing countries such as Malaysia (Hussein et al., 2015; Letchuman et al., 2010).

Even though many complications were affecting people with diabetes, none were more devastating than complications involving the foot (Jain & Barman, 2017). Non-healing DFU decreases the quality of life for the diabetics and an inevitable increase in the treatment cost for the patients (Coffey et al., 2019; Goie & Naidoo, 2016). According to Edwards & Stapley (2010), "diabetic peripheral neuropathy had been identified as one of the major underlying factors behind DFU". Diabetes peripheral neuropathy is one of the major microvascular complications (Ogurtsova et al (2017), which is defined as nerve damage caused by chronically high blood glucose in the blood leading to numbness, loss of sensation, and sometimes pain in the feet, legs, or hands (Sorg, Tilkorn, Hager, Hauser, & Mirastschijski, 2017). Musa and Ahmed (2012) reported that diabetics with peripheral neuropathy may not feel heat, cold, or pain in the extremities like feet, hands, or legs. Thus, they would not be able to realize or know when there is a cut or sore on their feet, thus they develop DFUs. These ulcers are the most common, costly, and devastating complications of diabetes to date and significantly affect patients' quality of life, morbidity, and even mortality (Leone et al., 2012).

DFU does not heal in a timely manner because it is not an acute wound that follows the normal process of healing. Acute wound is defined as a traumatic injury, instigated by a sudden, solitary insult and proceed through the healing process in an orderly manner; hemostasis, inflammation, proliferation, and maturation (Hinchliffe et al., 2016). Acute wounds generally are not as challenging as chronic wounds and most of the time go through a smooth healing process. Thus, acute wound heals faster