THE ASSOCIATED FACTORS OF DEPRESSION AND QUALITY OF LIFE IN PATIENTS WITH DIABETIC FOOT ULCER IN HOSPITAL TENGKU AMPUAN AFZAN

DR CHAN TZE LIN

DEPARTMENT OF PSYCHOLOGICAL MEDICINE

FACULTY OF MEDICINE

UNIVERSITY OF MALAYA

KUALA LUMPUR

2016

CERTIFICATION

This is to certify that the candidate, Dr. Chan Tze Lin, has carried out this research project, and to the best of my knowledge, this dissertation is entirely her work.

Professor Dr. Nor Zuraida Bt Zainal

Professor
Department of Psychological Medicine
Faculty of Medicine
University of Malaya

Professor Dr. Ramli Bin Musa

Consultant Psychiatrist and Head of Department
Department of Psychiatry
Kulliyyah of Medicine
International Islamic University Malaysia

ABSTRACT (ENGLISH)

The associated factors of depression and quality of life in patients with diabetic foot ulcer in Hospital Tengku Ampuan Afzan.

Introduction:

Diabetic foot complications are one of the common causes of lower extremity amputations. Furthermore, diabetic patients with foot ulcer have high hospitalization rates as compared with those without foot complications. Diabetic foot ulcer patients with comorbid depression have high morbidity and mortality as well as poor quality of life. However, there is limited study available in Malaysia.

Objective:

The primary aim was to determine the prevalence of depression in patients with diabetic foot ulcer in Hospital Tengku Ampuan Afzan and to determine the sociodemographic and clinical factors associated with depression in diabetic foot ulcer patients. The study was also to determine the quality of life and social support among diabetic foot ulcer patients and compared between the depressed and non depressed diabetic foot patients.

Method:

This was a cross sectional study where a total of 150 diabetic foot ulcer patients were recruited. Sociodemographic data and clinical variables were determined in diabetic foot ulcer patients. The prevalence of major depressive disorder among the diabetic foot ulcer patients was determined using Mini International Neuropsychiatry Interview (M.I.N.I). Hospital Anxiety and Depression Scale (HADS) was used as screening tool. M.I.N.I questionnaire was used as diagnostic tool. Both HADS and M.I.N.I were used for all the study subjects to confirm the validation between the positive cases of HADS with positive

cases of M.I.N.I. The study also investigated the association between major depressive disorder with clinical and sociodemographic factors of diabetic foot ulcer patients. The Quality of life was assessed using the WHOQOL-BREF and social support was evaluated using Multidimensional Scale of Perceived Social Support (MSPSS).

Result:

The prevalence of depression in diabetic foot ulcer patients using M.I.N.I (diagnostic tool) was 20.7% and prevalence of depression based on HADS-D (screening tool) with cut off point of ≥8 was 24%. In this study, all the positive cases of M.I.N.I were also screened positive using HADS. Major depressive disorder was found to be significantly associated with the family history of depression (p=0.015, OR=8.667), another chronic medical illnesses (1-2 chronic illnesses p=0.033, OR=5.093; ≥3 chronic medical illnesses p=0.009, OR=13.200), three and more diabetes complication(p=0.025, OR=5.564). In this study, quality of life of diabetic foot ulcer patients with comorbid depression was found lower compared to those without depression. The mean total score for WHOQOL-BREF was 76.6 (SD=8.8) for diabetic foot ulcer patients with depression and 89.2 (SD=10.9) for non depressed group. In this study, all the diabetic foot ulcer patients had perceived overall good social support with mean total score 5.5 (SD=0.98). There was no significant association found between level of social support among diabetes foot ulcer patients with comorbid major depressive disorder.

Conclusion:

This study found a high prevalence of depression among the patients with diabetic foot ulcer. The diabetic foot ulcer with comorbid depression had significantly poorer quality of life compared to non depressed group. Medical practitioners should regularly screen high risk group for early detection of depression and improve the quality of life.

ABSTRAK (MALAY)

Faktor-faktor berkaitan penyakit kemurungan dan kualiti hidup di kalangan pesakit ulser kaki diabetes di Hospital Tengku Ampuan Afzan.

Pengenalan:

Penyakit ulser kaki diabetes (diabetic foot ulcer) merupakan salah satu komplikasi yang serius dan penyebab utama 'amputasi' bahagian anggota kaki. Pesakit yang menghidapi ulser kaki dengan kadar kemasukan ke hospital yang tinggi berbanding dengan peaskit diabetes tanpa komplikasi kaki. Pesakit ulser kaki diabetes yang mengalami kemurungan mempunyai morbiditi dan mortaliti yang tinggi serta kualiti hidup yang tidak memuaskan. Walau bagaimanapun, hanya kajian yang terhad yang terdapat di Malaysia.

Objektif:

Tujuan utama adalah untuk mengenalpasti prevalen kemurungan pesakit ulser kaki diabetes di Hospital Tengku Ampuan Afzan dan untuk menentukan sosiodemografi dan faktor-faktor klinikal yang berkaitan dengan kemurungan pesakit ulser kaki diabetes. Kajian ini juga adalah untuk menentukan kualiti hidup dan sokongan sosial di kalangan pesakit-pesakit ulser kaki diabetes dan berbanding antara pesakit yand mengalami kemurungan dengan pesakit tanpa kemurungan.

Tatacara:

Ini adalah satu kajian rentas dan seramai 150 pesakit ulser kaki diabetes telah menyertai kajian ini. Data sosiodemografi dan klinikal telah dikenalpasti di kalangan pesakit ulser kaki diabetes. Prevalen kemurungan antara pesakit ulser kaki diabetes diselidik dengan menggunakan Mini International Neuropsychiatry Interview (M.I.N.I). Hospital Anxiety and Depression Scale (HADS) digunakan sebagai soalan saringan untuk tanda-tanda kemurungan.

M.I.N.I digunakan sebagai soalan diagnosis. Kedua-dua soalan kajiselidik digunakan untuk semua pesakit yang menyertai kajiselidik ini untuk menvalidate bahawa semua kes positif untuk M.I.N.I juga kes positif untuk HADS. Kajian juga menyiasat perkaitan antara kemurungan dengan factor klinikal dan faktor sosiodemografi di kalangan pesakit ulser kaki diabetes. Kualiti hidup dinilai menggunakan WHOQOL-BREF dan sokongan sosial dinilai menggunakan Multidimensional Scale of Perceived Social Support (MSPSS).

Keputusan:

Prevalens kemurungan pesakit ulser kaki diabetes yang diselidik dengan menggunakan M.I.N.I (kes diagnosis) adalah 20.7% dan prevalens kemurungan berdasarkan HADS-D (kes saringan positive) dengan penanda aras markah ≥8 adalah 24%. Dalam kajian ini, semua kes positif M.I.N.I adalah kes positif saringan HADS. Kemurungan didapati berhubungkait dengan sejarah keluarga kemurungan ($p = 0.015$, SD= 8.667), penyakit perubatan yang kronik yang selain daripada diabetes (1-2 penyakit kronik, $p= 0.033$, SD = 5.093; ≥3 penyakit kronik, $p = 0.009$, SD= 13.200), tiga dan lebih komplikasi kencing manis ($p = 0.025$, SD = 5.564). Dalam kajian ini, kualiti hidup pesakit ulser kaki diabetes yang murung didapati lebih rendah berbanding dengan mereka yang tanpa kemurungan. Purata markah keseluruhan bagi WHOQOL-BREF adalah 76.6 (SD = 8.8) untuk pesakit ulser kaki diabetes yang murung dan 89.2 (SD = 10.9) untuk kumpulan tanpa kemurungan. Dalam kajian ini, pesakit ulser kaki diabetes yang mengalami kemurungan mempunyai keseluruhan sokongan social yang baik dengan jumlah purata markah 5.5 (SD = 0.98). Dalam kajian ini, semua pesakit ulser kaki diabetes mempunyai sokongan sosial yang baik dengan purata markah 5.5 (SD= 0.98). Dalam kajian ini, adalah didapati tiada hubungkait antara tahap sokongan social dengan penyakit kemurungan di kalangan pesakit ulser kaki diabetes.

Kesimpulan:

Kajian ini mendapati prevalens kemurungan yang tinggi di kalangan pesakit yang menghidapi ulser kaki diabetes. Pesakit-pesakit yang mengalami kemurungan didapati mempunyai tahap hidup yang tidak sebaik berbanding dengan pesakit yang tidak mengalami kemurungan. Pengamal perubatan harus kerap mengeskrin kumpulan berisiko tinggi untuk pengesanan awal kemurungan dan memperbaiki kualiti hidup yang lebih baik.

ACKNOWLEDGEMENTS

Firstly, I would like to express my deepest gratitude and appreciation to Professor Dr. Nor Zuraida Bt Zainal and Professor Dr. Ramli Bin Musa, both my thesis supervisors for their guidance, supervision, and suggestions throughout the research and writing up of this thesis.

I would like to thank to Dato Dr. Prem, Head of Department of Orthopedic for his kind permission to allow me to conduct the study in Diabetic foot ulcer clinic (outpatient orthopedic clinic).

I would like to convey my gratitude to Associate Professor Dr. Ng Chong Guan Faculty of Medicine & Health Sciences, University Malaya for the permission to use the Malay Version of Multidimensional Scale of Perceived Social Support, MSPSS-M.

I would like to express my appreciation to the doctors and staffs of outpatient Orthopedic clinic Hospital Tengku Ampuan Afzan (HTAA) who had been very helpful during the data collection in the clinic.

My deepest gratitude also goes to Miss Lim Bee Chiu who was the clinical statistician in Clinical Research Centre (CRC) HTAA who had taught me and guided me the correct way on the statistical analyses of this study.

I would like to thank to the patients for the consent to participate in this study.

Last but not least, I would like to express my appreciation to my colleagues who had helped and encouraged me to accomplish my thesis dissertation.

TABLE OF CONTENTS

APPENDICES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BDI	Beck Depression Inventory
BMI	Body Mass Index
CRC	Clinical Research Centre
CVD	Cardiovascular Disease
DFU	Diabetic Foot Ulcer
DM	Diabetes Mellitus
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
GWAS	Genome-wide Association Studies
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton depression rating scale (HAM-D)
HRQL/HRQoL	Health Related Quality of Life
HTAA	Hospital Tengku Ampuan Afzan
IDF	International Diabetes Federation
LR	Logistic Regression
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
M.I.N.I	Mini International Neuropsychiatry Interview
MSPSS	Multidimensional Scale of Perceived Social Support
NHMS III	Third National Health Morbidity Survey
PHQ	Patient Health Questionnaire
QoL	Quality of Life
SCAN 2.1	Schedules for Clinical Assessment in Neuropsychiatry 2.1
SPSS	Statistical Package for Social Sciences
WHO	World Health Organization

WHOQOL-BREF World Health Organization Quality of Life- BREF

LIST OF APPENDICES

1.0 INTRODUCTION

Diabetes mellitus (DM) is one of the world's commonest chronic diseases. According to the World Health Organisation, the global prevalence of DM is estimated to be 9% among adults aged 18 years and above (World Health Organization [WHO], 2015) . In 2012, there were 1.5 million deaths due to diabetes (WHO, 2013) . It was estimated that about 80% of deaths due to diabetes occur in low and middle-income countries (International Working Group on the Diabetic Foot, 2003). The diagnostic fasting plasma (blood) glucose value has been lowered to $\geq$7.0 mmol l^{-1} (previously cut-off point: 6.1 mmol l^{-1}) (Zimmet & Alberti, 2006). The International Diabetes Federation (International Diabetes Federation [IDF], 2009) predicted that the global prevalence of DM is estimated to increase from 6.6% in 2010 to 7.8% in the year 2030. This represents a rise in the number of diabetic patients from 285 million people to 438 million people worldwide in 20 years' time. This increase is mainly due to population growth, aging, urbanization and the increasing prevalence of obesity and physical inactivity (Wild, Roglic, Green, Sicree, & King, 2004).

In Malaysia, the Third National Health Morbidity Survey (National Health Morbidity Survey [NHMS] III, 2006) showed that the prevalence of DM was 11.6%. It increased from 8.3% as reported in NHMS II ten years earlier. Among all the races, Indians have the highest prevalence (19.9%) of DM, followed by Malays, 11.9% and Chinese, 11.4%. The prevalence of diabetes was found higher in urban areas or cities compared to rural areas (Letchuman et al., 2006). The NHMS III 2006 results showed that the prevalence of DM in Malaysia has exceeded the estimated prevalence for the year 2030. This is alarming.

The prevalence of DM patients with a history of amputation is 4.3%. Other complications are 3.4% of these patients have a history of stroke and 1.6% have chronic kidney disease (Letchuman et al., 2010).

There was an upward trend of DM among Malaysian diabetic patients age 30 and above from 6.3% to 8.3% and to 14.9% in 1986, 1996 and 2006, respectively (Letchuman et al., 2010).

The common consequences of DM are damage to the heart, blood vessels, eyes, kidneys, and nerves. According to a multinational study, almost half of DM patients have complications of cardiovascular disease (primarily heart disease and stroke) (Bonham, 2001). A reduced blood flow with neuropathy (nerve damage) in the foot would increase the risk of foot ulcers, infection and subsequently limb amputation. Diabetic retinopathy due to long-term accumulated damage to the small blood vessels in the retina is an important cause of blindness. There was one percent of diabetes retinopathy which caused blindness in the population (Bonham, 2001). DM is one of the leading causes of kidney failure (Armstrong, Abu-Rumman, Nixon, & Boulton, 2001). The overall risk of mortality of patients suffering from diabetes is at least double the risk of their peers without diabetes (Borssén, Bergenheim, & Lithner, 1990).

According to Andrew (2000), approximately 15% of the more than 150 million people with diabetes world-wide, develop diabetic foot ulceration (DFU) at any stage of the disease. The prevalence of active foot ulceration may vary from approximately 1% in certain European and North American studies to more than 11% in reports from some African countries (Andrews, 2000) .

Recent studies showed that the lifetime risk of foot ulcer in diabetic patients can be as high as 25% (Singh, Armstrong, & Lipsky, 2005). DFU requires long term and intensive treatment, and thus, it has important effects on the quality of life of both patients and care-givers (Nabuurs-Franssen, Huijberts, Nieuwenhuijzen Kruseman, Willems, & Schaper, 2005) and is also associated major healthcare costs (Apelqvist, Ragnarson-Tennvall, Persson, & Larsson, 1994, 1995).

1.1 Problem statement

DM is the commonest chronic medical illness. The International Diabetes Federation (IDF, 2009) forecast that the global prevalence of DM is estimated to increase from 6.6% in 2010 to 7.8% in the year 2030. DM patients are at high risk of foot complication. This is because the raised blood sugars in the body can cause damage to the sensation and circulation of the feet. If left untreated, it causes foot ulcers with complications of infections which may lead to amputations. However, most foot problems are preventable with good, regular foot care.

Ulcers of the lower limbs are the most common complications especially those related to the circulatory system and DM (Lucas, Martins, & Rozazzi, 2008). In Brazil, lower limb complications due to degenerative problem and chronic illness have become a serious public health issue. Yet there is no record of the number of individuals affected. DM patients are estimated to have 15% risk of developing at least one foot injury throughout their illness (Lavery, Armstrong, Wunderlich, Tredwell, & Boulton, 2003; Torquato et al., 2003).

Patients with lower limb wounds sometimes will have negative feelings such as fear, discontent and helplessness. Patients dependent on others in their daily activities would develop fear and frustration. The feeling of fear can lead to a mixture of emotions such as conflict, doubts and unexpected reactions. Patients with chronic diabetic foot ulcer with a risk of amputation also experience feelings such as fear, sadness, helplessness, frustration and isolation (Goodridge, Trepman, & Embil, 2005).

Having a diabetes foot has significant impact on one's quality of life. For example, the loss of mobility to perform simple daily tasks and to participate in leisure activities (Geraldo, Leila, & Lydia, 2011). Several studies have shown that people with diabetes and foot ulcers were more depressed and had poorer quality of life than those who did not have diabetes complications (Vedhara et al., 2010).

Depression is one of the ten leading causes of disability worldwide. It affects the physical, social and personal skills of a person suffering from it. However, only a small number of patients suffering from depression are diagnosed and receive appropriate treatment. There are still a lot of undiagnosed cases and the stigma still weighs significantly over those who are diagnosed with depression. Society's perception of the symptoms of depression may influence the process of seeking help and treatment adherence. This also affects the community's attitude and behaviour in relation to those with the disorder (Docherty, 1997; Klassen, Jenkinson, Fitzpatrick, & Goodacre, 1996; McQuaid, Stein, Laffaye, & McCahill, 1999).

About 50 - 60% of cases of depression are under diagnosed and under treated. The majority of depressed patients do not receive adequate and specific treatment (Peluso & Blay, 2008). However, the morbidity and mortality associated with depression can be prevented (around 70%) with the right treatment (McQuaid et al., 1999).

Foot ulcer in patients with diabetes can negatively impact on their daily lives and may have consequences, such as psychosocial disorders (Beck, Ward, Mendelson, Morck, & Erbaugh, 1961; Docherty, 1997), including depression, so this study aims to evaluate the prevalence of depression and the associated factors of depression among diabetic foot ulcer patients.

1.2 Significance of the study

The increasing rate of diabetic foot wounds in the population is an alarming fact known by health professionals and has provided several discussions on the subject. Wound care is a main issue which challenges both the patient as well as the caregiver. Unfortunately, living with a diabetic wound creates a number of changes in the lives of the patient and his family members. Most of

them do not understand the illness well and are not prepared to cope with this problem in the short term and subsequently this has a significant impact on the biopsychosocial aspect (Lavery et al., 2003). Besides the physical health complications of DM, the psychosocial impact of DM is also being studied by the medical professional group. DM is viewed as a multi-dimensional biopsychosocial problem.

Diabetic foot ulcers (DFU) have increased the burden on patients and the healthcare system (Boulton, Vileikyte, Ragnarson, & Apelqvist, 2005). Infection and peripheral arterial disease always have poor outcomes (Boulton, 1996; Prompers et al., 2008). In addition, foot ulcers are associated with disability and the loss of health-related quality of life (HRQOL). Studies have shown that the improvement in HRQOL is unlikely without considering all dimensions of personal functioning, which include the physical, social and psychological aspects.

Ribu, Hanestad, Moum, Birkeland and Rustoen (2007) reported that a high percentage of DFU patients stay alone with poor social support. They also have much worse HRQOL compared to those diabetes patients without complications (Ribu, Hanestad, Moum, Birkeland, & Rustoen, 2007).

The association between depression and diabetes is bidirectional. There is a lack of documentation regarding relevant factors associated with the disease state (e.g., number of diabetes complications, other medical co-morbidity). A meta-analysis by Anderson et al. (2001) which demonstrated that 11% of patients with diabetes fulfilled the criteria for major depressive disorder (MDD) and 31% experienced significant depressive symptoms. Women were found to have higher prevalence than men. In the controlled studies, the odds of having depression were twice as great in patients with diabetes compared to the normal population.

Although the negative impact of foot ulcer on physical health among persons with diabetes is well known, however, there is limited research regarding the association between foot ulcer, perceived

health and quality of life and psychological distress (Iversen et al., 2009). Results from various studies are difficult to compare due to different study designs, samples and/or different questionnaires which have been used. Depression and DFU also lead to higher health care costs due to patients' poor diabetic control and poor wound care. Surprisingly, although the consequences of this co-morbidity are widely studied, the incidence of depression in DFU patients is relatively under diagnosed and under treated.

To date, we are unaware of studies that look into the association between depression, DFU, quality of life and social support in Malaysia. The aim of this study is to determine the prevalence of depression, psychological well-being, perceived health and quality of life, social support and the associated risk factors of patients with diabetic foot ulcer which co-morbid with depression in hospital settings. This study hopes to create a better understanding about depression in patients with DFU in order to improve the outcome of DFU and the quality of life of the patients.

2.0 LITERATURE REVIEW

2.1Diabetes Foot Ulcer (DFU)

DFU and amputations are one of the major causes of morbidity and mortality in patients with diabetes. In the 2006 Third National Health Morbidity Survey, the prevalence of lower limb amputation among patients with diabetes was 4.3% (NHMS III, 2006). According to Clinical Practice Guidelines on Management of Diabetic Foot 2004, there are 12% of diabetic patient with foot complication for hospital admissions in Malaysia. Forty eight percent (48%) of patients (30 years old and above) are not diagnosed with diabetes before the foot complication (Clinical Practice Guidelines [CPG], 2004; NHMS III, 2006).

Diabetic foot complication poses a substantial economic burden to society, patients and their families (Boulton et al., 2005). The burden of cost can be measured as a direct cost or indirect cost. The direct costs are attributed to treatment such as medication, dressing and surgical procedures. The indirect costs are including unemployment, loss of social services, home care and quality of life (Boulton et al., 2005).

In the United States, there are 16 million patients with diabetes (diagnosed and undiagnosed). Among the entire diabetes patients, an estimated 1200 amputations are performed each week. Moreover, 84% of these patients are preceded by a foot ulcer (Pecoraro, Reiber, & Burgess, 1990). The incidence and prevalence for diabetic foot ulcers are estimated at 2% and 5–7% per year, respectively (Ramsey, Newton, & Blough, 1999). Reiber, Vileikyte, Boyko, del Aguila, and Smith (1999) found that first limb amputation in patients with diabetes is associated with an increased risk for further amputation. This has a 5-year mortality rate of 39% to 68% (Reiber et al., 1999). In the United States, the direct costs for diabetic foot ulceration and amputation range from $20,000 to $60,000 (Eckman, Greenfield, & Mackey, 1995).

Duration of diabetes illness (treated and untreated), uncontrolled DM, and peripheral neuropathy (reduced pain sensation) are considered to be significant biological risk factors for the onset and recurrence of foot ulcers (Apelqvist, Larsson, & Agardh, 1993). Peripheral neuropathy predisposes to ulcerations and vascular disease delays the healing process.

According to the Clinical Practice Guideline, Management of Type II DM (2009), risk factors for DFUs are (Clinical Practice Guideline [CPG], 2009):

1) Previous amputation

2) Past foot ulcer history

3) Peripheral neuropathy

4) Foot deformity

5) Peripheral vascular disease

6) Visual impairment

7) Diabetic nephropathy (especially patients on dialysis)

8) Poor glycaemia control

9) Cigarette smoking

Recent HRQOL studies have shown the significant poor quality of life in diabetic patients with foot complication (Mazlina, Shamsul, & Saini Jeffery, 2011). Diabetic foot patients experience severe restriction in daily life as a result of the ulcer (Mazlina et al., 2011). They encounter social isolation due to limited mobility, require regular clinical treatment and follow up and continuous precaution to take care of their feet (Kinmond, McGee, Gough, & Ashford, 2003).

Subsequently, this had a negative psychological impact on patients. Patients with diabetic foot ulcers would experience higher levels of depression, worry for the future, have high level of dissatisfaction with their personal lives and poorer psychosocial adjustment to illness (Carrington, Mawdsley, & Morley, 1996; Ribu & A. Wahl, 2004). Studies show the significant psychological impact of foot complications in diabetic foot patient daily life (Mazlina et al., 2011).

Both patients with lower extremity amputation and diabetic foot ulcer perceived equally impaired quality of life (Boutoille, Féraille, Maulaz, & Krempf, 2008; Willrich, Pinzur, McNeil, Juknelis, & Lavery, 2005). Both diabetic peripheral neuropathy and Charcot arthropathy patients had reported significant reduction in quality of life and mental health (Currie, Poole, & Woehl, 2006; Padua, Saponara, & Ghirlanda, 2001).

To avoid the complication of diabetic foot ulcer, multiple prevention and intervention can be achieved by daily foot examinations for invisible or painless injuries, regular clinic visits, not over expose foot wear, and maintenance of optimal diabetes self-care. Despite these precautions, amputation is the most common adverse outcomes following the onset of foot ulcers (Siitonen et al., 1993).

Apelqvist, Larsson, and Agardh (1993) found the significant rate of recurrence of foot ulcers which is estimated at 34% in 1 year; increase to 61% in 3 years and 70% in 5 years. Around 15% develop osteomyelitis, and there is a two fold increase in mortality compared with people with diabetes without a foot ulcer (Ramsey et al., 1999).

2.1.1Diabetic foot ulcer and psychiatric co-morbidity

The prevalence of anxiety is 32% and depression is 22.4% in diabetic foot ulcer patient (Ramsey et al., 1999). Diabetes complications, smoking, poor glycaemia control and being an ex-drinker or a heavy drinker were risk factors for both higher anxiety and depression scores in multivariate analysis (Ramsey et al., 1999). Female gender and poor glycaemia control were associated with risk of developing anxiety. However, Ramsey et al. (1999) found that good socio-economic status and older age were protective factors for both anxiety and depressive symptoms.

2.2 Diabetic foot ulcer and depression

Khalida, Kirsty, Daniel, Trudie and Micheal (2007) found that about one-third of patients with first episode of diabetic foot ulcer had clinically significant depression. The Khalida et al. (2007) study demonstrates that 25% of them have major depressive disorder, another 8% have a minor depressive disorder. Among the diabetic foot ulcer study subjects, there were 15.8% deaths, 15.5% amputations, and 43.2% recurrences. Furthermore, both are associated with high mortality compared with those who are not depressed. This was associated with threefold increased risk of death after 18 months. This study shows that there was no association between depression at baseline and glycaemia control 18 months later (Khalida, et al., 2007).

People with early stage of diabetic foot disease are at high risk to worry the worst for their future, such as gangrene or loss of a limb (Carrington et al., 1996). Depression is often undetected in people with diabetes, and, even when detected, treatment is not optimized (Lustman & Harper, 1987).

A recent study found that among diabetes patients, those who had chronic wounds had more mental health problems than those without wounds. They also have less ability to cope with

stressful events compared with those without chronic wound (Upton, Solowiej, & Woo, 2014). Study subjects expressed that living with chronic wounds was stressful, isolating, debilitating, worrisome, and depressing (Upton et al., 2014).

William and colleagues (2010) found an association between depression and DFU (William et al., 2010). They found that those diabetes patients who had comorbid major depressive disorders had a two-fold increased risk for DFU complication within 4 years duration of illness.

Another study showed that depression was significantly related to the development of first but not recurrent foot ulcers. Early depressive symptoms were significantly associated with increased risk of developing first foot ulcers (Gonzalez et al., 2010). This study found that higher depression scores were associated with greater frequency of foot self-care. These patients involved in more frequent foot self-care and they have been more aware of their health risk and, thus, would have high risk of developing depressive symptoms (Gonzalez et al., 2010).

Depression is also associated with poorer foot ulcers healing prognosis and more severe and larger foot ulcers (Khalida et al., 2007). Recent research in primary care with type 2 diabetes patients found that those who had comorbid depression had poor outcome. This group is associated with higher risk of microvascular and macrovascular complications throughout the course of illness, even after controlling for diabetes severity and self-care activities (Lin, Rutter, & Katon, 2010).

2.2.1 Major depressive disorder (MDD)

Depression was the fourth leading specific cause of disability in the nineties. It is expected to be the second in developed countries and the first in developing countries by 2020 (Beck et al., 1961). According to the WHO, major depressive disorder will become the second leading cause of disability by 2020 (Michaud, Murray, & Bloom, 2001). Major depressive disorder is the most severe form of depressive disorder with a lifetime prevalence of about 15% (Kaplan & Sadock, 2003). In Malaysia, a cross sectional study done among adult primary attendees reported the prevalence of major depressive disorder as 5.6% (Jammy, Norlaili, & Sherina, 2005).

Nevertheless, depression is often under recognized and under treated. It is estimated that about 30-50% of cases of depression in primary care and medical settings are undetected (Ronalds, Creed, & Stone, 1997). Depressive symptoms in physical illness, chronic illness or terminal illness might differ from the The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria, making it difficult for clinicians to detect the depressive symptoms. Based on Endicott's criteria, physicians can look for the following symptoms such as depressed appearance, social withdrawal, self-pity or pessimism and non-reactive mood in the patient suspected of depression (Endicott, 1984).

2.2.2 Depression in chronic illness

Thomas and colleagues (2003) found a positive association of type 2 diabetes with increased rates of depressive and/or anxiety disorders in patients with other chronic illnesses such as hypertension, asthma, and/or arthritis (Thomas, Jones, Scarinci, & Brantley, 2003). Their result also support prior research that type 2 diabetes serves as an indicator of depression and anxiety in low-income adults treated in primary care clinics.

A high prevalence rate of depressive and/or anxiety disorders was found in the total sample (29%) and in all three illness groups: type 2 diabetes (36%), other chronic illnesses (24%), and no chronic illness (31%) (Thomas et al., 2003).

2.2.3 Depression in patient with diabetic foot ulcer

-Bi-directional relationship

There are different pathways explaining the underlying mechanisms of depressive symptoms in diabetes increasing the risk of mortality.

"Direct" effects of depression. This is a physiological factor which increases the classic metabolic risk factors, and may cause diabetes.

Salynn (2009) suggests hormonal changes due to depression can cause diabetes. This specifically is the stress hormones adrenaline and cortisol. "Both of these hormones also alter glucose metabolism". Stress hormones also can increase cardiovascular risk (Salynn, 2009).

"Indirect" pathways involve a psychosocial and behavioral component. Studies show that most of the diabetic foot ulcer with depression are facing social isolation issue, poor compliance behavior, poor-self health management behaviour, poor coping skills and long term life stress event (Strine et al., 2005). The study suggests that modifying the risk behavioural such as smoking, proper control of diabetic diet, good adherence to medication may improve the diabetic foot healing and depressive symptoms (Gonzales, Langer, Conway, Berkus, & Xenakis, 2000).

One theory explained the changes in the neuroendocrine system with increased immunoinflammatory activation among the diabetic patients with comorbid depression (Musselman, Betan, Larsen, & Phillips, 2003). As a consequence, there was increased risk of

diabetes complications (de Groot, Anderson, & Freedland, 2001), and poor adherence to diabetes management as well as poor glycaemia control (Gonzalez, Safren, & Cagliero, 2007).

Findings from meta-analyses of cohort studies show a modestly sized bidirectional association where depression predicts diabetes onset and diabetes predicts future depression (Adam, Tasnime, David, & Mika, 2014). But, biological changes in the hypothalamic-pituitary-adrenal cortex axis, sympathetic nervous system, and subclinical inflammation, are not consistently associated with increased diabetes risk. The evidence for the association between depression and glycaemia traits (e.g., glucose, insulin, insulin sensitivity, and insulin secretion) is mixed. As other chronic illnesses such as. cardiac diseases, osteoarthritis, lung disease and poor hearing, diabetes shares the same risk of developing depression (Adam et al., 2014).

Van Dooren and colleagues (2013) analyzed that depression was associated with an increased risk of all-cause mortality (HR=1.46, 95% CI 1.29–1.66), and cardiovascular mortality (HR=1.39, 95% CI 1.11–1.73) (van Dooren, Nefs, Schram, Verhey, & Denollet, 2013). Among the sixteen studies included, five of them also reported on cardiovascular mortality. Park, Katon, and Wolf (2013) found that depression was significantly associated with the risk of mortality (Park et al., 2013).

However, Paschalides et al. (2004) reported that anxiety, depression and negative beliefs about illness had a significant influence on physical and mental functioning, but not metabolic control in patients with diabetes (Paschalides et al., 2004).

-Antidepressant drug

The major government-funded study found that taking antidepressants would increase the risk of developing type 2 diabetes among those who are at high risk of DM (Salynn, 2006).

Researchers from the Diabetes Prevention Program, sponsored by the National Institutes of Health, reported that depression alone did not predict progression of diabetes illness (Salynn, 2006). However, taking antidepressants was associated with a two- to threefold increase in risk of diabetes (Salynn, 2006).

Recent studies have highlighted the possibility that continuing antidepressant use might increase the risk of unwanted side effect such as type 2 diabetes (Rubin et al., 2008; Andersohn, Schade, Suissa, & Garbe, 2008).

Antidepressant medication especially SSRIs and tricyclic antidepressants are associated with a twofold risk of diagnosed type 2 diabetes. The 5-year risk of diagnosed diabetes depends on the level of exposure to antidepressant medication which includes 1.1% in nonusers, 1.7% for those treated with 200–399mg daily doses for 1 year, and 2.3% with ≥400mg daily doses (Mika et al., 2010).

A General Practice Research Database from the United Kingdom also revealed similar findings. The analysis found that antidepressant treatment with lower daily doses was not associated with risk of diabetes but long-term use of antidepressants with high or moderate daily doses was associated with increased risk of diabetes (Andersohn et al., 2008).

Mika et al. (2010) found that tricyclic antidepressants induce weight gain and promote hyperglycemia (Aronne & Segal, 2003; Lustman et al., 1997). However, SSRI use causes weight loss in the short term, but increased risk of weight gain in the longer term (Demyttenaere & Jaspers, 2008).

A meta-analysis of randomized trials of depression interventions in diabetes patients with comorbid depression found a few studies tested the efficacy of psychotherapy and efficacy of antidepressant medications (van der Feltz-Cornelis, Nuyen, & Stoop, 2010). The meta-analysis

showed both evidence based antidepressants medication and psychotherapy were efficacious in treating diabetes patients with depression (van der Feltz-cornelus et al., 2010).

Van der Feltz-Cornellis, Nuyen, and Stoop (2010) concluded that pharmacotherapy, except for sertraline (pharmacotherapy evaluated in RCTs included in this meta-analysis were nortriptyline, fluoxetine and paroxetine) had no effect on glycemic control. They also concluded that psychotherapy with self-care interventions are the first-line treatment for depression in DM.

There was also different finding by Deuschle (2013) who concluded that cognitive behavioral therapy combined with selective serotonin reuptake inhibitor (SSRI) treatment may improve glycemic control in depressed DM2 patients; however noradrenergic antidepressants and tricyclic antidepressants (TCAs) may deteriorate the metabolic situation. Thus, SSRIs are preferable in nondiabetic depressed patients with little effect on glycemic control. For depressed DM type 2 patients, SSRIs are the only class of antidepressants with confirmed favorable effects on glycemic control. Another study found that good glycaemic control was achieved by 50.9% of depressed subjects receiving SSRIs versus 34.6% of depressed subjects without antidepressant medication (Jay, Patrick, Jeffrey, Joanne, & David, 2016).

2.3 Quality of life

Diabetic foot ulcers have been estimated to increase the economic health care cost burden in the region of US$500 million (Ramsey et al., 1999). However, few studies have reported that diabetic foot ulcer had a negative impact on daily living regardless of the severity of the ulcer (Pecoraro, 1991).

According to Isaksson and Lundgren (1994) 5% of the population of Western Europe and the United States have DM (Isaksson & Lundgren, 1994). Oyibo, Jude, and Taraweh (2001) and Benotmane, Mohammedi, Ayad, Kadi, and Azzouz (2000) reported that infection is the most common complication of the diabetic foot. Both studies have suggested that infection does delay the healing process (Benotmane et al., 2000; Oyibo, Jude, & Tarawneh, 2001). Furthermore, a prospective study by Tennvall, Apelqvist, and Eneroth (2000), on 220 patients with repeated surgery, antibacterial and prolonged wound healing had increased the cost of medical treatment and living expenses (Tennvall et al., 2000).

This has a significant impact on quality of life (QoL). DFU patient have lost the ability to perform daily activities due to the limitation of mobility and subsequent loss of leisure activities involvement (Loretta, 2001). Loretta (2001) showed subsequently foot ulcers would lead to depression associated with poor quality of life. Several studies have shown that patients with DFUs were more depressed and had a poorer quality of life than those who had no diabetic complications (Loretta, 2001).

Research done by Brod (1998) on both the diabetic foot ulcer patient and care givers showed that both experienced a negative impact on all aspect of QoL and required an adaptation to an appropriate lifestyle (Brod, 1998).

Brod (1998) also found a significant reduction in social activities, increased family pressure, lost job and a poor general health were experienced by both groups. Thus, it is important to help improve both patients and care giver QoL and reduce the negative impact on their general condition. Furthermore, improved clinical understanding regarding the impact of diabetic foot ulcer on patient and caregiver QoL would improve the health care intervention and awareness on patient and caregivers' psychological aspect (Brod, 1998).

According to Ramsey, Newton, and Blough (1999), HRQoL scores in physical and social functioning were higher in a healed DFU compared with a non-healed ($p < 0.05$) (Ramsey et al., 1999). This study shows evidence that healed ulcer improved the HRQoL score and persistent ulcers worsen the score. There were emotional difficulties among the caregivers who were taking care of DFU patients.

Qualitative studies have confirmed that DFU have negative psychological and social effects, such as reduction in social activities, increased family tensions in both patients and their caregivers, limited employment, and financial hardship (Goodridge et al., 2005).

Research had found that diabetes patient had poorer HRQoL compared to non chronic illness patient, but better HRQoL compare to other chronic illness patients (Goodridge et al., 2005). Patient with DFU had a lower score of HRQoL especially for the physical functioning domain. One of the risks including number and severity of foot ulcer are affecting the HRQoL.

-Pain

According to Lis, Berit, Torbjorn, Kare, and Tone (2007), 75% reported minimal pain related to DFU and 57% reported DFU pain while mobilizing and also during the night. Some 25% percent reported pain none of the time (Lis et al., 2007). A higher percentage of analgesic medications are

prescribed. Lis et al. (2007) found that patients with pain had statistically and clinically significantly worsened HRQoL than those who did not. These findings suggest that DFU pain is a significant cause of psychological disturbances, depression and anxiety (Ribu & Wahl, 2004).

-employment

DM has significant negative impact on employment issue for all the patients regardless of its complication. Robert and Nanjundappa (1986) studied a computerized data base at a primary care clinic located in Orange Country, California, U.S.A and found that unemployment was associated with diabetes (Robert & Nanjundappa, 1986). The result also showed that DFU patient was associated with both depression and unemployment. Employment and counselling programs need to be organized for diabetic patients who had employment issues (Robert & Nanjundappa, 1986).

A Dutch cohort study on fatigue at work found that diabetic employees if without co-morbidity are less likely to report fatigue-related complaints, except if having depressed mood. Co-morbidity (chronic diseases) is increasing the fatigue-related complaints (Weijman et al., 2004) .

Survey of employment problem in a random sample of diabetes patient in the UK found that difficulties in obtaining employment were reported by 13% of diabetic patients (Robinson, Yateman, Protopapa, & Bush, 1990). Nine percent of diabetic patients had to change their job because of their illness ($p < 0.001$), and 7% of people with diabetes reported losing a job because of their illness ($p < 0.001$)(Robinson et al., 1990).

-Socioeconomic

Recent research has shown the relationship between poor socioeconomic status and low HRQoL score among the DFU patient (Lis et al., 2007).

-stigma

DFU patients do experience a certain level of stigma by the public. This is due to an extreme biophysical defect, which might precipitate misperceptions, stigma and/or discrimination (Ama, 2006). All these could lead to financial problem with psychosocial neglect (Ama, 2006). Handicap has caused pre-stigma roots in poverty and the socio-psychological and cultural impact of chronic illness (Ama, 2006). Thus a study done in Ghana emphasized the reality or threat of diabetes stigma has to be understood regarding diabetes handicap, which is due to shared responses to long-term illness in communities together with negotiating financial, health and psychological insecurities (Ama, 2006).

2.4 Impact of depression on patient with diabetes/ diabetic foot ulcer

Depression and diabetes marked increased risk of death compared to those who are not depressed (Khalida et al., 2007). One of the reasons is that depression may lead to compliance issue as reported in cross-sectional community studies (Ciechanowski, Katon, & Russo, 2000).

A few studies found that depression may impair self-care of diabetes by adversely effecting memory, energy, and executive function (Katon, 2003). The sense of helplessness among the depressed diabetes patient meant that they lacked motivation for maintaining their diabetes self care routine. A systematic review by Dimatteo and colleagues found that comorbid depression in patients with diabetes decreased adherence to self-care regimens by threefold (DiMatteo, Lepper, & Croghan, 2000) compared to the non depressed group.

Studies have shown that diabetes patients with comorbid depression had poor adherence to diet, exercise regimens, cessation of smoking, and taking the oral hypoglycemics, antihypertensives, and lipid control medications (Lin, Katon, &Von Korff, 2004).

In 2004, the American Diabetes Association found an association of poor self care among diabetes patients with concurrent depression which include medication adherence and self-care activities such as exercise or healthful diet. This behavioral change including smoking, unhealthy diet and lack of exercise can lead to other complications such as blindness, heart failure, or renal failure among patients with diabetes. However, better outcomes require behavioral changes to increase exercise, more healthy nutrition and decrease smoking require motivation, energy, confidence, and sustained effort which are lacking in depressed diabetes patients (Elizabeth et al., 2004).

Another study done by Lin and colleagues (2004) had similar finding which concluded that diabetes with comorbid major depression was associated with lack of physical activity, unhealthy diet, and poor adherence to oral hypoglycemic, antihypertensive, and lipid-lowering medications (Lin et al., 2004).

However surprisingly, most of these studies had also concluded that depression did not adversely affect the foot care among diabetes patients. Elizabeth et al. (2004) found that it is noteworthy that depression was not associated with less self-monitoring behavior for diabetes patients such as self glucose monitoring routines or foot checking routines (Elizabeth et al., 2004). Khalida et al. (2007) did not find an association between depression and diabetes foot-care. Lin et al. (2004) also concluded that preventive care of diabetes, including home-glucose tests, foot checks routines was similar among depressed and nondepressed patients.

Some prospective studies have reported that depression was associated with higher mortality in diabetes patients (Egede et al., 2005). However, randomized controlled trials of interventions for depression in diabetes patients showed that antidepressants improve the depression scores but had no positive effect on glycemic control (Lustman & Patrick, 2002). Several pathophysiological processes to explain the increased mortality in people with depressive disorders and cardiac mortality (Penninx, Beekman, & Honig, 2001) may also apply to diabetes. Mechanisms proposed

decreased heart rate variability secondary to changes in autonomic tone in diabetes patients (Carney, Blumenthal, & Stein, 2001). Other changes lead to peripheral neuropathy include impairment of platelet function (Musselman, Tomer, & Manatunga, 1996); cytokine activation (Owens & Nemeroff, 1994); and activation of the hypothalamic-pituitary-adrenal axis (Harris, Ferrucci, & Tracy, 1999), which may increase susceptibility to infection and to cardiovascular disease (Elenkov & Chrousos, 2002).

There is a positive association between depressive symptoms and mortality. One possible explanation is that people with diabetes complications and depression have a chronic and/or fluctuating course, and thus they have a greater burden of disease (Lustman et al., 2002).

.

3.0 RATIONALE OF THE STUDY

Diabetic foot patients have been increasing in the population and becoming an alarming fact. Many of the health professionals had organized several discussions on this issue. Wound care is a main issue which challenge both the patient as well as the caregiver. Unfortunately, living with diabetic wound has created a numbers of changes for the patients and family. Most of them do not understand well regarding the illness and are not prepare to cope with this problem in long term duration. Subsequently, this would cause significant impact on the biopsychosocial aspect for both patients and care giver.

Based on literature review, there is limited information regarding depression in a patient who was diagnosed with diabetic foot. The available data were mainly on prevalence of depression in Type 2 or Type 1 diabetes mellitus. Most of the data were mainly based on screening questionnaire rather than based on the diagnostic interview. Diabetes mellitus is one of the most psychologically and behaviourally demanding of the chronic medical illness. Diabetic foot is one of the most common complications among the diabetes patient. Diabetic foot patient who was depressed were known to have greater morbidity and mortality with the poor quality of life compare to those who were not depressed. However, there are limited data available in Malaysia.

This study aims to determine the prevalence of depression and its association with the quality of life in patients with diabetic foot. The second aim to investigate the associated factors with depression. Therefore, this study is very importance to increase awareness regarding this topic and provide more importance baseline data to help the healthcare provider for early detection of a co-morbid psychological problem in diabetic foot patient. Moreover, early intervention is importance to preserve a good quality of life and better recovery.

4.0 OBJECTIVES

4.1 General:

1. To determine the prevalence of depression among the patients with DFU attending the outpatient Orthopedic clinic.
2. To determine the socio-demographic data among the patients with DFU.
3. To elicit associated factor among the patients with DFU and depression.
4. To assess the association between depression and QoL of these patients.

4.2 Specific:

1. To screen depression and determine its prevalence among the patients with diabetic foot using HADS-D. HADS is more suitable to use as screening tool in hospital based study population as compare to DASS which is suitable for community population.
2. To determine the prevalence of MDD among patients with diabetic foot using M.I.N.I. M.I.N.I questionnaire was used as diagnostic tool. Both HADS and M.I.N.I were used for all the study subjects to confirm the validation between the positive cases of HADS with positive cases of M.I.N.I.
3. To describe the association between MDD with clinical and socio-demographic factors.
4. To evaluate the QoL of patients with DFU.
5. To compare the QoL between those depressed and not depressed.
6. To evaluate the social support among the DFU patients and compared among those depressed and not depressed.

4.3 Hypothesis of this study

1. There is no significant association between the QoL in patients with DFU with depression.
2. There is no significant association between socio-demographic and clinical variables with depression in patients with DFU.
3. There is no significant association between social supports in patients with DFU with depression.

5.0 MATERIALS AND METHOD/METHODOLOGY

5.1 Ethical approval

Approval for study was obtained from the Medical Research and ethic committee on 4 August 2015, with NMRR ID number: NMRR-15-842-26086 (IIR).

5.2 Background of study area and operational definition of term

Hospital Tengku Ampuan Afzan (HTAA) is a government hospital which is the state hospital of Pahang. It is a tertiary referral centre that accepts patients from another district in Pahang. The Orthopedic department offers both inpatient and outpatient services. Its specialist clinic for diabetic foot operates twice a week on Monday and Wednesday afternoon (2pm-4pm). However, it was not scheduled on Wednesday of 2nd and 4th week. The department provides clinical Orthopedic services, postgraduate training in Orthopedic and perform research in Orthopedic and its related sub-specialities including spine, hand, upper limb, lower limb.

-**DFU**

DFU is defined as an ulceration of the foot associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes.

-**Depressive symptoms**

Depressive symptom is not a disorder in itself, but rather is a description. The symptoms (according to DSM-V diagnostic criteria) are includes:

- Depressed mood or a loss of interest or pleasure in daily activities consistently for at **least a 2 week period**. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feeling sad or empty) or observation made by others (e.g., appears tearful). (In children and adolescents, this may be characterized as an irritable mood.)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
- Insomnia (inability to sleep) or hypersomnia (sleeping too much) nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

-Major depressive disorder

Major depressive disorder is diagnosed using DSM-V diagnostic criteria. A major depressive episode is also characterized by the presence of 5 or more of above symptoms. This mood changes cause impairment of social, occupational, educational or other important functioning

5.3 Study design

Cross sectional study: looking at the prevalence of depression in patients with diabetic foot ulcer. The level of their quality of life and associated factors will be determined.

5.4 Population, setting and duration of study

Period of study: June 2015-Disember 2015

Study population: all of the patients who was diagnosed with diabetic foot ulcer and fulfilled the selection criteria. Only diabetic foot ulcer that diagnosed by orthopaedic team was selected to participant in this study.

Place of study: Outpatient Orthopedic Clinic, HTAA, Kuantan Pahang on every Monday and Wednesday afternoon.

5.5 Sample collection

5.5.1 Sampling method

Universal sampling was used in this study. This was where all of the patients with diabetic foot ulcer came to the hospital for follow-up or dressing. Patients who were eligible were approached and included in the study once they had consented.

5.5.2 Study group

Informed consent was obtained from the patients with diabetic foot ulcer attending the Orthopedic clinic in HTAA, who were eligible and had agreed to participate in the study.

5.5.3 Sample size

The sample size was calculated using the following formula(Daniel, 1999)

$$N = \frac{Z^2 P (1-P)}{d^2}$$

n: sample size

Z: 1.96 (confidence interval 95%)

P: Proportion (8.1%)

d: Precision (0.05)

The proportion of 8.1% was chosen based on the prevalence depression of diabetic foot ulcer found by Khalida et al. (2007) (Khalida et al., 2007). The study aimed to recruit 113 patients with diabetic foot ulcer.

5.5.4 Inclusion criteria

Inclusion criteria:

(a) Patients who diagnosed with diabetic foot ulcer and followed up in outpatient orthopedic clinic in HTAA, Kuantan.

(b) Patient who can read or understand the Malay or English language adequately well

(c) Patient above 18 years old who consented to participate.

5.5.5 Exclusion criteria

(a) A patient who was refused to give consent.

(b) The patient who was having a physical disability such as deaf, blind.

(c) A patient who was unable to communicate in English or Malay.

(d) Existing substance dependence.

5.6 Flow of sample collection:

The patients were recruited from the Orthopedic clinic, HTAA during the study period until the target size was reached. The patients were given a Patient Information Sheet (Appendix A) and explained regarding the study. Once the patients agreed to participate, they were asked to sign an Informed Consent Form (Appendix B).

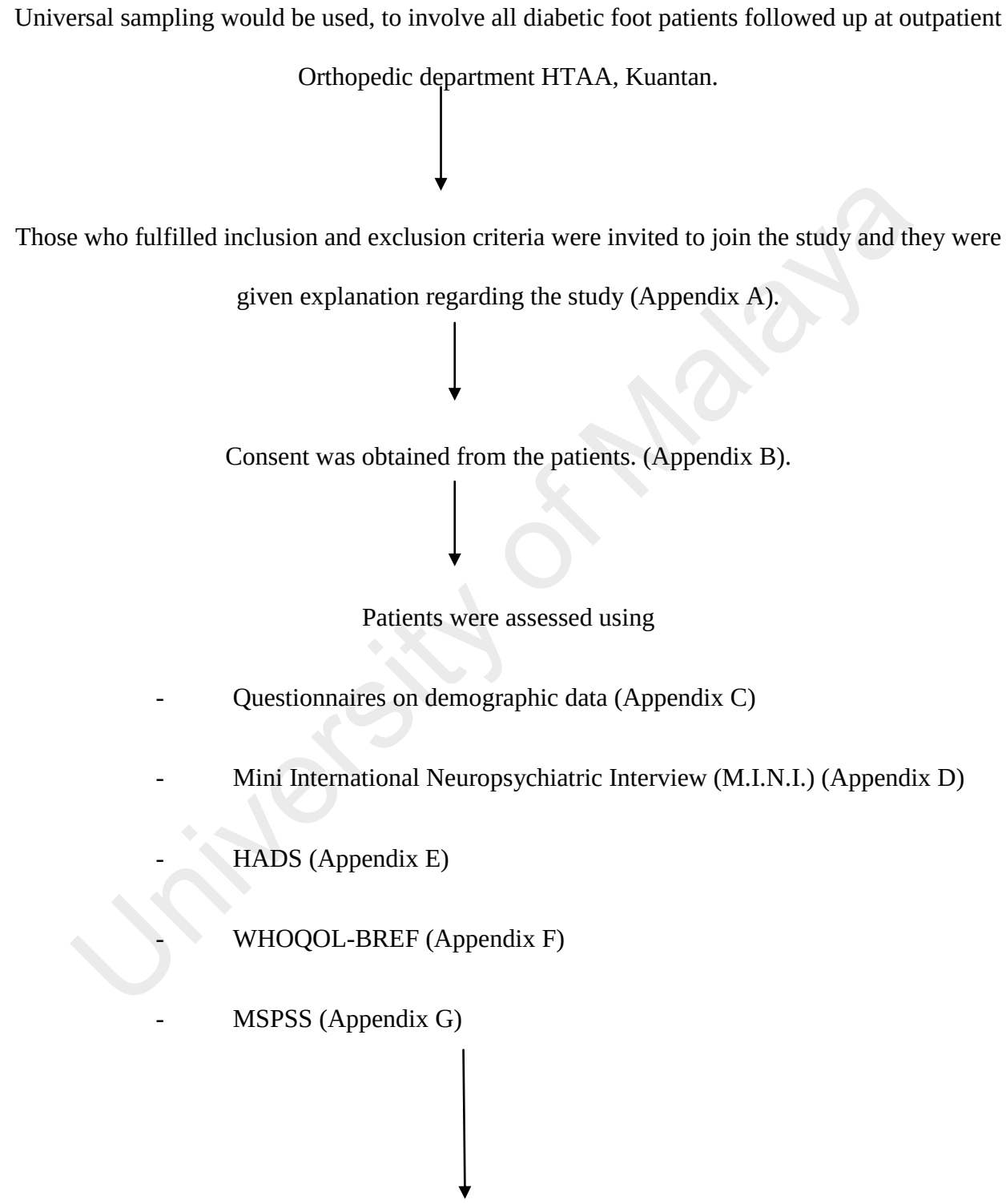
The data were collected by clinical interviews and from the patient's medical records.

All data collected remained confidential and were only used for this study.

Patients who agreed to the study were requested to complete questionnaires on demographic data (Appendix C), Mini International Neuropsychiatric Interview (M.I.N.I.) (Appendix D), Hospital Anxiety and Depression Scale (HADS) (Appendix E), WHOQOL-BREF (Appendix F), Multidimensional Scale of Perceived Social Support (MSPSS) (Appendix G). The investigator was available to provide any assisted guidance on answering the questionnaire that would not in any way influence patient's selection of answers and introduce bias in her answers. Clinical information was obtained by assessing pain score using visual analog scale from patients. Patients were reassured of the confidentiality of their responses to the questionnaire.

The patient was coded accordingly with numbers starting from 001, 002, and so forth. Data were kept confidential in a file by the investigator. Subsequently data will be entered into the latest version of SPSS software and then analyzed accordingly.

Figure 5.1 Flow chart of sample collection



5.7 Rating scales and instruments

1) Social demographic, clinical profile and disease profile questionnaire

A set questionnaire was devised to collect information from the study subjects. It consisted of three parts namely i) socio-demographic profile, ii) section on depression, iii) clinical profile.

Section 1

Consisted of questions on age, marital status, gender, race, education level and employment status.

Section 2

Consisted of questions on depression: family history and subject past history of depression

Section 3

Consisted of questions on clinical profile divided into general question, lifestyle factors and specific to DM subsections.

-under the general question was the presence of the other chronic illness (hypertension, ischemic heart disease, hypercholesterolemia)

-lifestyle factors: smoking status

-Specific to DM questions: age of diagnosis of DM, duration of DM, diabetes complication, the severity of diabetic foot ulcer, Visual Analogue Scale for pain score, latest fasting blood glucose.

2) Mini International Neuropsychiatric Interview (M.I.N.I.)

M.I.N.I. is a short structured diagnostic interview designed to diagnose DSM-IV and ICD-10 psychiatric disorders (lifetime and current). It is a relatively brief instrument divided into modules corresponding to diagnostic categories such as major depressive disorder,

dysthymia, mania/hypomania, panic disorder, social phobia, post-traumatic stress disorder, non-alcohol psychoactive substance use disorders, psychotic disorders, anorexia nervosa and generalized anxiety disorder. The M.I.N.I. has a good validity and reliability and has been translated into many different languages. It was designed to meet the need for diagnostic purposes and accurate structured interview for multicenter clinical trials and epidemiological studies. The MINI questionnaire can be administered by psychiatrists without any training. The MINI International Neuropsychiatric Interview (MINI) is a short, structured diagnostic interview compatible with the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). Excellent inter-rater and test-retest reliabilities have been reported for the English and Malay version. According to Sheehan et al. (1997) the inter-rater (kappa) 0.97, Retest (kappa) 0.79 have been reported for the English version of M.I.N.I. Sheehan et al. (1997) reported that the major depressive disorder kappa:0.84, observed agreement: 92%. For the Malay version of M.I.N.I, the inter-rater reliability was satisfactory (0.67 to 0.85) and the concordance between the MINI's and expert diagnoses was good, with kappa values greater than 0.88 (Firdaus et al., 2012).

In this study, all the subjects were interviewed based on M.I.N.I to confirm the diagnosis of major depressive disorder after they had completed the HADS-D.

3) Hospital Anxiety and Depression Scale (HADS)

HADS is a self-rated questionnaire commonly used to assess levels of anxiety and depression. HADS comprises statement which the patients rate based on their experience over the past week. Even-numbered questions relate to depression and odd-numbered questions related to anxiety. Each question has 4 possible responses. Responses are scored on a scale from 3 to 0. The maximum score is therefore 21 for depression and 21 for

anxiety. A score of 11 or higher indicates the probable presence of mood disorder. A score of 8 to 10 indicates possible presence of the depressive disorder. In its current form the HADS is now divided into four ranges: normal (0-7), mild (8-10), moderate (11-15) and severe (16-21).

For this study, the cut-off point of 8 and above was taken as possible case of depression as suggested by Zigmond and Snaith in 1983. The authors recommended 2 cut-off scores for both the anxiety and depression subscales 7/8 for possible and 10/11 for probable anxiety or depression (Zigmond & Snaith, 1983).

The two HADS subscales that are anxiety and depression subscales have been found to be independent measures. As there is usually a high comorbidity of depression and anxiety, it is a benefit that the HADS enables measurement of the two disorders separately. For the purpose of this study, only the depression subscale (HADS-D) was used. Cameron et al. (2008) in their study had found that HADS-D demonstrated reliability, convergent/discriminant validity, the robustness of factor structure, and responsiveness to change in a sample of primary care patients (Cameron, Crawford, Lawton, & Reid, 2008). HADS-D had been used in studies of depression in diabetes as a screening tool for depression. Somatic symptoms of depression (e.g. insomnia and weight loss) are not part of this scale, and therefore findings were not confounded by symptoms of uncontrolled diabetes. Apart from that, HADS is available in Malay and English language, is easy to use and had been validated in the local population. The Malay version of HADS was validated by Hatta et al. (1997).

A validity study of the Malay version of HADS by Fariza in 2003 revealed that HADS had a sensitivity of 92.3% and specificity of 90.8% for depression at 8/9 cut off points whereas for the anxiety subscale, the sensitivity is 90% and specificity is 86.2% at 8/9 cut-off

points (Fariza, 2003). Therefore, for the purpose of this study, only the depression subscale was analyzed using the cut-off point of 8 or more as having depression.

4) WHOQOL-BREF

WHO developed two instruments for measuring the QoL (the WHOQOL-100 and the WHOQOLBREF), that can be used in a variety of cultural settings while allowing comparison of the results from different populations and countries. These instruments have many uses, including use in medical, research, and policy making.

The WHOQOL-BREF, an abbreviated 26 item version of the WHOQOL-100, was developed using data from the field-trial version of the WHOQOL-100. The WHOQOL is now available in over 20 different languages.

The WHOQOL instruments, by focusing on individuals' own views of their well being, provide a new perspective on the disease. For example, that diabetes involves poor blood glucose control is well understood, but only received little systematic attention on the effect of the illness on the perception of social relationship, financial and functionality.

The WHOQOL-BREF is self-administered if respondents have sufficient ability: otherwise, interviewer-assisted or interview-administered forms should be used. Malay version of WHOQOL-BREF had been validated by Hasanah, Naing, and Rahman (2003).

The WHOQOL-BREF produces domain scores (e.g. physical, psychological, social relationships and environment). The four domains scores denote an individual's perception of QoL in each particular domain. Domain scores are scaled in a positive direction (i.e., higher scores reflect higher QoL). The mean score of items within each domain is used to calculate the domain score. Mean scores are then multiplied by 4 to make domain scores comparable with the scores used in the WHOQOL-100. The WHOQOL-BREF has good content validity and test-retest reliability.

5) Multidimensional Scale of Perceived Social Support

The Multidimensional Scale of Perceived Social Support (MSPSS) is a simple instrument, developed to rate perceived social support. The original English version has been used worldwide. The original scale has demonstrated good psychometric properties in different settings. The validated Malay version has been available by a study done by Ng, Amer Siddiq, Aida, Zuraida, and Koh (2010).

There are 12 items assess 3 sources of support: family, friends, and significant other. Items are rated on a 7-point Likert-scale ranging from 1 (very strongly disagree) to 7 (very strongly agree).

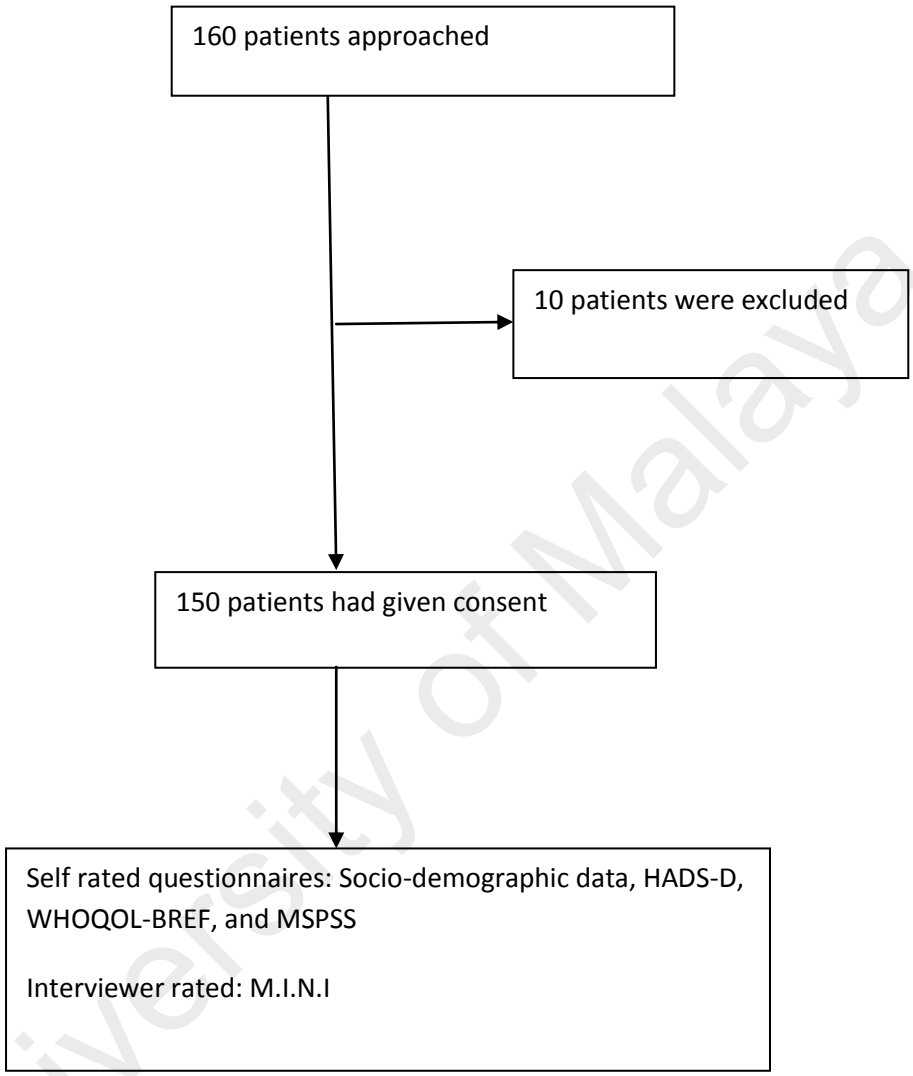
The MSPSS can be scored to measure perceived support from family, friends, and a significant other, or global perceived support. It is a self-administered questionnaire. The scales have demonstrated strong test-retest reliability over a 2- to 3-month interval (r = .72 to .85). Validity has been established through the negative association of scores on the MSPSS with scores on measures of depression (Zimet, Dahlem, Zimet, & Farley, 1988).

For scoring, to calculate mean scores as divided category:

- Significant Other Subscale: Sum across items 1, 2, 5, & 10, and then divide by 4.
- Family Subscale: Sum across items 3, 4, 8, & 11, and then divide by 4.
- Friends Subscale: Sum across items 6, 7, 9, & 12, and then divide by 4.
- Total Scale: Sum across all 12 items, then divide by 12.

Mean scale score ranging from 1 to 2.9 could be considered low support; 3 to 5 is considered moderate support; a score from 5.1 to 7 means high support (Zimet et al., 1988)

Figure 5.2 Algorithm of patients' recruitment and data collection



5.8 Statistical analyses

Data were analyzed using the Statistical Packages for the Social Sciences (SPSS) software Version 20.0.

Firstly, summary of the socio-demographic and clinical variables were done by using descriptive statistics.

Prevalence of MDD based on M.I.N.I and possible cases of depression based on HADS-D score with the respective cut-off point were determined.

The relationship between MDD as dependent variable and socio-demographic and clinical variables as independent variables were analyzed by using cross tabulation analysis.

All of the statistical tests were interpreted at the 5% significant level. The socio demographic and clinical variables were compared between depressed and non-depressed and in a separate analyses based on the M. I. N.I result for the confirmed case of depressed.

Regression analyses were carried out to study the strength of association between outcome and factors of interest and adjustment for covariates/confounders.

Three different approaches were used to assess the goodness of fit. The methods were the Hosmer-Lemeshow test, Classification table and area under the receiver operating characteristic (ROC) curve.

WHOQOL-BREF data were analyzed. The data from the WHOQOL-BREF were categorized into total score, Domain 1 score, Domain 2 score, Domain 3 score and Domain 4 score. Then, the mean of each group was analyzed using SPSS. Mean score of each group were compared between the depressed and non-depressed using the

Independent Samples *t*- test for normally distributed variables and Mann Whitney *U* test for non-normally distributed variables.

Finally, MSPSS data were analyzed. The data were categorized into total mean score, significant others group mean score, friend group mean score and family group mean score. Then mean scores of each group were compared between the depressed and non-depressed and tested for clinical significance.

6.0 RESULTS

6.1. Demographic Data

There were 160 diabetic patients who attended the outpatient orthopedic clinic during the study period. However, 10 patients were excluded from the study as they did not fulfill the selection criteria.

A total of 150 patients with DFU were approached and there was no refusal as they all agreed to participate in the study (response rate of 100%). The socio-demographic profiles of study objects were summarized in Table 6.1.

6.1.1 Age

The mean age group for the sample was 58.0 years old with a standard deviation of 10.92 years.

6.1.2 Race

The majority of the subjects in this study (84.0%) (n= 126) were Malay. The next highest ethnic subgroup was Indian with 8.0% (n=12) and followed by Chinese 7.3% (n=11). There was one study subject foreigner who was categorized in "other" group (0.7%). For further analyses later, these groups were categorized into Malay and Non-Malays.

6.1.3 Sex

The majority of the study subjects were female consisting of 89 patients (59.3%) while male comprised 61 patients (40.7%).

6.1.4 Marital Status

In this study, 76.0% (n=114) of the study subjects were married. This was followed by those who were divorced/separated/widow(er) 19.4% (n = 29) and single 4.7% (n = 7). In the later analyses, this group was categorized into married, single and divorced/separated/widow(er).

6.1.5 Education level

Half of the study subjects had primary education 51.3% (n = 77). Among the DFU patients, 52 of them (34.7%) had secondary school education. This was followed by no formal education 11.3% (n = 17). Only 4 of the study subjects (2.7%) had higher education in the tertiary level including college and university. In the later analyses, this group was categorized into without formal education and with formal education.

6.1.6 Occupation

Among the diabetic foot patients, 44.7% (n = 67) of them were unemployed. This was followed by 36.6% (n = 55) who were employed (semi-skilled and professional). Some 27 (18.0%) of the study subjects were retired and only one of them was still studying. In the later analyses, this group was categorized employed and unemployed.

Table 6. 1 Socio-demographic of the study samples

Variables	n (%)	Mean (SD)
Age		58.0 (10.92)
Gender		
Male	61 (40.7)	
Female	89 (59.3)	
Race		
Malay	126 (84.0)	
Chinese	11 (7.3)	
Indian	12 (8.0)	
Others	1 (0.7)	
Marital Status		
Single	7 (4.7)	
Married	114 (76.0)	
Divorce/Separated/Widower	29 (19.4)	
Education level		
No formal education	17 (11.3)	
Primary	77 (51.3)	
Secondary	52 (34.7)	
Tertiary	4 (2.7)	
Occupation		
Student	1 (0.7)	
Employed	55 (36.6)	
Unemployed	67 (44.7)	
Retired	27 (18.0)	

Note: n = frequency, % = percentage, SD = standard deviation

6.2 Clinical variables

The clinical characteristics of DFU patients in this study (n=150) are summarized in Table 6.2.

6.2.1 Duration of DM (years)

Some 43.3% (n = 65) of the study subjects had DM for more than 10 years. This was followed by 28.7% (n = 43) of them were diagnosed DM for 6-10 years. Another 28.0% (n = 42) of the study subjects had DM for shorter duration of about 1-5 years. This is in keeping with the fact that DM is a chronic illness.

6.2.2 Family history of DM

The majority of the study subjects, 72.7% (n =109) had a family history of diabetic mellitus.

6.2.3 Family history of depression

In this study, 4.0% (n = 6) of the diabetic foot patients had a family history of depression.

6.2.4 Past history of depression

Only 5 (3.3%) study subjects had experienced depression before.

6.2.5 Number of other chronic illness besides diabetes, present at the time of study

The majority of the study subjects had one chronic medical disease, which was about 36.7% (n = 55). Followed by 34.0% (n = 51) who had two chronic medical illnesses, while 23.3% did not have other chronic medical illness. 6.0% (n = 6) had three and more chronic medical illness. These chronic medical illnesses include hypertension, hypercholesterolemia, ischemic heart disease and others. There was one patient who was diagnosed with breast carcinoma and was on treatment.

6.2.6 Smoking

The majority of the diabetic foot ulcer patients (n = 111, 74.0%) were not smokers currently, including patients who never smoked at all and those patients who had quit smoking.

6.2.7 DFU duration (months)

Half of the diabetic patients had foot ulcer for 1-5 months (n = 76, 50.7%); some 11.3% (n = 17) had diabetic foot ulcer less than 1 month. The majority of the patients were acute diabetic foot cases, while 38.0% (n = 57) of the patients were having chronic DFU with duration six months and above.

6.2.8 Condition of the foot ulcer at time of study

Some 127 (84.7%) of the patients had an unhealed DFU. Only 15.3% (n = 23) patients had healed DFU.

6.2.9 Amputation

The majority of the DFU condition had progressed and worsened; 61.3% (n = 92) of the sample had underwent amputation operation. However, 38.7% (n = 58) of DFU patient did not require any amputation during illness.

6.2.10 Intensity of pain

The majority of the patients had moderate pain score (42.7%, n = 64), followed by 41.3% (n = 62) of the patients who had mild pain score and 8.7% (n = 13) did not complain of pain. Only 11 (7.3%) of the patients had severe pain score.

6.2.11 Numbers of diabetic illness complications

Some 38.7% (n = 58) of the patients had one diabetic complication. This was followed by 25.3% (n = 38) of the DFU patients who had 2 diabetic illness complications. Most of the patients were diagnosed with peripheral neuropathy and retinopathy which were already diagnosed by the doctors and under follow-up or patient reported to the investigator about some of the symptoms such as numbness. Only 13.4% (n = 20) had 3 and more diabetes illness complication. The diabetic illness complications include retinopathy, nephropathy, stroke, skin lesion, peripheral neuropathy and others.

6.2.12 Diabetic control (Fasting Blood Glucose)

The majority of the patients regular follow up at the government clinic (Klinik Kesihatan) for DM. The mean of fasting blood glucose (latest result taken at Klinik Kesihatan) among all the study subjects was 8.6 with standard deviation of 2.73.

Table 6. 2 Clinical characteristics of the study samples

Variables	n (%)	Mean (SD)
Diabetes duration (years)		
1-5	42 (28.0)	
6-10	43 (28.7)	
>10	65 (43.3)	
Family history of diabetes		
Yes	109 (72.7)	
No	41 (27.3)	
Family history of depression		
Yes	6 (4.0)	
No	144 (96.0)	
Past history of depression		
Yes	5 (3.3)	
No	145 (96.7)	
Number of other chronic illness besides diabetes, present at the time of study		
None	35 (23.3)	
1	55 (36.7)	
2	51 (34.0)	
≥3	6 (6.0)	
Smoking		
Yes	39 (26.0)	
No	111 (74.0)	
Diabetic Foot Ulcer duration (months)		
< less than 1	17 (11.3)	
1-5	76 (50.7)	
≥ 6	57 (38.0)	
Foot Ulcer		
Healed	23 (15.3)	
Unhealed	127 (84.7)	
Amputation		
Yes	92 (61.3)	
No	58 (38.7)	
Intensity of pain (score)		
No pain	13 (8.7)	
Mild	62 (41.3)	
Moderate	64 (42.7)	
Severe	11 (7.3)	

Variables	n (%)	Mean (SD)
Number of other diabetes complications		
None	34 (22.7)	
1	58 (38.7)	
2	38 (25.3)	
≥3	20 (13.4)	
Fasting blood glucose (FBS)		8.6 (2.73)

Note: n = frequency, % = percentage, SD = standard deviation

6.3 Prevalence of depression

The number of possible cases of depression in patients with DFU detected using the HADS-D with a cut-off point of 8 or more was 24.0% (n = 36). According to the M.I.N.I, 20.7% (n = 31) of the sample was diagnosed to have MDD (Table 6.3). Those who were screened positive using HADS-D were the same patients who were also diagnosed as MDD using M.I.N.I.

Table 6.3 Prevalence of depression among diabetic foot ulcer patients based on HADS and M.I.N.I

Assessment	Depression status	
	Depressed, n (%)	**Non-depressed, n (%)**
HADS-D	36 (24.0)	114 (76.0)
M.I.N.I_MDD	31 (20.7)	119 (79.3)

Note: HADS-D = "Hospital Anxiety and Depression Scale (depression sub-scale)", M.I.N.I = Mini International Neuropsychiatric Interview (M.I.N.I), n = frequency, % = percentage

HADS-D rating scales result were further analyzed into possible cases and probable cases (Table 6.4). Among all the positive cases of depressive symptoms using HADS rating scales, 27 (18.0%) of the cases were considered as possible cases and 9 were considered as probable cases.

Table 6. 4 Depression characteristics of diabetic foot ulcer Patients using HADS

Depression characteristics	n(%)
Normal (0-7)	114 (76.0)
Possible Case (8-10)	27 (18.0)
Probable Case (11-21)	9 (6.0)

Out of the 31 patients diagnosed with MDD using M.I.N.I, 25 (80.6%) of them were current episodes, 5 (16.1%) of them were recurrent episodes and only 1 had past episode (Table 6.5).

Table 6.5 Depressive Episode characteristics among diabetic foot ulcer patients with MDD, n =31

Major Depressive Episode	n (%)
Current	25 (80.6)
Past	1 (3.2)
Recurrent	5 (16.1)

Among all the patients who had MDD and DFU, the majority of them either had DFU for 1-2 months or more than 6 months, which was both 32.3% respectively. This was mainly because of

those patients who had just done debridement or amputation and those patients who had a chronic and unhealed ulcer. There were 16.1% of the patients who had DFU for less than one month but also had major depressive symptoms. This was mainly due to sudden onset of profound pain and disability (Figure 6.1).

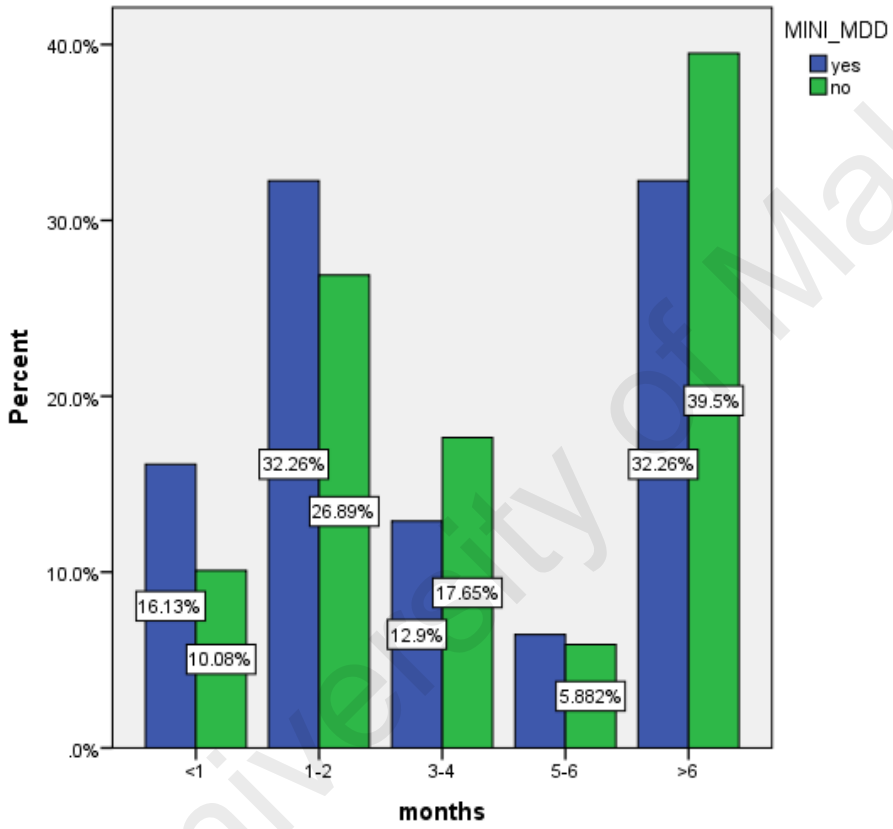


Figure 6.1 MDD by duration of DFU

6.3.1 Socio-demographic and clinical characteristic of depressed and non-depressed DFU patients

From Table 6.6, the mean age of patients who had MDD was 57.3 (*SD* 7.42). This was comparable to the non depressed study group with mean 58.2 (*SD* 11.68). Among 31subjects of

the depressed group, 10 (16.4%) were male and 21 (23.6%) were female. In this study, Malay was the highest in the depressed group (87.1%), followed by Indian 9.7% and Chinese 3.2%. This was because Malay was the highest group who is visiting the orthopaedic DFU clinic (84.0%).

Among the 31 depressed subjects, 27 of them were married and only 4 were single/divorced/widow(er). The majority of them had primary or secondary education. Most of them were unemployed/ retired and did not have a stable income.

For the clinical characteristic (Table 6.7), the majority of the depressed subjects had DM of more than 10 years duration. Among 31 DFU subjects with MDD, 24 of them had strong a family history of diabetes, only 4 had a family history of depression and only 3 had past history of depression. Thirteen of the depressed subjects had at least 1 chronic medical illness and 12 of them had at least 2 chronic illnesses. The majority of them (n = 16) had suffered from diabetic foot ulcer for 1-6 months. This was because the tertiary hospital emphasized acute setting patient who needed amputation or wound debridement or complicated chronic cases. Almost all of the subjects with DFU and MDD (n = 30) had an unhealed ulcer, and 17 of them had history amputation with a moderate degree of pain status. Some 12 of them had one diabetes complication, 9 of them had 2 diabetes complications and 7 of them had 3 or more diabetes complication. Mean reading for fasting blood glucose was 8.6 (SD 2.92). This indicated that the study subjects had poor diabetes control.

Table 6.6 Socio-demographic of the depressed and non-depressed patients with diabetic foot ulcer

Variables	Depressed (n =31) (%)	Non-Depressed (n = 119) (%)
Age[a]	57.3 (7.42)	58.2 (11.68)
Gender		
Male	10 (16.4)	51 (83.6)
Female	21 (23.6)	68 (76.4)
Race		
Malay	27 (21.4)	99 (78.6)
Chinese	1 (9.1)	10 (90.9)
Indian	3 (25.0)	9 (75.0)
Others	0 (0.0)	1 (100.0)
Marital Status		
Single/ Divorced/Separated/Widower	4 (23.7)	32 (76.3)
Married	27 (23.7)	87 (76.3)
Education level		
No formal education	3 (17.6)	14 (82.4)
Primary	14 (18.2)	63 (81.8)
Secondary	13 (25.0)	39 (75.0)
Tertiary	1 (25.0)	3 (75.0)
Occupation		
Employed	10 (22.1)	45 (77.9)
Unemployed/ Student / Retired	21 (18.2)	74 (81.8)

Table 6.7 Clinical characteristics of the depressed and non-depressed patients with diabetic foot ulcer

Variables	Depressed (n =31)	Non-Depressed (n = 119)
Diabetes duration (years)		
1-5	8 (19.0)	34 (81.0)
6-10	6 (14.0)	37 (86.0)
>10	17 (26.2)	48 (73.8)
Family history of diabetes		
Yes	24 (22.0)	85 (78.0)
No	7 (17.1)	34 (82.9)
Family history of depression		
Yes	4 (66.7)	2 (33.3)
No	27 (18.8)	117 (81.2)
Past history of depression		
Yes	3 (60.0)	2 (40.0)
No	28 (19.3)	117 (80.7)
Number of other chronic illness besides diabetes, present at the time of study		
None	2 (5.7)	33 (94.3)
1	13 (23.6)	42 (76.4)
2	12 (23.5)	39 (76.5)
3	4 (44.4)	5 (55.6)
Smoking		
Yes	5 (12.8)	34 (87.2)
No	26 (23.4)	85 (76.6)
Diabetic Foot Ulcer duration (months)		
< less than 1	5 (29.4)	12 (70.6)
1-6	16 (21.1)	60 (78.9)
> 6	10	47 (82.5)
Foot Ulcer		
Healed	1 (4.3)	22 (95.7)
Unhealed	30 (23.6)	97 (76.4)
Severity of amputation		
Yes	17 (18.5)	75 (81.5)
No	14 (24.1)	44 (75.9)
Intensity of pain (score)		
No pain	3 (23.1)	10 (76.9)
Mild	9 (14.5)	53 (85.5)
Moderate	15 (23.4)	49 (76.6)
Severe	4 (36.4)	7 (63.6)

Table 6.7 Continued

Variables	Depressed (n =31)	Non-Depressed (n = 119)
Number of other diabetes complications		
None	3 (8.8)	31 (91.2)
1	12 (20.7)	46 (79.3)
2	9 (23.7)	29 (76.3)
≥3	7 (35.0)	13 (65.0)
Fasting blood glucose (FBS)[a]	8.6 (2.92)	8.6 (2.69)

Note: [a]Mean (SD)

6.4Association and Regression

6.4.1 Simple regression analysis

Simple logistic regression (LR) analyses were performed on all the independent variables to determine factors associated with the MDD in DFU patient. As a result, a total of three independent variables found to be statistically significant. The family history of depression was found to be statistically significantly associated with major depressive disorder with *p*-value of 0.015 (Table 6.8).

Another independent clinical variable found significantly associated with MDD was other chronic medical illness (except diabetes). One to two chronic medical illnesses were found to be significantly associated with MDD with *p*-value 0.033, and three and more chronic medical illness were strongly significant with *p*-value 0.009.

Diabetes complication was found to be associated with MDD. Three and more diabetes complications present at the time of the study was strongly significantly associated with MDD with *p*-value 0.025.

6.4.2 Multiple logistic regression analysis

Multiple logistic regression (MLR) analysis was used to determine the independent variables that best predict the MDD. Deviance method was used instead of Maximum Likelihood method to identify factors associated with MDD.

6.4.2.1 Variable selection

The variables selected for the study were based on the statistically significant and clinically meaningful variables with p-value < 0.25. Such variables selected were marital status, family history of depression, the number of other chronic illness besides diabetes, smoking status, the severity of DFU, and the number of other diabetes complication.

Variable selection methods such as forward LR and backward LR method were used in this study. Eliminated variables were re-evaluated by adding those variables into the study by forceful entry to check the significance of the variable.

Table 6.8 Associated factors of Major Depressive Disorder (MDD) by simple logistic regression model

Variables	Regression coefficient (b)	Crude OR (95% CI)	Wald Statistic	*P*-value
Age (years)	-0.008	0.992 (0.957, 1.029)	0.173	0.678
Gender				
Male	0	1		
Female	0.454	1.575 (0.683, 3.634)	1.134	0.287
Race				
Malay	0	1		
Non-Malay	-1.299	0.733 (0.231, 2.327)	0.277	0.599
Marital Status				
Single/ Divorce/Separated/Widower	0	1		
Married	-2.079	2.453 (0.806, 7.652)	2.508	0.113
Education level				
Without formal education	0	1		
With formal education	0.219	1.244 (0.344, 4.634)	0.106	0.744
Occupation				
Employed	0	1		
Unemployed/ Student/Retired	0.245	1.277 (0.552. 2.956)	0.326	0.568

Table 6.8 Continued

Variables	Regression coefficient (b)	Crude OR (95% CI)	Wald Statistic	*P*-value
Diabetes duration (years)				
1-5	0	1		
6-10	-0.372	0.689 (0.217, 2.191)	0.398	0.528
>10	0.409	1.505 (0.583, 3.885)	0.714	0.398
Family history of diabetes				
No	0	1		
Yes	0.316	1.371 (0.540, 3.480)	0.714	0.398
Family history of depression				
No	0	1		
Yes	2.159	8.667 (1.509, 49.784)	8.667	**0.015**
Past history of depression				
No	0	1		
Yes	1.835	6.268 (0.999, 39.312)	3.839	0.260
Number of other chronic illness besides diabetes, present at the time of study				
None	0	1		
1-2	1.628	5.093 (1.141, 22.734)	4.458	**0.033**
≥3	2.580	13.200 (1.896, 91.907)	6.791	**0.009**
Smoking				
No	0	1		
Yes	-0.732	0.481 (0.171, 1.355)	1.918	0.166
Diabetic Foot Ulcer duration (months)				
Less than 1	0	1		
1-6	-0.446	0.640 (0.187, 2.083)	0.549	0.459
> 6	-0.672	0.511 (0.147, 1.776)	1.116	0.291
Foot Ulcer				
Healed	0	1		
Unhealed	1.918	6.804 (0.880, 52.612)	3.376	0.066
Severity of amputation				
No	0	1		
Yes	-0.339	0.712 (0.320, 1.584)	0.692	0.406
Intensity of pain				
No pain	0	1		
Mild	-0.569	0.566 (0.130, 2.464)	0.575	0.448
Moderate	0.020	1.020 (0.248, 4.196)	0.001	0.978
Severe	0.644	1.905 (0.321, 11.312)	0.503	0.478

Table 6.8 Continued

Variables	Regression coefficient (b)	Crude OR (95% CI)	Wald Statistic	*P*-value
Number of other diabetes complications				
None	0	1		
1-2	1.062	2.893 (0.804, 10.407)	2.646	0.104
≥3	1.716	5.564 (1.242, 24.926)	5.032	**0.025**
Fasting blood glucose (mmol/dL)				
4.4 - 7.0	0	1		
≥7.1	-0.174	0.840 (0.358, 1.968)	0.161	0.688

Note: *P*-value < 0.05 is significant, CI = confidence interval, OR = Odds Ratio

Table 6.9 on results of using multiple logistic regression showed marital status, family history of depression, the number of other chronic illness besides diabetes, smoking, and severity of foot ulcer were retained in the model using backward LR elimination. In forward LR method, only family history of depression and number of other chronic illness were retained. Hence, the result of backward LR method was selected as the most parsimonious model to further the analysis. Although the *p*-values of marital status, smoking, and severity of DFU were > 0.05 the variables were retained based on clinical importance. Hence, the preliminary main effect model was obtained using backward LR.

Table 6.9 Multiple logistic regression (preliminary main effect model: Forward LR method) of factors associated with Major Depressive Disorder (MDD)

Variables	Regression coefficient (b)	Adjusted OR (95% CI)	Wald Statistic	*P*-value
Marital Status				
Single/ Divorce/Separated/Widower	0	1		
Married	1.335	3.799 (0.999, 14.446)	3.837	0.050
Family history of depression				
No	0	1		
Yes	2.835	17.023 (1.598, 181.400)	5.513	**0.019**
Number of other chronic illness besides diabetes, present at the time of study				
None	0	1		
1-2	1.786	5.965 (1.102, 32.285)	4.297	**0.038**
≥3	3.228	25.238 (2.723, 233.890)	8.076	**0.004**
Smoking				
No	0	1		
Yes	1.223	0.294 (0.086, 1.005)	3.812	0.051
Foot Ulcer				
Healed	0	1		
Unhealed	1.870	6.490 (0.809, 52.061)	3.099	0.078

Note: CI = confidence interval, OR = Odds Ratio

6.4.3 Interaction

In order to produce a preliminary final model, the presence of interaction between the variables in the study was determined. In this study, only clinically or biologically plausible using two-way interaction terms were performed. The interaction terms were included in the model one at a time to evaluate its *p*-values. The result shows that there was no statistically significant two-way interaction found in this study (Table 6.10).

Table 6.10 Possible two-way interaction in the model

Interaction term	*P*-value
Marital Status * Family history of Depression	>0.950
Marital Status * Number of Chronic illnesses	0.813
Marital Status * Smoking	0.802
Marital Status * Foot Ulcer	0.554
Family history of Depression * Number of Chronic illnesses	0.384
Family history of Depression * Smoking	0.287
Family history of Depression * Foot Ulcer	>0.950
Number of Chronic illnesses * Smoking	>0.950
Number of Chronic illnesses * Foot Ulcer	>0.950
Smoking * Foot Ulcer	>0.950

Table 6.11 Associated factors of Major Depressive Disorder (MDD) by Multiple logistic regression (final model)

Variables	Regression coefficient (b)	Adjusted OR (95% CI)	Wald Statistic	*P*-value
Family history of depression				
No	0	1		
Yes	2.835	17.023 (1.598, 181.400)	5.513	0.019
Number of other chronic illness besides diabetes, present at the time of study				
None	0	1		
1-2	1.786	5.965 (1.102, 32.285)	4.297	0.038
≥3	3.228	25.238 (2.723, 233.890)	8.076	0.004

[a] Forward LR Multiple logistic regression model was applied
Interaction term were checked and not found
Model fitness were checked using Hosmer-Lemeshow test, overall classification table, and area under the ROC curve.

6.4.4 Overall fit of the model

Three different approaches were used to assess the goodness of fit. The methods were the Hosmer-Lemeshow test, Classification table and area under the receiver operating characteristic (ROC) curve. Hosmer-Lemeshow test indicated no significant difference between the observed and predicted probabilities (p = 0.874). Meanwhile, the classification table showed that the model accurately classified 80.7% of the cases in this study. Finally, the area under the ROC curve was 0.779 (95%CI: 0.699, 0.859), p - value < 0.001. Hence, the model could accurately discriminate 77.9% of the cases. Therefore, it was assumed that the model was fit for assessing the MDD outcome (Table 6.12).

Table 6.12 Overall fit of the model

Goodness of Fit Test	**Result**
Hosmer-Lemeshow Test[a]	0.874
Overall Classification Table	80.7%
Area under the curve	0.779

Note: [a] *P*-Value

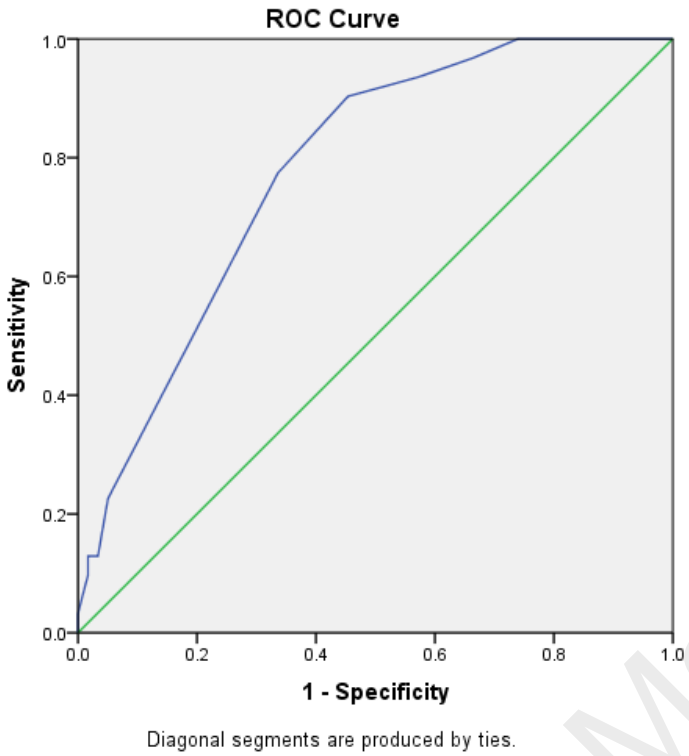


Figure 6.2 Area under the ROC curve

6.5 Analysis of Quality of life

The QoL of a patient in this study was assessed using WHOQOL- BREF questionnaires. The scores were summarized into 5 groups that included total QoL score, domain 1, domain 2, domain 3, and domain 4. Domain 1 summarized the physical component, domain 2 measured the psychological component, domain 3 included all the social relationship aspect and domain 4 measured the environment component.

Table 6.13 showed the means and standard deviations of the QoL for DFU patients. The mean total score for total QoL score was 86.6 (SD 11.65). The mean score for domain 1 score was 21.6 (SD 5.01), domain 2 was 19.4 (SD 2.44), domain 3 was 10.3 (SD 1.91), domain 4 was 28.4 (SD 4.65).

Table 6.13 Means and standard deviations of quality of life among diabetic foot ulcer patients

Domain	Mean[a] (SD)
Physical	21.6 (5.01)
Psychological	19.4 (2.44)
Social relationship	10.3 (1.91)
Environment	28.4 (4.65)
Total QoL	86.6 (11.65)

Note: [a] mean score

6.5.1 Comparison of quality of life domains between depressed and non-depressed groups

The mean scores of all the domains were analyzed and compared between those with MDD and non-MDD group. The DFU patients with comorbid depression had a lower score of all the domains mean score and mean total score compared to those without comorbid depression. All the domains differences were statistically significant. (Table 6.14).

Table 6.14 Comparison of quality of life domains between depressed and non-depressed groups

QoL Domain	Depressed (n=31) Median (IQR)	Non-depressed (n = 119) Median (IQR)	Z-statistic[b]/ t-statistic[c](df)	*P*-value
Physical	18.0 (4.0)	22.0 (5.0)	-5.293[b]	<0.001
Psychological	18.0 (3.0)	20.0 (4.0)	-4.461[b]	<0.001
Social relationship	9.0 (3.0)	11.0 (3.0)	-3.229[b]	<0.001
Environment	25.9 (2.7)[a]	29.0 (4.8)[a]	-3.488 (148)[c]	0.001
Total	76.6 (8.8)[a]	89.2 (10.9)[a]	-5.970 (148)[c]	<0.001

Note: [a]Mean (SD), [b]Mann-Whitney test was applied, [c]Independent t-test was applied, df = degree of freedom, *p<0.05, **p<0.01

6.6 Analysis of social support

The social support of DFU patient in this study was assessed using MSPSS questionnaires. The scores were summarized into 4 groups that included significant other, friends, family, and total perceived social support.

The mean scale score ranging from 1.0 to 2.9 was considered as low support; a score of 3.0 to 5.0 was considered as moderate support and a score from 5.1 to 7.0 could be considered as high support.

Table 6.15 shows the means and standard deviations of social support among DFU patient. The total mean scale score was 5.5 (SD 0.89). This showed that overall DFU patients perceived that they had high social support. The mean scale score for significant others (husband or wife) was 5.8 (SD 1.27). This study showed that the majority of married DFU patients had a very supportive spouse. The mean scale score for friends group was 4.6 (SD 1.38) and family group was 3.5 (SD 0.36). In general, DFU patients perceived that they had moderate support from both family and friends.

Table 6.15 Means and standard deviations of perceived social support of among DFU patients

Perceived Social Support	Mean (SD)
Significant other	5.8 (1.27)
Family	3.5 (0.36)
Friends	4.6 (1.38)
Total Perceived Social Support	5.5 (0.89)

6.6.1 Associated factors of Major Depressive Disorder with perceived social support subscales

Table 6.16 shows the associated factors of MDD with perceived social support subscales by the simple logistic regression model. All of the subscales were statistically not significant. This shows that none of the variables were found to be associated with MDD. Further analysis of multiple logistic regression was not performed.

Table 6.16 Associated factors of Major Depressive Disorder with perceived social support subscales by simple logistic regression model

Variables	Regression coefficient (b)	Crude Odds Ratio (95% CI)	Wald Statistic	*P*-value
Significant other	0.519	1.688 (0.880,3.207)	2.478	0.115
Family	-0.555	0.574 (0.173, 1.907)	0.821	0.365
Friends	-0.111	0.895 (0.466, 1.718)	0.111	0.739
Total	-0.653	0.520 (0.133, 2.036)	0.881	0.348

7.0 DISCUSSION

Overall respondents in this study were from middle age group, predominant married female, Malay ethnic, primary education level and employed status. The majority of them had diabetes illness for more than 10 years duration and had strong family history of diabetes. Six of the study subjects had family history of depression and 5 had experienced past history of depressive episodes.

Most of them have at least one to three of another chronic medical illnesses except diabetes. Only 23.3% of the study subjects had only diabetes illness. Some 26.0% of the study subjects were smokers. Majority of the foot ulcer were more than 1 month and 38% were chronic ulcer of more than 6 months duration. Some 84.7% of the ulcers were unhealed despite regular DFU dressing and proper follow up and monitoring. Unfortunately, 61.3% of the DFU patients had experienced amputation throughout their illness. Even though diabetic neuropathy was the commonest complication among the DFU patients, majority of subjects in this study had experienced mild to moderate pain score. Only 8.7% did not experience any pain. This was mainly because most of the study subjects had just done the operation following acute and complicated foot ulcer management in this tertiary hospital setting. The majority of the study subjects were diagnosed with at least one to three diabetes complications. Only 22.7% of the study subjects were not diagnosed with any diabetes complication during the participation periods. The average level of fasting blood glucose among the participants was 8.6. This was slightly high as compared to the Malaysia Clinical Practice guidelines of the target fasting blood glucose in type 2 diabetes (4.4-6.1mmol/L). This indicated that the majority of the participants had poor diabetes control despite taking medication. However, this might be due to confounding factors such as poor adherence to medication, inadequate dosage of medication, improper fasting duration or unhealthy diet which was not analyzed in this study design.

7.1 Socio demographics data and clinical variables of diabetic foot ulcer patients with MDD

Demographic data

In this study, the mean age of patients having major depressive disorder was 57.3 (SD 7.42). This was comparable with the non depressed group with mean of 58.2 (SD 11.68). This study was consistent with another similar study done by Geraldo et al. (2011), where about half of the DFU patients were married women aged between 60 and 69 years. DFU mainly affect the middle age and elderly group because these groups of patients have high risk of comorbid peripheral arterial disease, hypertension and hypercholesterolemia. Charnogursky, Lee, & Lopez (2014) found one of the risk factors for DFU was age above 40 years. Other risk factors include smoking, history of periods of poor glycaemic control, prevalence increases with increased duration of diabetes, people with signs of neuropathy are likely also to have evidence of diabetic nephropathy and diabetic retinopathy, hypertension, and ischaemic heart disease (Charnogursky et al., 2014). Bawo et al. (2010) showed younger mean age (*SD*) which was 47.2 (9.6) years.

Geraldo et al. (2011) displayed that 50% DFU patients with depression were aged between 60 and 69 years, majority were female; 50% were married, 58% were illiterate and 56% retired (Geraldo et al., 2011). This was consistent with the current finding that more female patients had depressive symptoms than male. In this study, among the 31 depressed DFU patients, 67.7% were female and 32% were male. This reflected that female were at double the risk of depression comorbid with DFU. However in this study, women were the dominant study subjects (59.3%). Women are approximately two times at higher risk than men to be diagnosed with MDD (American Psychiatric Association [APA], 1994). In the present study, majority of the women were

housewives and of low socioeconomic status. McGrath et al. (1990), had reported that the majority of women who developed depressive symptoms had low socioeconomic status (McGrath et al., 1990). Women who were less educated and unemployed were prone to develop MDD (McGrath et al., 1990). Another theory suggested a biological cause; hormonal changes especially estrogen depletion with menopausal symptoms were seen when women reached age 50 and above (Katon & Sullivan, 1990).

Bawo et al. (2010) showed that the majority of DFU with depression were female (54%), and married (83.5%). However, Bawo et al. (2010) showed that those DFU patients who were at high risk of developing depressive symptoms were employed (66.5%) (Bawo, George, Ambrose, & Joyce, 2010). As compared with the current study, among the 31 depressed subjects, 87.1% were married as compared with non depressed group 73.1% were married. Majority of depressed and non depressed DFU patients had only primary education, 25.1% and 52.9% respectively. In the present study, most of the depressed DFU patients (67.7%) were unemployed/ retired and lacked a stable income. Some of them were unable to sustain a permanent job due to chronic diabetic foot ulcer and disability. Majority of them were female who were housewives and could not financially support themselves. Once they face a challenge and obstacle in their life such as infected ulcer and amputation, they would easily feel worthlessness, guilt and self blaming. They believed they were a burden to their family members (both for health care and financial support).

Another study suggested that genetic predisposition linked to chromosome X would affect the women's behavior by making them more willing to express their emotions and seeking treatment compared to men (Jones, Robinson, & Barr, 2008; Murray & Lopez, 1997).

In this study, Malay was the highest ethnic group in the depressed group (87.0%), followed by Indian 9.7% and Chinese 3.2%. This was consistent with the non depressed group as Malay was the dominant group as well. This was probably due to the over-representation of Malays who visit

the orthopaedic diabetic foot ulcer clinic (84%). According to the Malaysia demographic profile in 2014, ethnic distribution in Malaysia was: Malay 50.1%, Chinese 22.6%, indigenous 11.8%, Indian 6.7%, other 0.7%, non-citizens 8.2%. Thus, this study result did represent our population.

Geraldo et al. (2011) found that 56% of diabetic foot ulcers patients were under retirement. This was mainly attributed to the ulceration having affected their work performance, causing disability and early retirement, limitation of daily living and leisure activities (Lavery et al., 2003).

Clinical Variables

Most studies hypothesized that long duration of illness, such as a chronic illness, was associated with depression (Tarsitani & Bertolote, 2006). In this study, majority of the depressed subjects (54.8%) had DM of more than 10 years duration. This was comparable with the non depressed group (40%) as DM is a chronic debilitating illness. Bawo et al. (2010) found that the DFU patients with depression had mean duration (SD) of being diagnosed with DM was 5.2 (5.3) years. In Malaysia, there is high carbohydrate and sugar content in our traditional food. It was reported that the onset of DM had shifted to the younger age group in Malaysia. Thus, the nature, course and duration of illness were more prolonged in the younger generation. Moreover, more complications would develop during the course of the illness. This would be attributed to the risk of developing depression.

Okura et al. (2009), who studied cognitive impairment among adults with diabetes, found that non-Caucasian race with longer diabetes duration would have high depression scores and poor diabetes control (Okura, Heisler, & Langa, 2009). This is consistent with the current study findings that most of the depressed DFU in HTAA were diagnosed with DM for 10 years duration and majority of them (51.6%) had complication of DFU for 1-6 months. It was comparable with the non

depressed group as the majority of them (50.4%) had ulcer for 1-6 months. This was because HTAA is a tertiary hospital and most of the cases were acute cases and needed prompt treatment such as debridement and amputation. Those who had chronic and unhealed ulcer without complication would be discharged to the nearest government clinic for continued dressing.

In this study, 72.7% of 150 DFU patients had strong family history of DM. For the depressed group, 24 (77.4%) of them had family history of diabetes. For non depressed group, 85 (71.4%) of them also had strong family history of DM. This finding was high compared with another study which found that 20% of depressed DFU patients had family history of DM (Bawo et al., 2010). The association between family history of diabetes and risk for DM has been well documented (Harrison et al., 2003). A study done in the US found that 69.8% of the US adults were in the average, 22.7% in the moderate, and 7.5% in the high familial risk for diabetes (Rodolfo et al., 2007). Since 2007, genome-wide association studies have identified > 65 genetic variants that increase the risk of type 2 diabetes by 10–30% which some might run in families (McCarthy, 2010).

This study showed that 4% of 150 subjects of DFU had family history of depression and 3.3% of them had past history of depression. Further analysis between depressed and non depressed groups showed that among the depressed DFU patients, 12.9% (n=4) had family history of depression while for the non depressed group only 1.7% (n=2) had family history of depression. For the past history of depression, 3 of the 31 subjects of DFU with depression had previous depressive episodes. However, 2 of the currently non depressed DFU patients had also experienced past episode of depression and currently have no depressive symptom. Generally, those who have first degree family members with depression are 10 times at risk of developing depression in. their life (Goodwin & Jamison, 2007). Moreover, an estimated 40-60% of depressed people had past episodes of depression and with increasing risk for further recurrence (Monroe & Harkness, 2011).

In this study, 36.7% of the DFU patients had 1 chronic illness, 34% had 2 types of chronic illnesses and 6% had 3 and more chronic illnesses. Further analysis between the depressed and non depressed group showed that 13 (41.9%) of the depressed subjects had 1 chronic medical illness and 12 (38.7%) of them had 2 chronic illnesses and 4 (12.9%) had more than 3 chronic illnesses. Only 2 (6.5%) of depressed DFU subjects had not been diagnosed with other chronic medical illness as compared to non depressed DFU patients, 27.7% of them did not have any other chronic medical illness except DM. And the majority of the DFU patients had vascular disease, for example hypertension, peripheral artery disease. Chronic illnesses increase the risk of health complication and burden to patients and family. This will indirectly cause significant psychological impact on the patients. The theory of association between depression and chronic medical illnesses had been discussed as above.

Almost half of the DFU had suffered from diabetic foot ulcer for 1-6 months for both depressed and non depressed group. This was because the tertiary hospital emphasized on acute setting patient who needed amputation or wound debridement or complicated chronic cases. Those DFU patients who were more stable with chronic wound had been referred to the nearest government clinic for regular dressing. In this study, almost all of the subjects (84.7%) with DFU had unhealed ulcer. Among the unhealed ulcer patients, 23.6% had developed depressive symptoms and 76.4% were without depressive symptoms. Only one of the DFU patients with comorbid depression had a healed wound. Among the depressed group, more than half of them (n = 17, 54.8%) had history amputation. This finding was supported by another study which found that 34% of DFU patients develop new ulcer after 1 year, the risk was increased to 61% after 3 years and further increased to 70% after 5 years (Apelqvist, Larsson, & Agardh, 2009). Moreover, the study had determined that post amputation recurrent rate of foot ulcer was also high. The long-term survival ratio was better on those who had previously primary healed ulcer compared to those who had healed ulcer post amputation (Apelqvist et al., 2009). Prolonged unhealed ulcer would

indirectly cause more stress and impaired DFU patients' daily function. If this condition persists without recovery, subsequently they would develop negative emotion and feelings such as worthlessness, hopelessness, guilt, and frustration. These findings had pointed out the importance of preventive foot care and life-long surveillance of diabetes care, especially among those with history of amputation.

In this study, about 61.3% of the DFU patients with comorbid depression had moderate to severe degree of pain score. As compared to non depressed patients about 47% had moderate to severe pain score. This was because the majority of the study subjects had an operation for wound debridement or amputation within 1 month duration prior to the interview session. Thus, the majority of them had experienced severe pain especially at night and this disturbed their sleep. Moreover, sleepless night with pain and restricted movement would cause negative psychological impact such as irritable mood, frustration and subsequently depressive symptoms.

In this study among the depressed DFU patients, 38.7% of them had one diabetes complication, 29% of them had 2 diabetes complications and 22.6% of them had 3 or more diabetes complications. In the non depressed group, 26% of them had no diabetes complication and 38.7% of them had 1 diabetes complication and about 35.3% had 2 and above diabetes complications. According to Geraldo et al. (2011), 80% o DFU patients were hypertensive, 38.0% was diagnosed with heart disease and 32% were smokers (Geraldo et al., 2011).

In this study, both the depressed and non depressed group had mean reading for fasting blood glucose of 8.6 (*SD* 2.92). This indicated that the study subjects had poor diabetes control. This showed that depressed patients had poor adherence to diabetes treatment and monitoring.

In this study, only 16.1% of the depressed DFU patients were smokers during the time of interview. As compared to all the smokers in this study, 87.2% did not have depressive symptoms. There was no significant association between smoking and DFU with comorbid depression.

However, another study showed that smokers had high risk of amputation which contributed 95% of all leg amputations in DFU patients (Uchimoto et al., 1999).

7.2 Prevalence of depression

In our study, the number of possible cases of experiencing depressive level in patients with DFU detected using the HADS-D with a cut-off point of 8 or more was 24% (n=36). However, the prevalence of MDD in DFU patients using M.I.N.I was 20.7% (n=31) out of 150 participants. This present study showed that HADS-D had detected more possible cases of depressive symptoms among the DFU patients. This was because HADS was a screening test and there were false positive cases. Among all the positive cases of depressive symptoms using HADS rating scales, 27 (18%) of the cases were considered as possible cases and 9 were considered as probable cases. Anyway, the finding was confirmed with M.I.N.I test for diagnosis of MDD. The prevalence of MDD among the DFU patients was determined using M.I.N.I. Both HADS and M.I.N.I were used for all the study subjects to confirm the validation between the screen positive cases of HADS with positive cases of M.I.N.I. In this study, all of the positive cases diagnosed by M.I.N.I questionnaire were also positive cases screened using HADS.

Our study is comparable with the finding from meta-analyses study on chronic DM illness. One of the meta-analysis studies concluded that the prevalence of major depressive disorder in patients with DM was around 12% (ranging from 8-18%), while mild depressive symptoms was about 15-35% (Andreoulakis, Hyphantis, Kandylis, & Iacovides, 2012). This is because the study population are those diagnosed with chronic DM and also diagnosed with multiple diabetes

complication. In this meta-analysis study, there were numerous studies focused on diabetic foot ulcer complication with depressive disorder.

A cross-sectional study on diabetes patients with Charcot foot was carried out in London King's College Hospital in 2010 (Zahra, Charles, & Jörg, 2014). The study design was similar with our study design as it was a tertiary hospital which received referral for complicated cases. Zahra et al. (2014) summarized that ulcerations and Charcot foot had been grouped together (Willrich et al., 2005) as Charcot foot (neurogenic osteoarthropathy) is not mentioned as a distinct diagnosis. This study also used HADS as a screening tool. As the comparison of the result, there was no far different of possible and probable cases detected in our study and Zahra et al. (2014). Zahra et al. (2014) reported that 28% of borderline (possible) cases and 14% of probable cases. This study had detected higher rate of borderline cases as compared to our study due to the nature of the illness. Charcot joint is a chronic and progressive illness, resulting in neuropathy and joint destruction. As disease progress, patient may have complication such as ulceration and inflammation which might be triggered by traumatic injury. Due to the nature of illness and devastating complication of Charcot joint, this explained the higher rate of possible cases detected in their study. In fact, our research and Zahra et al. (2014) both had reported the probable cases as between 9%-14%.

My study result was consistent with the study done by Marjolein et al. (2009) which also used the HADS-D rating scale. Their study reported that 18.8% of DFU patients had score of 8 and above and 7.6% had scored 11 and above (Marjolein et al., 2009). This was a hospital-based study with a sample of 150 participants. Both my study and this study are using hospital-based study design with same number of study population and using a similar questionnaire.

Bala et al. (2015) conducted a prospective cohort study in India over a period of 24 months. The Hamilton depression rating scale (HAM-D) was used to detect depression among the DFU patients. There were 64 (22.06%) patients who had depression according to the ICD-10 criterion

(HAM-D) (Bala et al., 2015). This result was consistent with my study result. This might be because both Malaysia and India are Asian countries having similar cultural and religious backgrounds. Majority of the Asian people tend to minimize their feeling and symptoms. Most of them are not good in expressing their feeling as well. Thus, the prevalence of depression is lower in Asian country compared to western countries.

My study finding was lower as compared with another population-based cohort study done by Khalida et al. (2007) in London. Khalida et al. (2007) found that 32% (n=82) of the study population (n=253) was diagnosed with major depressive disorder. This was because the present study design was a cross-sectional study whereas the Khalida et al. (2007) study design was a population-based cohort study in which DFU patients were recruited between August 2000 and October 2002 and prospectively followed up for 18 months. My study only recruited the sample from one tertiary hospital; however their study sampling included all the community chiropody and five hospital diabetic foot clinics involved in the National Health Service in London. Their study population was 253 as compared with my study population of 150 subjects. In Khalida et al. (2007) prevalence of depression would be more appropriate in representing their population compared to our study.

Besides that, Khalida et al. (2007) used a different assessment tool which was Schedules for Clinical Assessment in Neuropsychiatry 2.1 (SCAN 2.1). SCAN 2.1 and M.I.N.I also using the DSM-IV criteria for diagnosing major depressive disorders. However the difference between SCAN 2.1 and M.I.N.I was that the SCAN 2.1 was able to clarify the severity of psychiatric symptoms. Khalida et al. (2007) found the prevalence of minor and major depressive disorder to be 8.1% (n= 21) and 24.1% (n= 61), respectively in their study (Khalida et al., 2007). Another advantage of using SCAN 2.1 was that it could exclude the depressive symptoms secondary to medical condition (Khalida et al., 2007). Both the tests had good specificity and sensitivity. However, M.I.N.I had better sensitivity and specificity as compared to SCAN 2.1. M.I.N.I test

sensitivity was 0.89 and specificity 0.98 (Firdaus et al., 2012) as compared with SCAN 2.1 test sensitivity was 0.87 and specificity 0.92 (Nienhuis, van de Willige, Th. Rijnders, de Jonge, & Wiersma, 2009). Therefore, there was low risk of false positive and false negative cases detected from the M.I.N.I test.

Another study showed a significant high prevalence of depression in DFU as compared to my study. Geraldo et al. (2011) reported that 64% of DFU patients had moderate depression and 10% severe depression. One of the reasons for the difference was that the screening tool used for this study was the Beck Depression Inventory (BDI). Beck Depression Inventory had high sensitivity (88%) and high specificity (92%) (Karen, Smarr, Autumn, & Keefer, 2011). As comparison to our study, the sensitivity and specificity for both HADS-A and HADS-D were 80% (Ingvar, Alv, Tangen, & Neckelmann, 2002; Karen et al., 2011). BDI has high sensitivity and specificity in detecting positive cases. However, BDI has been found to be sensitive to change in depression in cross-cultural studies (Karen et al., 2011). BDI might be affected by confounded medical physical symptoms among the DFU patients (Forkmann et al., 2009). The HADS-D emphasize anhedonia, excluding the somatic symptoms. Thus, construction of the HADS-D reduces the psychological effect of somatic disorders associated with depression (Karen et al., 2011). Thus, HADS was recommended as a better screening tool compared to BDI.

Toni, Vanessa, and Sue (2013) had done another similar study in Australia using a validated self reporting 9 item Patient Health questionnaire (PHQ) to diagnose depressive disorder. Toni et al. (2013) reported that among 60 participating DFU patients, 51.7% (n = 31) were diagnosed with depression. This study found higher prevalence of depression compared to my study because their study subjects all had diabetes for more than 10 years and were having the DFU complications for more than 6 months. As comparison, my study setting was at tertiary hospital which was an acute setting. Majority of the participants from the DFU clinic were acute cases (duration of 1-5 months of DFU complication). Most of the patients in my study might experience adjustment period in the

beginning of the ulcer complication. Once it was slowly healed and recovered within 2-3 months, they were most likely able to get rid of all the negative feeling. Thus, there was lower prevalence of depression in acute setting compared with chronic setting. Toni et al. (2013) had further interpreted the finding as 10 patients (17%) having had a previous diagnosis of depression and 21 (35%) of the participants being newly diagnosed depression. Toni et al. (2013) had summarized that majority of patients became depressed after prolonged treatment duration with unsuccessful healing process (Toni et al., 2013).

There is limited study done in Malaysia regarding depression among DFU patients. The Malaysia CPG, Management of Type 2 DM 2015, emphasizes that prevalence of depression increased to 15% in diabetes population compared to non diabetes population (Ali, Stone, Peters, Davies, & Khunti, 2006; Mezuk, Eaton, Albrecht, & Golden, 2008). In a study done in 2013 involving 2508 diabetes patients from 12 health clinics in Malaysia, 11.5% were found to have depression (Kaur, Tee, Ariaratnam, Krishnapillai, & China, 2013). This is the only local study available to compare with the current study. My study shows higher prevalence (20.7%) as compared to study done by Kaur and colleagues (2013). This is because their study focused on general diabetes population who visited 12 health clinics in Malaysia. This group of diabetes patients are the stable patients who might not have severe diabetes complication such as DFU, diabetic nephropathy, and diabetic retinopathy. Majority of them do not experience acute changes in their lifestyle as compared to DFU patient who might need amputation hence affecting their daily living activities. Thus, this would explain why diabetic foot ulcer patients have higher prevalence of depression as compared to diabetes population. Unfortunately, there is lack of local study on depression among diabetic foot ulcer patients to compare with the current study.

In our study, out of the 31 patients diagnosed with Major depressive episode (MDE) using M.I.N.I, 25 (80.6%) of them were current episodes, 5 (16.1%) of them were recurrent episodes and only 1 (3.2%) was past episode. There was lack of other study which analyzed the type of episode of

depression among the diabetic foot ulcer patients. This distinction is likely due to the possibility of misclassification and recall bias. However, M.I.N.I questionnaire uses the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) (Sheehan, Lecrubier, & Sheehan, 1998) which was validated for diagnosis of depressive episode and type of episodes. This questionnaire is used worldwide for the standard classification. However, the MINI does not assess the severity of MDE. Thus in future study, rating the severity of depression could have been assessed and added to the data. This is important to determine the risk of developing diabetic complication, risk of further amputation and adherence to treatment.

7.3 Associated risks with major depressive disorder among diabetic foot ulcer

Overall in this study, three independent variables were found to be statistically significant with major depressive disorder in DFU patients.

Family history of depression in DFU patients was found to be statistically significantly associated with MDD with *p* value of 0.015. In reality, the interaction between genetic predisposition and life event determines the risk of depression in DFU patients. Lustman et al. (2002) concluded greater risk of depression was found in patients with diabetes who have a family history of depression which may be indicative of a genetic vulnerability (Lustman et al., 2002).

Depression is a complex disease which is interrelated between multiple genes and non genetic risk factors, such as stressful life events (John & Hettema, 2010). Scott et al. (2015) reported that participants with family history of depression experienced more lifetime episodes of depression. Their study had proposed a 3-way interaction involving positive family history, major life events and lifetime episodes in depressive patients (Scott, Monroe, George, Slavich, & Ian, 2015). Patients with DFU had experienced various stressful event and challenges for the wound

healing process. This had become their major life event especially for those who had poor social support and poor QoL.

Those who have positive family history of depression have became sensitized or kindled to the repeated stressful life event (Monroe & Simons, 1991; Post, 1992). Individual with pre-depression onset of major life event plus a positive family history would experience fewer lifetime episodes of depression. This could be explained by the 'kindling' hypothesis and stress sensitization. The DFU patients would have increased susceptibility to stress with repeated unhealed wound episodes (Post, 1992). However, these positive family history of participants still require major stress to trigger depressive episodes (Monroe & Simons, 1991). Perhaps, DFU patients with positive family history of depression were genetically and psychobiologically susceptible to depression with underlying challenges from the diabetic foot care.

Another clinical independent variable found significant associated with MDD was other chronic medical illness. One to two chronic medical illnesses was found to be significantly associated with MDD with *p* value 0.033; and three and more chronic medical illness was strongly significant with *p* value 0.009.

A systematic review found 8 studies reported the significant association of depression with myocardial infarction (Wayne & Katon, 2011). Another meta-analysis also found 7 studies reported type 2 diabetes increasing the risk of developing depression (Wayne & Katon, 2011). Many researchers had explained that a bidirectional relationship between depression and chronic medical disorder exists. There are negative health behaviors with significant psychobiological changes secondary to depression had precipitated the risk for chronic medical disorders. At the same time, biological changes and multiple complications due to chronic medical disorders may also precipitate depressive episodes. In consequence, this had increased medical care and cost burden, impaired functionality, prompted poor self care behaviors, and increased the risk of

morbidity and mortality in patients with chronic medical disorders comorbid depression (Wayne & Katon, 2011). Furthermore, depression showed significant effect on proinflammatory factors, hypothalamic-pituitary axis, autonomic nervous system, and metabolic factors. All this biological changes would worsen the course of chronic medical illnesses (Wayne & Katon, 2011).

Wayne and Karton (2011) explained the conceptual model for depression and chronic medical illness which involve both genetic predisposition and exposure to childhood adversity. Early exposure to childhood adversity (abuse, lack of love) may result in maladaptive attachment patterns and subsequently cause significant poor social support with multiple interpersonal relationships problem. Thus lack of social support among the chronic medical illnesses patients would precipitate and worsen depressive episodes (Bifulco, Ball, & Lillie, 2002; Bifulco, Moran, Ball, & Bernazzani, 2002) At the same time, maladaptive attachment may have adverse effect on the doctor-patient therapeutic alliance (Wayne & Katon, 2011). As a consequence, chronic medical illnesses comorbid with depression would be associated with adverse health behaviors such as uncontrolled diet, weight gain, sedentary lifestyle, and smoking, which increase the risk of morbidity and mortality diabetes and CVD (Goodman & Whitaker, 2002; Katon et al., 2010; Von Korff, Scott, & Gureje, 2009). Another explanation was these negative behaviors could also link to biological factors associated with both depression and childhood adversity, such as increased cortisol levels or high proinflammatory factors which may lead to early development of chronic medical disorders such as diabetes or CHD (Wayne & Katon, 2011). Depression increases the symptoms burden and functional impairment in patients with multiple chronic illnesses (Wells, Stewart, & Hays, 1989). In other words, the negative symptoms and impaired daily function secondary to chronic medical illnesses may also precipitate or worsen major depression. Comorbid depression also worsens the course of chronic medical illness due to adverse effect on compliance to self-care regimens (diet, exercise, smoking cessation, medications) (Carney & Freedland, 2008; Katon, Lin, & Von Korff, 2004) as well as direct pathophysiological effects on

inflammatory and metabolic factors, hypothalamic pituitary axis and autonomic nervous system (Carney & Freedland, 2008). However, the effects of these risk factors may be buffered by easy access to good quality of health care services and good social and environmental support.

In the present study, diabetes complication was found to be associated with major depressive disorder. Three and more diabetes complications present at the time of study were strongly significant associated with major depressive disorder with *p* value 0.025. Another study done by Niraula et al. (2013) reported that at least one diabetic complication associated with comorbid depression (Niraula et al., 2013). Majority of patients would have at least one complication such as peripheral neuropathy, retinopathy, foot ulcer, skin lesion and more severe complications include nephropathy, stroke, peripheral arterial disease. The more complications of diabetes indicate the higher risk of developing depression. Stress secondary from the direct effect of the diabetic complications and metabolic effects of diabetes on the brain would predispose them to the risk of developing depression. Cienchanowski et al. (2000) found that depression and diabetes complication could be bidirectional risk factors. This study suggested that people with depression are more likely to develop more diabetes complication than those without depression. (Ciechanowski et al., 2000). This was because in DFU patients the depressive symptoms manifested as anhedonia, lost of interest in life, lack of motivation to achieve healing process, feeling of worthlessness and hopelessness for the future. Thus, this would further predispose to other risk factor such as failure to adhere to diabetes treatment and follow up, giving up on regular blood glucose level monitoring, refusing to attend DFU wound dressing. As a consequence, poor diabetic control exacerbates the poor wound healing process. Persistent high blood glucose level would destroy the peripheral arterial system, eye, kidney, peripheral nerve and precipitate more wound and skin lesion. Thus, those who had comorbid depression with DFU had higher risk of developing more diabetic complications as compared to the non depressed group.

In my study, there was no clinical significant association between intensity of pain with MDD among DFU patients. Furthermore, Jefferey et al. (2005) also found no significant relationship between pain intensity in diabetic foot ulceration with depression. Thus this study had supported the finding of my study result. However, my study does not demonstrate the relationship between diabetic neuropathy pains with depressive disorder. Jefferey et al. (2005) gave a possible explanation for pain on DFU being not associated with depression; it could be that neuropathic foot ulcers are typically painless, thereby cause little individual's consciousness and minimal emotional distress (Jefferey et al., 2005). However, in my study most of the perceived pain was due to the post operative procedure secondary to acute management of complicated DFU. Study population were from tertiary hospital where majority of them had just done operation a few weeks before the follow up at the outpatient orthopaedic clinic. Majority of the participants had received adequate pain reliever post operatively. Thus, this explains why intensity of pain in our study population is not clinically significant with MDD.

However, study done by Jefferey et al. (2005) provides evidence that severity of diabetic neuropathy is associated with depressive symptoms. Each symptom of diabetic nephropathy including pain, unsteadiness, and reduced feeling in the feet was independently associated with depressive symptoms. The association between diabetic neuropathy symptoms and HADS was mediated by two psychosocial theories: perceptions of diabetic neuropathy symptom unpredictability and the lack of treatment control and restrictions in ADLs and changes in social self-perception (Jefferey et al., 2005).

Another cohort study found a high prevalence of affective distress (51.4%) involving both symptoms of anxiety and depression reported in diabetic neuropathic pain studies. It was found that higher self-reported pain intensity was strongly associated with anxiety symptoms compared to depressive symptom scores. The experience of diabetic neuropathic pain had initiated negative

thoughts and fears which led to maladaptive avoidance behavior such as limitation of activity for harm avoidance (Dinesh et al., 2015).

Obilor and Adejumo (2015) found that DFU-related pain at rest, during activity of daily living and during dressing was significantly related to physical health status (physical functioning only) and mental health status (social functioning only). However, this study also found that psychological distress and well-being was found to be significantly related to DFU related pain.

There was limited data available for association factors of depression in DFU patients. Most of the research focused on general disease.

However, Marjolein et al. (2009) found that female, elderly, high BMI, low education level, current smoking status and a history of stroke were significantly associated with poorer perceived health and psychological well-being (Marjolein et al., 2009).

7.4 Quality of life

In this study, the QoL of the study subjects was assessed using WHOQOL- BREF questionnaires. Four domains included physical component, psychological component, social relationship aspect and environment component were analyzed. Mean scores of all the domains were compared between those with MDD and non-MDD group. The DFU patients with co morbid depression had lower mean score on all the domains compared to those non-MDD groups. All the domains differences were statistically significant (p value < 0.05). This reflected that overall DFU patients were not satisfied with their QoL. Physical limitation as a result of chronic leg ulcer and amputation was the most common reason to restrict them from daily and leisure activity. As a consequence, DFU patients would isolate themselves; feel hopeless as they were jobless and faced high risk of developing depressive symptoms. This would indirectly affect their psychological

aspect and cause feeling of guilt, anger, frustration, irritability, sadness, worthlessness, and hopelessness. This would also affect the social relationship of the patients with their family and friends. They felt ashamed to be useless and jobless in front of their relatives and friends. As a result, they would isolate themselves from their relatives and friends.

A cross-section study of 200 of DM patients were assessed using WHOQOL-BREF. DM patients in Nigeria who were diagnosed with depression had poor QoL compared to non depressed group (Bawo et al., 2010). MDD patients were significantly associated with low mean scores in overall QoL ($p < 0.01$) and health satisfaction ($p < 0.01$). However, MDD was not significant associated with quality of physical health ($p = 0.67$), psychological health ($p = 0.59$), environment ($p = 0.70$), or social relations ($p = 0.58$) (Bawo et al., 2010).

Lis et al. (2007) found that DFU patients had poor HRQoL compared with the diabetes population as well as the general population, mainly in physical health. These patients also had poor social support (Lis et al., 2007). According to Lis et al. (2007) who used the SF-36 questionnaire, DFU patients had significantly low HRQoL on all scales, especially on role limitation-physical (32.1 vs. 74.3, $p < 0.001$), physical functioning (57.5 vs. 85.2, $p < 0.001$) and general health (50.1 vs. 74.3, $p < 0.001$).

Lower limb ulcers are very common in DM patients. However, these are very difficult to treat and cause poor QoL. These ulcers can be painful, limit physical activities and subsequently result in unemployment, loss of financial support and low self-esteem. Because of the unpleasant odor and distorted appearance, the sufferers tend to isolate themselves. Majority of the patients from my study had exudates and odor from their wounds.

However, Bawo et al. (2010) using WHOQOL-BREF questionnaire had found a different finding where MDD did not significantly affect the outcomes in all four domains.

The diabetic foot is always associated with neurological disorders and various peripheral vascular diseases of the lower limbs. This has great impact on the both social and economic standing because those who have had amputation would lose the ability to work and at the same time they had to maintain high cost of foot care and DM treatment (Porciúncula, Rolim, Garofolo, & Ferreira, 2007).

Another study showed a similar finding where QoL of those who had a current foot ulcer was significantly lower than those who had healed ulcer without amputation. Further analysis found that QoL deteriorated with diabetic complication but improved with care by a healthy partner (Gunnel & Apelqvist, 2000).

7.5 Social Support

Social support is a dynamic process involving personal and social networks that help to satisfy peoples' needs with available resources. This would enable individuals to face new challenges and situations. However, studies analyzing the perception of social support in DFU are scarce in the literature.

The social support of DFU patient in this study was assessed using the MSPSS questionnaire. The scores were summarized into 4 groups which included significant other, friends, family, and total perceived social support. The mean scale score was categorized into three groups; 1 to 2.9 was considered low support; 3 to 5 was moderate support and a score from 5.1 to 7 was considered as high support.

Total mean scale score was 5.5 (*SD* 0.89). This showed that overall DFU patients perceived that they had high social support. The mean scale score for significant others (husband or wife) was 5.8 (S.D 1.27). This study showed that majority of patients (married) had a very supportive spouse. As far as being observed throughout the data collection periods, majority of the diabetic foot

patients came to clinic with their spouse and family members. None of them came alone. Some of them even could get help from the neighbour if their children were unable to bring them to hospital. This could reflect that Malaysian culture has strong family value. This strong family value is instilled from the older generation to the young generation. Family members always offer mutual support. Furthermore, majority of the participants are from rural areas around Kuantan town and most of them have a big family and good relationship with the neighbors. Thus, this could explain the good social support perceived by diabetic foot ulcer patients who follow up in HTAA. Moral support from spouse was associated with more regular foot examinations (Schiotz, Bogelund, Almdal, Jensen, & Willaing, 2012).

In this study, the mean scale score for friends group was 4.6 (*SD* 1.38) and family group was 3.5 (*SD* 0.36). Overall the DFU patients in this study perceived that they had moderate support from both family and friends. Good family support was associated with better foot care. This resulted from better understanding of the family regarding the illness and good foot care provided by family members. Besides the health care and foot care, good social support included moral support and motivation. There were mixed feelings in diabetic foot patients who had deterioration of health including denial, grief, rebellion, anxiety, and sometimes these feelings led to depression when they overwhelmed the patients' coping skills. With support, concern and understanding from the spouse and family members, DFU patients would have better coping skills and mechanism and reduce the risk of developing depression. Social support from friends was associated with fewer psychosocial problems, good wound care and health-promoting self-management (Schiotz et al., 2012).

A cross-sectional study in an outpatient clinic at an academic hospital had found a higher perception of social support among the DFU patients. This finding is consistent with our study result where family support was cited as the main source of support. This study found that family support was 86.7%, followed by health professionals (26.7%). Total mean of social support was

4.3 showing that diabetic foot patients have perceived high social support (in scale pointed of 1-5) (Gomes-Villas Boas, Santos, Foss-Freitas, & Pace, 2009). This finding is consistent with the current study result. However, my study using MSPSS questionnaire did not analyze the health care social support among the DFU patients. According to Hanestad (1993), frequent visits to clinics and hospitals for dressing had given DFU patients a break from their usual social isolation, which they perceive as a great support source (Hanestad, 1993).

In this study, all of the MSPSS questionnaire subscales were statistically not significantly different between the depressed and non-depressed DFU patients. This showed that none of the variables were found to be associated with MDD. Perhaps other characteristics such as duration of DFU, chronic illnesses, employment status, and marital status, education level were confounders. There are other limitations to be considered. First, social support is a dynamic process, thus it is important for ongoing assessment to identify the influence of continuous events in the perception of support. The cross-sectional study design allowed assessment of social support only one time. Second, using questionnaires to evaluate social support does not reflect the actual supportive perception. This is because each individual's personal experience and life events can influence his or her perception.

A cross-sectional study evaluating Portuguese community with DFU did not find statistical significance in the mean of social support between depressed and non depressed DFU patients. However, the study found statistical significance in the mean of social support between genders. This is because women are taking care of household responsibilities, children and aged parents. Women always perceive social support less than men. Women often need to provide more support for themselves (House, Umberson, & Landis, 1988). Statistically significant correlations were seen between social support and age, social support and formal education (Gomes-Villas Boas, Santos, Foss-Freitas, & Pace, 2009). Heitzmann and Kaplan (1984) found that men with a good

perception of social support had poor metabolic control, while greater satisfaction with social support was associated with good metabolic control in women.

Iida et al. (2010) studied how spousal support influenced the dietary health behaviors among 126 Type 2 DM patients. The mean age of the study subjects approximately 66 years; subjects had been married for approximately 38 years. (Iida et al., 2010). This study determined that diabetes symptom severity correlates with support given by spouse.

Mayberry et al. (2012) found that patients with advancing age significantly received better support from the family. This study also found that family with better income showed more family support. However, patient who perceived low family support was associated with poor medication adherence and poor diabetes control (Mayberry & Osborn, 2012).

A systematic review was conducted by van Dam et al. (2005) evaluating social support in diabetes patients showed that improvement of compliance in patients with a chronic disease such as diabetes need strong support strategies (van Dam et al., 2005). Another systematic search was conducted to evaluate literature published from 2006 to April 2013 regarding social support in adults with diabetes conducted in the USA and Europe. Overall the study found that good social support can encourage better self care of diabetic foot and subsequently result in positive health outcomes (Julienne, Christine, Ginger, & Edward, 2013).

Pearce et al. (2008) conducted a study of 199 subjects showing that no significant health care effects were found after 9–12 months with involvement of a non healthcare support person such as a friend or relative (Pearce, Love, & Shelton, 2008).

National Health and Nutrition Examination Survey evaluated data regarding the social support and ethnicity among white, black and Latino respondents (n = 450) from 2005 to 2006 (Rees, Karter, & Young, 2010). There was no association between social support with ethnicity, lower education,

depression, functional and poorer self health status and diabetes foot care behavior. This finding was consistent with the current study where there was no significant clinical association between the social support and depressed DFU patients.

In summary, support from family and friends has been shown to have some effects on patient diabetes behaviors and/or diabetes foot outcomes. However, this was not to be dependent on race or ethnicity, but good family relationships, possibly high income can have positive effect on the outcomes. Inability to get appropriate help in the event of severe illness and poor social skill was associated with greater psychological distress, poor wound care, inadequate health-promoting behavior and foot examinations (Schiotz et al., 2012). Among Type 2 diabetes patients, health promoting behavior and well-being of patients improved significantly with good social support (Schiotz et al., 2012).

The findings are intriguing enough to warrant further study about how to successfully harness family social support to aid patients in diabetes management. Intervention research is needed to determine the causal relationship between social support and self care behaviors in DFU patients. This knowledge could be used in clinical setting when targeting education, support and health care for patients with Type 2 diabetes and DFU patients.

7.6 Methodological discussion

7.6.1 Study design

My study design was cross-sectional aimed at measuring the associations between depression in DFU, perceived quality of life and social support. The cross-sectional design is suitable for describing associations between variables at a specific point of time (Polit & Beck, 2008). However, the limitation of a cross-sectional study is that causality is not identified.

7.6.2 Information bias

Definition of information bias is errors of information received from subjects

in a study; this may cause incorrect measurement of the outcome (Rothman & Greenland, 1998).

7.6.3 Self-report bias

There was no exact definition for the diagnosis of healed ulcer. Health care personnel were unable to correctly verify DFU status. As the result, participant might have incorrectly reported their DFU status, which might have contributed to misclassification.

Due to self reported questionnaire, thus it would have some limitation. Moreover, it was not feasible for clinically validating the diagnosis by clinical data or by interview in a large population.

Clinical experts have suggested 3 weeks for the diagnostic duration for any ulcer and that ulcers need more than 3 weeks to heal. However, it was well known that diabetes condition prolonged the healing process. Furthermore, some participants might have other type of ulcer such as venous leg ulcer which was mistaken for DFU who with comorbid DM.

Majority of the participants were above 50 years old with chronic DM; many of them could not recall how long they were diagnosed with DM and how long they had the ulcer. Some of the information was confirmed with participants' spouse or children who are their caretaker. Fortunately, most of the DFU patients were accompanied by their spouse and children during the follow up in clinic.

Two questions were having some missing values. They were question 18 and 21 in the WHOQOL-BREF questionnaire. Question 18 was "how satisfied are you with your capacity for work?"; question 21 was "how satisfied are you with your sex life?." Majority of the participants

were retired, housewives or unemployed due to physical disability. For question 21, most of the elderly patients were reluctant to answer questions regarding sex. First, in our culture, sex related issue is a sensitive issue and this creates a barrier to sexual and reproductive information. Furthermore, almost half of the men between ages 40 to 70 have erectile dysfunction (Morgentaler, 1999). The prevalence of ED in diabetic populations is ranging from 20 to 71% (David, Penson, & Hunter, 2004). Missing values were recorded as neither satisfied nor dissatisfied (score 3). The rationale for this was that I assumed that participants were neutral regarding those questions. However, the missing values were very small, about 5%.

7.6.4 Confounding

One of the challenges was to identify between a confounder or factor. Age and sex are well-known confounders in the association between exposure and outcome. Factors such as smoking, duration of DM, DFU duration, status of ulcer, amputation, marital status are often associated with risk of depression in diabetes illnesses. In this study, we therefore adjusted for these variables in multivariate analyses to determine if there were confounders. In this study, because amputation was most likely an effect of a DFU, we did not adjust for this variable. Family history of depression, more number of chronic medical illnesses, and 3 or more numbers of diabetes complication are considered risk factors for a DFU. In regression analyses among those with DFU comorbid depression, these variables were considered as covariates. This study using multiple logistic regressions showed marital status, past history of depression, number of other chronic illness besides diabetes, smoking, and severity of foot ulcer were retained in the model using backward LR elimination. In forward LR method, only family history of depression and number of other chronic illness were retained. Hence, the result of backward LR method was selected as the most parsimonious model to further the analysis. Although the *p*-value of marital status,

smoking, and severity of diabetic foot ulcer were > 0.05 the variables were retained based on clinical importance. Hence, the preliminary main effect model was obtained using backward LR. Past history of depression, married status with *p* value 0.050, and smoking with *p* value 0.051 were considered as borderline clinically significant.

7.7 Strengths and limitation of this study

7.7.1 Strengths

1. This was the first study conducted in Malaysia to determine the prevalence of MDD in DFU patients using screening questionnaire (HADS-D) and gold standard diagnostic interview (M.I.N.I). Together with this study, quality of life was assessed using the WHOQOL-BREF and social support was assessed using the MSPSS. This study can be used as references and baseline information for future research in similar field.
2. All the participants of this study had completed three self rated questionnaires and M.I.N.I was done by the researcher. Therefore, this could avoid missing data and incomplete analyses.
3. All of the rating scales and instrument of interview used in this study were validated and available in Malay and English language and widely used in our country.
4. Multivariate and regression analysis were done to determine the association of the variables with MDD in DFU patients.
5. The screening test HADS-D has good specificity and sensitivity. This was strong in detecting the possible and probable cases of depression in DFU patients.

7.7.2 Limitations

1. This study design was cross sectional and this would limit interpretations as to causality.
2. The universal sampling method was chosen due to limitation of manpower and time. This could lead to selection bias because universal sampling restricted the randomization of the samples collection.
3. The study samples were outpatients who attended the Outpatient orthopaedic clinic in a tertiary hospital setting. The study was conducted at only one center in Malaysia. Therefore the results might not be representative of the overall population of diabetes foot patients in Malaysia.
4. Due to samples from only one tertiary referral center, the prevalence of major depression from this study did not reflect the true prevalence of depression in DFU patients in Malaysia.
5. Other confounding factors such as stressor in life, significant life event, premorbid personality were not studied in this study.
6. This study had restricted the generalization of the data as it had excluded those who were unable to understand or converse in Malay and English language.
7. This study did not use a control group for comparison; and did not factor in anthropometric measures such as BMI or blood pressure reading. These factors and together with other psychiatric illness such as anxiety disorder, might be the confounders of depression and QoL outcomes.
8. The MINI questionnaire included sleep, appetite, lack of energy and fatigue symptoms for the diagnosis of MDE. However, these symptoms could be secondary to the primary illness which was DM and foot ulcer. These questions were necessary, as the MINI assessment was only valid when all the questions were answered. Thus the MINI might overestimate the prevalence of MDE in this study.

8.0 IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE STUDIES

8.1 Implications for clinical practice

The following implications may be drawn from this study.

- Health care providers especially primary health care team have to pay more attention on DFU healing progress as majority of our participants have unhealed ulcer with duration of 6 months. Those with unhealed ulcer have restricted their daily activities; increased treatments cost, increased the psychological stress and risk of depression.
- Early prevention of foot ulcers among the diabetes patients need to be promoted by health care personnel. Patients who are at risk of foot ulcer complication need to be followed up closely. Those with multiple diabetes complication should screen for depression, anxiety or other mental health problem. Early detection of mental health problem could prompt an appropriate treatment and prevent the unnecessary risk such as self harm behavior.
- Women with DFU have higher prevalence of depressive disorder than men. Health care workers and family members need to be more sensitive to their changes in emotion and psychological aspect. Family members have to give them more support and improve their QoL.
- The majority of DFU patients had long diabetes duration with several complications affecting their functioning and social relationship. Thus, systematic screening of perceived health related quality of life and depressive symptoms among the DFU patients should be considered.

- Prevalence of diabetes is increasing and thus would increase the diabetes related complications. Diabetes related complications were significantly associated with the risk of depression.
- In this study, most patients had a chronic wound for at least 6 months and relapsing wounds. The health professional is necessary to help them by supporting them physically and psychologically, so that the patient feels motivated to seek aid.
- Psychological and social factors would influence the patients' capability to cope with overall diabetes management. Primary health care profession should address these at the time of diagnosis or first presentation and during scheduled clinic visits or hospitalizations. It is also important to reassess the psychosocial status when diagnosis of complications, poor diabetes control and when there are suggestions to change oral hypoglycemic to insulin injection. All the changes faced by diabetes patients during the course of illness would give a significant impact on their psychology and mental health.
- Psychoeducation and supportive counseling to both DFU patients and caretaker is also pertinent. The pressures of dealing with diabetes have been associated with a higher incidence of depression. It resulted in reduced QoL and increased distress levels as self-care management is affected in patients with higher depressive symptoms. Family history of depression is also a significant risk factor for developing depression throughout the course of DFU illness.
- All the healthcare professions including primary health care or tertiary hospital professions must be aware and sensitive to the mental health problems faced by DFU patients. Indications for referral to a mental health specialist may include:

a) Depression with the possibility of self-harm

b) Debilitating anxiety (alone or with depression)

c) Indications of an eating disorder

d) Cognitive functioning that significantly impairs judgment

In conclusion, clinicians in all settings must provide a holistic care for DFU patients for early detection of depressive symptoms. Assessment of psychological and social status should be performed as continuous care of diabetes management; at diagnosis, onset of complications, when diabetes is out of control and whenever indicated. This intervention would improve the adherence to treatment and reduce the complications which might impair the QoL.

8.2 Implications for future studies

The findings of this study encourage more interesting study in different areas.

Emphasize on perceived health and self care management among DFU patients

Diabetes is a chronic and complex illness. Perceived health and psychological well-being were significantly poorer among DFU patients. Future study is to focus on perceived health, to offer them more intensive individual support and a foot care program and finally to evaluate the program outcome.

Efficacy of antidepressant and psychotherapy among diabetes/DFU patients, and side effect of antidepressant on glucose control

There is high prevalence of depressive disorder among the diabetes/ DFU patients. There is lack of local study on the efficacy of different groups of antidepressant medication and side effect of

antidepressant on blood glucose control. Future study can investigate the efficacy of different groups of antidepressant in combination with psychotherapy treatment among the DFU/ diabetes patients. Furthermore, focusing on glucose control with antidepressant would be another interesting study too.

Determining the association of mental health issues with different diabetes complications

DM is a chronic, debilitating and complex illness. Those diagnosed with DM would have high risk of developing multiple complications such as diabetes retinopathy, diabetes neuropathy, diabetes nephropathy, DFU, skin lesion and stroke. Future study can aim to determine the prevalence of depression, anxiety or other psychological distress among the diabetes patients with different type of diabetes complications. This is because diabetes management involves a multidisciplinary team. Therefore, multidisciplinary team professions should be alert with the prevalence of mental health problem and early detection with prompt treatment is important.

Relationship of depressive symptoms and healing process of DFU

Mental health specialists have to integrate into the multidisciplinary treatment of DFU. This could help in balancing between the medical and psychological model of treatment in DFU patients. Early intervention, diagnosis, and management of depression in DFU patients may improve the healing rate and reduce healthcare costs. There has been no published research to determine the relationship between depressive symptoms and healing rates of DFUs in Malaysia, and thus further research in this area is recommended.

Determining if early detection of DFU and good primary preventive foot care strategies can improve patient well being.

Future studies should follow up the participants and examine whether those reporting regular preventive care and with appropriate psychological support from the family and health care personnel would reduce prevalence of depressive episode and improve the quality of life. A prospective study which determines early detection of DFU and good primary preventive foot care strategies might show a different result.

Monitor and report on the standard of quality of foot care in Malaysia.

In order to identify the quality of foot ulcers care and their treatment at an early stage, a nationwide registry data in primary health care setting is needed. This is because there were a lot of cases of equal condition but treated unequally. Studies done by using this registry data of DM patients can easily monitor and report on the quality of foot care in the primary setting. Thus, this could help to introduce a gold standard guideline for the proper foot care for future intervention.

To improve the standard of foot care in community setting.

An intervention study that studied all levels of DFU health care would update knowledge and information concerning DM and DFU. This updated knowledge would help to improve the quality of DFU health care and QoL.

9. 0 CONCLUSION

This study had investigated a few important psychological and wellness aspects of DFU patients, which had helped to give knowledge and information regarding DFU in the general population.

Major findings from this study include:

In this study, the prevalence of MDD in DFU patients was 20.7% as diagnosed using M.I.N.I questionnaire.

Three variables were statistically significant associated risk factors that might predict MDD with DFU in this study. These variables were family history of depression, chronic medical illnesses and three and more diabetes complications.

The DFU patients with comorbid depression were associated with poor perceived QoL in all four domains including physical health, psychological health, social relationship and environment. All the domains differences were statistically significant (p value < 0.05).

Overall, the DFU patient in this study perceived that they had good social support from their spouse, family and friends.

REFERENCES:

Adam, G.T., Tasnime, N.A., David, B., & Mika, K. (2014). Depression and type 2 diabetes: a causal association?*The Lancet Diabetes and Endocrinology*, *2*(3), 236-245.

Ali, S., Stone, M.A., Peters, J.L., Davies, M.J., Khunti, K. (2006). The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med*, 23(11), 1165-1173.

Ama, G. (2006). Reframing applied disease stigma research: a multilevel analysis of diabetes stigma in Ghana. *Journal of Community & Applied Social Psychology*, *16*(6), 426-441.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Association.

Andersohn, F., Schade, R., Suissa, S., Garbe, E. (2009). Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus. *Am J Psychiatry*, 166, 591-598.

Andreoulakis, E., Hyphantis, T., Kandylis, D., & Iacovides, A. (2012). Depression in diabetes mellitus: a comprehensive review. *Querteriy Medical Journal, 16*(3), 205-214.

Andrews, K.L. (2000). The at-risk foot: what to do before and after amputation. *J Vasc Nurs.*, *29*(3), 120-123.

Apelqvist, J. J. , Larsson, & Agardh, C.D. (1993). "Long-term prognosis for diabetic patients with foot ulcers." *Journal of Internal Medicine*, *233*(6), 485-491.

Apelqvist, J., Larsson, J., & Agardh, C. (2009). Long-term prognosis of diabetes with foot ulcers. *Journal of internal medicine*, *233*(6), 485-491.

Apelqvist, J., Ragnarson-Tennvall, G., Larsson, J., & Persson, U. (1995). Long-term costs for foot ulcers in diabetic patients in a multidisciplinary setting. *Foot Ankle Int*, *16*(7), 388-394.

Apelqvist, J., Ragnarson-Tennvall, G., Persson, U., & Larsson, J. (1994). Diabetic foot ulcers in a multidisciplinary setting. An economic analysis of primary healing and healing with amputation. *J Intern Med.*, *235*(5), 463-471.

Armstrong, D.G., Abu-Rumman, P.L., Nixon, B.P., & Boulton, A.J. (2001). Continuous activity monitoring in persons at high risk for diabetes-related lower-extremity amputation. *J Am Podiatr Med Assoc.*, *91*(9), 451-455.

Aronne, L. J., Segal, K. R. (2003). Weight gain in the treatment of mood disorders. *J Clin Psychiatry,* 64 (8), 22-29.

Bala, N., Kaur, G., Attri, J.P., Sukhminder, J.S. B., Sawney, H., & Kumar, R. (2015). Psychosocial, psychiatric, and clinical implications of diabetic foot ulceration: A prospective analysis. *Journal of Social Health and Diabetes*, *3*(2), 89-94.

Bawo, O. J. , George, O. E., Ambrose, O. L., & Joyce, O. O. (2010). Depression and subjective quality of life among outpatients with diabetes mellitus at a teaching hospital in Nigeria. *Ment Health Fam Med.*, *7*(3), 179-183.

Beck, A.T., Ward, C.H., Mendelson, M., Morck, J., & Erbaugh, J. (1961). An Inventory for measuring depression. *Arch Gen Psychiatry 4*, 561-571.

Benotmane, A., Mohammedi, F., Ayad, F., Kadi, K., & Azzouz, A. (2000). Diabetic foot lesions: etiologic and prognostic factors. *Diabetes Metab, 26*, 113-117.

Bifulco, A. M.P., Ball, C., & Lillie, A. (2002). Adult attachment style. II: Its relationship to psychosocial depressive-vulnerability. *Socience Psychiatry Epidemiology, 37*, 60-67.

Bifulco, A., Moran, P.M., Ball, C., & Bernazzani, O. (2002). Adult attachment style. I: Its relationship to clinical depression. *Soc Psychiatry Psychiatr Epidemiol, 37*, 50-59.

Bonham, P. (2001). A Critical Review of the Literature: Part I: Diagnosing osteomyelitis in patients with diabetes and foot ulcers. *Journal of Wound, Ostomy & Continence Nursing wound care, 28*(2), 73-88.

Borssén, B., Bergenheim, T., & Lithner, F. (1990). The epidemiology of foot lesions in diabetic patients aged 15-50 years. *Diabet Med, 7*(5), 438-444.

Boulton, A.J. (1996). The pathogenesis of diabetic foot problems: an overview. *Diabet Med, 13*(1), 12-16.

Boulton, A. J., Vileikyte, L., Ragnarson, G., & Apelqvist, J. (2005). The global burden of diabetic foot disease. *Lancet 366*, 1719-1724.

Boutoille, D., Féraille, A., Maulaz, D., & Krempf, M. . (2008). Quality of life with diabetes associated foot complications: comparison between lower-limb amputation and chronic foot ulceration. *Foot Ankle Int., 29*, 1074-1078.

Brod, M. (1998). Quality of life issues in patients with diabetes and lower extremity ulcers: patients and their care givers. *Qual Life Res, 7*, 365-372.

Cameron, I.M., Crawford, J.R., Lawton, K., & Reid, I.C. (2008). Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care. *British Journal of General Practice, 58*, 32-36.

Carney, R.M., Blumenthal, J.A., & Stein, P.K. (2001). Depression, heart rate variability, and acute myocardial infarction. *Circulation, 104*(17), 2024-2028.

Carney, R.M., & Freedland, K.E. (2008). Depression in patients with coronary heart disease. *Am J Med, 121*(11), 20-27.

Carrington, A.L. , Mawdsley, S.K.V., & Morley, M. et al. (1996). Psychological status of diabetic people with or without lower limb disability. *Diabetes Res ClinPract., 32*, 19-25.

Charnogursky, G., Lee, H., & Lopez, N. (2014). Diabetic neuropathy. *Handb Clin Neurol, 120*, 773-785.

Ciechanowski, P.S., Katon, W.J., & Russo, J.E. (2000). Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Archives of Internal Medicine,, 160*(21), 3278-3285.

Clinical Practice Guideline. (2009). Management of Type II Diabetes Mellitus.(4th ed.). Putarjaya, Selangor: Ministry of Health Malaysia.

Clinical Practice Guidelines. (2004). Clinical Practice Guidelines Management of Diabetic Foot. Kuala Lumpur: Ministry of Health Malaysia.

Currie, C.J., Poole, C.D. , & Woehl, A. et al. (2006). The health-related utility and healthrelated quality of life of hospital-treated subjects with type 1 or type 2 diabetes with particular reference to differing severity of peripheral neuropathy. *Diabetologia., 49*, 2272-2280.

Daniel, W.W. (1999). *Biostatistic: A foundation for analysis in the health sciences*, (7th ed.). New York: John Wiley &Sons.

David, F., Penson, & Hunter, W. (2004). Erectile Dysfunction in Diabetic Patients. *American Diabetes Association, 17*(4), 225-230.

de Groot, M., Anderson, R., & Freedland, K.E. et al. (2001). Association of depression and diabetes complications: a meta-analysis. *Psychosom Med., 63*, 619-630.

Demyttenaere, K., Jaspers, L. (2008). Review: bupropion and SSRI-induced side effects. *J Psychopharmacol*, 22, 792-804.

Deuschle, M. (2013). Effects of antidepressants on glucose metabolism and diabetes mellitus type 2 in adults. *Curr Opin Psychiatry, 2*6 (1), 60-5.

DiMatteo, M.R., Lepper, H. S., Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*, 160, 2101–2107.

Dinesh, S., Thomas, C., Adhithya, S., Lloyd, T., Jennifer, D., Elaine, C., …Solomon, T. (2015). The contributors of emotional distress in painful diabetic neuropathy. *Endocinology & Metabolism J*, 23 (3), 27-30.

Docherty, J.P. (1997). Barriers to the diagnosis of depression in primary care. *J Clin Psychiatry, 58*(1), 5-10.

Eckman, M.H., Greenfield, S., & Mackey, W.C. et al. (1995). Foot infections in diabetic patients: decision and cost-effectiveness analyses. *JAMA*, 273712- 273720.

Elenkov, I.J. , & Chrousos, G.P. (2002). Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Annals of the New York Academy of Sciences, 966*, 290-303.

Elizabeth, H.B.L., Wayne, K., Michael, V.K., Carolyn, R., Greg, E.S., Malia, O.,…Bessie, Y. (2004). Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diacare*, 27 (9), 2154-2160.

Endicott, J. (1984). Measurement of depression in patients with cancer. *Cancer*, 53, 2243-2248.

Fariza, Y. (2003). *Psychological distress, anxiety and depression amog employees attending Staff Clinic in HUSM.* M.Med thesis. Kelantan, Malaysia: University Sains Malaysia,

Firdaus, M., Abdul, K.A.B. , Mazni, M.J., Azizul, A., Salina, A.A., Marhaini, M., Maniam, T. (2012). A Preliminary Study on the specificity and sensitivity valuew and inter-rater reliability of MINI International Neuropsychiatric Interview (M.I.N.I) in Malaysia. *ASEAN Journal of Psychiatry, , 13*(2), 35-39.

Forkmann, T., Vehren, T., Boecker, M. , Norra, C., Wirtz, M. , & Gauggel, S. (2009). Sensitivity and specificity of the Beck Depression Inventory in cardiologic inpatients: how useful is the conventional cut-off score? *J Psychosom Res, 67*(4), 347-352.

Geraldo, M.S., Leila, B., & Lydia, M.F. (2011). Assessment of depressive symptoms in people with diabetes mellitus and foot ulcers, *38*(5), 26-35.

Gomes-Villas Boas, L. C., Santos, C. B., Foss-Freitas, M. C., Pace, A. E. (2009). A relação entre o apoio social e as características sociodemográficas das pessoas com diabetes mellitus. *Rev Gaúcha Enferm*,30(3), 390-6.

Gonzales, O., Langer, O., Conway, D.L., Berkus, M.D., & Xenakis, E.M. (2000). A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med, 343*(16), 1134-1138.

Gonzalez, J.S., Safren, S.A., & Cagliero, E. et al. (2007). Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. *Diabetes Care, 30*, 2222-2227.

Gonzalez, J.S., Vileikyte, L., Ulbrecht, J.S., Rubin, R.R, Garrow, A.P., Delgado, C.,…Peyrot, M. (2010). Depression predicts first but not recurrent diabetic foot ulcers. *Diabetologia*, 53, 2241-2248.

Goodman, E., & Whitaker, R.C. (2002). A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics*, 110, 497-504.

Goodridge, D., Trepman, E., & Embil, J.M. (2005). Health-related quality of life in diabetic patients with foot ulcers: literature review. *J Wound Ostomy Continence Nurs, 32*(6), 368-377.

Goodwin, F.K., & Jamison, K.R. (2007). *Manic-depressive illness: bipolar disorders and recurrent depression*. Oxford University Press: New York.

Hanestad, B. R. (1993). Self-reported quality of life and the effect of different clinical and demographic characteristics in people with type 1 diabetes. *Diabetes Res Clin Pract*, 19(2), 139-49.

Harris, T.B., Ferrucci, L., & Tracy, R.P. et al. (1999). Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *American Journal of Medicine, 106*, 506-512.

Harrison, T.A., Hindorff, L.A., Kim, H., Wines, R.C., Bowen, D.J., McGrath, .B.B., & Edwards, K.L. (2003). Family history of diabetes as a potential public health tool. *Am J Prev Med, 24*, 152-159.

Hasanah, C.I., Naing, L., & Rahman, A.R.A. (2003). World Health Organization Quality of Life Assessment: Brief Version in Bahasa Malaysia. *Med JMalaysia 58*(1), 79-88.

Hatta, S. M., Hamid, A.R., Jaafar, R., Hamed, N., Jalil, N.F., & Mustafa, N. (1997). Depressive symptoms among women after abortion. *Malaysia Journal of Psychiatry, 5*, 27-33.

Heitzmann, C. A., Kaplan, R. M. (1984). Interaction between sex and social support in the control of type II diabetes mellitus. *J Consult Clin Psychol*, 52(6), 1087-9.

House, J. S., Umberson, D., Landis, K. R. (1988). Structures and processes of social support. *Annu Rev Sociol*, 14, 293-318.

International Diabetes Federation. (2009). *Diabetes Atlas* (4th ed.). Belgium.

Iida, M., Parris, Stephens, M.A., Rook, K.S., Franks, M.M., & Salem, J.K. (2010). When the going gets tough, does support get going? Determinants of spousal support provision to Type 2 diabetic patients. *Pers. Soc. Psychol. Bull. , 36*(6), 780-791.

Ingvar, B., Alv, A.D., Tangen, T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Distress Scale. *Journal of Psychosomatic Research, 52*(2), 69-77.

International Working Group on the Diabetic Foot. (2003). International Consensus on the Diabetic Foot and Practical Guidelines on the Management and the Prevention of the Diabetic Foot., *50*, 106-8.

Isaksson, L., & Lundgren, F. (1994). Vein bypass surgery to the foot in patients with diabetes and critical ischaemia. *Br J Surg 81*, 517-520.

Ismail, K., Winkley, K., Stahl, D., Chalder, T., & Edmonds, M. (2007). A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. *Diabetes Care, 30*(6), 1473-1479.

Iversen, M.M., Midthjell, K., Tell, G.S., Moum, T., Ostbye, T., Nortvedt, M.W., Hanestad, B.R. (2009). The association between history of diabetic foot ulcer, perceived health and psychological distress: the Nord-Trøndelag Health Study. *BMC Endocr Disord., 25*(9), 18-23.

Jammy, S. , Norlaili, M.T. , & Sherina, M.S. (2005). The Prevalence of Depressive Disorders Among Adult Patients Attending Primary Care Clinics. *The Malaysian Journal of Psychiatry*, 5 (5), 20-25.

Jay, A. B., Patrick, J. L., Jeffrey, F. S., Joanne, S., David, S. F. (2016). Ntidepressant medication use and glycemic control in co-morbid type 2 diabetes and depression. *Family Practice*, 10, 1093-1095.

Jeffrey, S. G., Loretta, V., Howard, L., Mark, P., Richard, R. R., Jan, S. U. (2005). Diabetic peripheral neuropathy and depressive symptoms. *Diabetes care*, 28 (10), 2378-83.

John, M. , & Hettema. (2010). Genetics of Depression. *Genetics and Genomics*, *8*(3), 316-322.

Jones, J.E., Robinson, J., & Barr, W. (2008). Impact of exudate and odour from chronic venous leg ulceration. *Carlisle C.Nurs Stand 22*(45), 53-54.

Julienne, K. K., Christine, N. E. , Ginger, P. G. C. , & Edward, E. (2013). Social Support Strategies in Adult Patients With Diabetes. A Review of Strategies in the USA and Europe, *Expert Rev Endocrinol Metab, 8*(4), 379-389.

Kaplan, & Sadock. (2003). *Synopsis of Psychiatry* (9th ed.). Philadelphia: Lippincott Williams & Wilkins.

Karen, L., Smarr, Autumn, L., & Keefer. (2011). Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9. *American College of Rheumatology, 63*(11), 454-466.

Katon, W.J. (2003). Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry*, 54, 216–226.

Katon, W., Lin, E.H., & Von Korff, M. (2004). Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care., 27*, 2154-2160.

Katon, W., & Sullivan, M.D. (1990). Depression and chronic mental illness. *Journal of Clinical Psychiatry, 51*, 3-14.

Katon, W.R.L., Russo, J., McCarty, C.A., Rockhill, C., McCauley, E., Richards, J., & Grossman, D.C. (2010). Depressive symptoms in adolescence: the association with multiple health risk behaviors. *Gen Hosp Psychiatry, 32*, 233-239.

Kaur, G., Tee, G.H., Ariaratnam, S., Krishnapillai, A.S., China, K. (2013). Depression, anxiety and stress symptoms among diabetics in Malaysia: a cross sectional study in an urban primary care setting. *BMC Fam Pract*, 14, 69.

Khalida, I., Kirsty, W., Daniel, S., Trudie, C., & Micheal, E. (2007). A Cohort Study of People With Diabetes and Their First Foot Ulcer: The role of depression on mortality. *Epidemiology/Health Services/Psychosocial ResearchDiabetes Care, 30*, 1473-1479.

Kinmond, K. , McGee, P. , Gough, S. , & Ashford, R. (2003). 'Loss of self': a psychosocial study of the quality of life of adults with diabetic foot ulceration. *Journal of Tissue Viability, 13*, 6-16.

Klassen, A., Jenkinson, C., Fitzpatrick, R. , & Goodacre, T. (1996). Patient's health related quality of life before and after aesthetic surgery. *Br J Plast Surg, 49*(7), 433-438.

Knol, M.J., Twisk, J.W., Beekman, A.T., Heine, R.J., Snoek, F.J., & Pouwer, F. (2006). Depression as a risk factor for the onset of type 2 diabetes mellitus: a meta-analysis. *Diabetologia*, *49*(5), 837-845.

Knol, M. J., Geerlings, M. I., Egberts, A. C., Gorter, K. J., Grobbee, D. E., Heerdink, E.R. (2007). No increased incidence of diabetes in antidepressant users. *Int Clin Psychopharmacol*, 22, 382-386.

Lavery, L.A., Armstrong, D.G., Wunderlich, R.P. , Tredwell, J., & Boulton, A.J. (2003). Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican

Americans and non-Hispanic whites from a diabetes disease management cohort. *Diabetes Care 26*(5), 1435-1438.

Letchuman, G.R., Wan Nazaimon, W.M., Wan Mohamad, W.B., Chandran, L.R., Tee, G.H., Jamaiyah, H., Ahamd Fauzi, Y. (2006). Prevalence of Diabetes in Malaysia National Health Morbidity Survey III. *Medical Journal of Malaysia 2010, 65*(3), 173-179.

Letchuman, G.R., Wan Nazaimoon, W.M., Wan Mohamad, W.B., Chandran, L.R., Tee, G.H., & Jamaiyah, H. (2010). Prevalence of diabetes in the Malaysian National Health Morbidity Survey III 2006. *Med J Malaysia, 65*, 173-179.

Lin, E.H., Katon, W., Von Korff, M. Rutter, C., Simon, G.E., Oliver, M.,… Young, B. (2004). Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care,* 27, 2154–2160.

Lin, E.H.B., Rutter, C.M., Katon, W. (2010). Depression and advanced complications of diabetes: a prospective cohort study. *Diab Care*, 33, 264–269.

Lis, R., Berit, R.H., Torbjorn, M., Kåre, B., & Tone, R. (2007). A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population. *Quality of Life Research, 16*(2), 179-189.

Loretta, V. (2001). Diabetic foot ulcers: a quality of life issue. *Diabetes Metabolism Research and Review, 17*(4), 246-249.

Lucas, L.S., Martins, J.T., & Rozazzi, M.L. (2008). Qualidade de vida dos portadores de ferida em membros inferiores - úlcera de perna. *14*(1), 43-52.

Lustman, P., & Harper, G. (1987). Nonpsychiatric physicians' identification and treatment of depression in patients with diabetes. *Compr Psychiatry 28*, 22-27.

Lustman, P. J., Griffith, L. S., Clouse, R E., Freedlamd, K. E., Eisen, S. A., Rubin, E. H., Carney, R. M., McGill, J. B. (1997). Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom Med*, 59, 241-250.

Lustman, Patrick, J., & (2002). Depression, Mood Disorders, Major Depressive Disorder. *Depression in Adults With Diabetes*,31(6), 38-45.

Marjolein, M. , & Grethe, S. (2015). Is depression a risk factor for diabetic foot ulcers? 11-years follow-up of the Nord-Trøndelag Health Study (HUNT), *Diabetes Care*, *29*(1), 20-25.

Marjolein, M. , Kristian, M., Grethe, S. T., Torbjørn, M., Truls, O, & Monica, W. (2009). The association between history of diabetic foot ulcer, perceived health and psychological distress: the Nord-Trøndelag Health Study. *BMC endocrine disorder*, *9*(18), 72-86.

Mayberry, L.S., & Osborn, C.Y. (2012). Family support, medication adherence, and glycemic control among adults with Type 2 diabetes. *Diabetes Care, 35*(6), 1239-1245.

Mazlina, M., Shamsul, A. S., & Saini Jeffery, F. A. (2011). Health-related Quality of Life in Patients with Diabetic Foot Problems in Malaysia. *Med J Malaysia*, *66*(3), 234-238.

McCarthy, M.I. (2010). Genomics, type 2 diabetes, and obesity. *England Journal Medicine, 363*, 2339-2350.

McGrath, E., Keita, G. P., Stickland, B. R., & Russo, N. F. (1990). Women and depression: Risk factors and treatment issues. *JAMA*, 3, 46-57.

McQuaid, J.R., Stein, M.B., Laffaye, C., & McCahill, M.E. (1999). Depression in a primary care clinic: the prevalence and impact of an unrecognized disorder. *J Affect Disord 55*(1), 1-10.

Mezuk, B., Eaton, W.W., Albrecht, S., & Golden, S.H. (2008). Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care., 31*(12), 2383-2390.

Michaud, C.M., Murray, C.J., & Bloom, B.R. (2001). Burden of disease: Implications for future research. *JAMA, 285*, 535-539.

Mika, K., Mark, H., David, B. G., John, R. G., Adam, G. T., Jaana, P., Marianna, V., Jussi, V. (2010). Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetic care*, 33 (12), 2611-2616.

Monami, M., Longo, R., Desideri, C.M., Masotti, G., & Marchionni, N. (2008). The diabetic person beyond a foot ulcer: healing, recurrence, and depressive symptoms. *E. J Am Podiatr Med Assoc, 98*(2), 130-136.

Monroe, S.M. , & Simons, A.D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin, 110*, 405-425.

Monroe, S.M., & Harkness, K.L. (2011). Recurrence in major depression: a conceptual analysis. *Psychological Review ,118*, 655-674.

Morgentaler, A. (1999). Male impotence. *Lancet 354*, 1713-1718.

Murray, C.J., & Lopez, A.D. (1997). Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet 349*(9063), 1436-1442.

Musselman, D.L., Betan, E., Larsen, H., & Phillips, L.S. (2003). Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. . *Biol Psychiatry., 54*, 317-329.

Musselman, D.L., Tomer, A., & Manatunga, A.K. et al. (1996). Exaggerated platelet reactivity in major depression. *Am J Psych, 153*, 1313-1317.

Nabuurs-Franssen, M.H., Huijberts, M.S., Nieuwenhuijzen Kruseman, A.C., Willems, J., & Schaper, N.C. (2005). Health-related quality of life of diabetic foot ulcer patients and their caregivers. *Diabetologia., 48*(9), 1906-1910.

Ng, C.G., Amer Siddiq, A.N., Aida, S.A., Zainal, N.Z., & Koh, O.H. (2010). Validation of the Malay version of the Multidimensional Scale of Perceived Social Support (MSPSS-M) among a group of medical students in Faculty of Medicine, University Malaya. *Asian J Psychiatr. , 3*(1), 3-6.

NHMS III. (2006). The Third National Health Morbidity Survey (NHMS III) Diabetes Group. *Ministry of Health Malaysia*.

Nienhuis, F.J. , van de Willige, G. , Th. Rijnders, C.A., de Jonge, P., & Wiersma, D. (2009). Validity of a short clinical interview for psychiatric diagnosis: the mini-SCAN. *British Journal of Psychiatry, 196*(1), 64-68.

Niraula, K., Kohrt, B.A., Flora, M.S., Thapa, N., Mumu, S.J., Pathak, R., Shrestha, R. (2013). Prevalence of depression and associated risk factors among persons with type-2 diabetes mellitus without a prior psychiatric history: a cross-sectional study in clinical settings in urban Nepal. *BMC Psychiatry. , 15*(13), 309.

Obilor, H. N. & Adejumo, P. O. (2015). Assessment of diabetic foot ulcer-related pain and its relationship to quality of life. *Endocinology & Metabolism J*, 23 (3), 27-30.

Okura, T., Heisler, M., & Langa, K.M. (2009). Association between cognitive function and social support with glycemic control in adults with diabetes mellitus. *J. Am. Geriatr. Soc, 57*(10), 1816-1824.

Owens, M.J., & Nemeroff, C.B. (1994). Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem, 40*, 288-295.

Oyibo, S.O., Jude, E.B., & Tarawneh, I.(2001). The effects of ulcer size and site, patient's age, sex, and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med, 18*, 133-181.

Padua, L., Saponara, C., & Ghirlanda, G. (2001). Health-related quality of life in type 1 diabetic patients and influence of peripheral nerve involvement. *Neurol Science, 22*, 239-245.

Park, M., Katon, W., & Wolf, F. (2013). Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. *Gen Hosp Psychiatry, 35*, 217-225.

Paschalides, C., Wearden, A.J., Dunkerley, R., Bundy, C., Davies, R., & Dickens, C.M. (2004). The associations of anxiety, depression and personal illness representations with glycaemic control and health-related quality of life in patients with type 2 diabetes mellitus. *J Psychosom Res, 57*, 557-564.

Pearce, K.A, Love, M.M., & Shelton, B.J.(2008). Kentucky Ambulatory Network. Cardiovascular risk education and social support (CaRESS): report of a randomized controlled trial from the Kentucky Ambulatory Network (KAN). *J. Am. Board Fam. Med. , 21*(4), 269-281.

Pecoraro, R. (1991). *The nonhealing diabetic ulcer: a major cause for limb loss*. New York: Wiley-Liss.

Pecoraro, R. E., Reiber, G. E. , & Burgess, E. M. (1990). Pathways to diabetic limb amputation: Basis for prevention. *Diabetes Care, 13*, 513-521.

Peluso, E.T, & Blay, S.L. (2008). Public perception of depression in the city od São Paulo. *Rev Saúde Pública 42*(1), 41-48.

Penninx, B.W., Beekman, A.T., & Honig, A. (2001). Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry, 58*(3), 221-227.

Polit, D.F., & Beck, C.T. (2008). *Nursing research: generating and assessing evidence for nursing practie*. Philadelphia :Lippincott Williams & Wilkins.

Porciúncula, M.V., Rolim, L.C., Garofolo, L., & Ferreira, S.R. (2007). Analysis of factors associated with extremity ulceration in diabetic subjects with peripheral neuropathy. *Arq Bras Endocrinol Metabol 51*(7), 1134-1142.

Post, R.M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry, 149*, 999-1010.

Prompers, L., Schaper, N., Apelqvist, J., Edmonds, M. , Jude, E. , & Mauricio, D. (2008). Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. *The EURODIALE Study.Diabetologia, 51*, 747-755.

Ramsey, S.D., Newton, K., Blough, D. (1999). Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care, 22*, 382-387.

Ramsey, S.D., Newton, K., & Blough, D. (1999). Incidence outcomes and costs of foot ulcers in patients with diabetes. *Diabetes Care, 22*, 382-387.

Rees, C.A., Karter, A.J., & Young, B.A. (2010). Race/ethnicity, social support, and associations with diabetes self-care and clinical outcomes in NHANES. *Diabetes Educ., 36*(3), 425-445.

Reiber, G.E.L. , Vileikyte, E.J. , Boyko, M. , del Aguila, D.G., Smith. (1999). "Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings." *Diabetes Care, 22*(1), 157-162.

Ribu, L. , & Wahl, A. (2004). Living with diabetic foot ulcers: a life of fear, restrictions,and pain. *Ostomy Wound Management, 50*, 57-67.

Ribu, L., Hanestad, B.R., Moum, T., Birkeland, K., & Rustoen, T. (2007). A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population. *Qual Life Res, 16*(2), 179-189.

Robert, F., & Nanjundappa, G. (1986). Diabetes, depression and employment status. *Social Science & Medicine, 23*(5), 471-475.

Robinson, N., Yateman, N.A., Protopapa, L.E., & Bush, L. (1990). Employment problems and diabetes. *Diabet Med 7*, 16-22.

Rodolfo, V., Paula, W. , Yoon, S.C.D., Tiebin, L., Muin, J. , & Khoury. (2007). Family History and Prevalence of Diabetes in the U.S. Population, The 6-year results from the National Health and Nutrition Examination Survey (1999–2004). *Diabetes Care, 30*(10), 2517-2522.

Ronalds, C., Creed, F., & Stone, K. (1997). Outcome of anxiety and depressive disorders in primary care. *British Journal of Psychiatry, 171*, 427-433.

Rothman, K.J., & Greenland, S. (1998). *Modern epidemiology*. Philadelphia: Lippincott Williams & Wilkins.

Rubin, R. R., Ma, Y., Marrero, D. G., Peytot, M., Barrett-Connor, E. L., Kahn, S. E., Haffner, S. M., Price, D. W., Knowler, W. C. (2008). Elevated depression symptoms, antidepressant medicine use and risk of developing diabetes during the diabetes prevention program. *Diabetes Care*, 31, 420-426.

Salynn. (2006). Depression Drugs May Up Diabetes Risk. *WebMD, 2*, 45-50.

Salynn, B. (2009). Depression, anxiety linked to weight gain. *WebMD Health News., 2*(3), 118-126.

Schiotz, M.L., Bogelund, M., Almdal, T., Jensen, B.B., & Willaing, I. (2012). Social support and self-management behaviour among patients with Type 2 diabetes. *Diabet Med. , 29*(5), 654-661.

Scott, M., Monroe, George, M. , Slavich, & Ian, H. (2015). Life Stress and Family History for Depression: The Moderating Role of Past Depressive Episodes. *J Psychiatr Res, 49*, 90-95.

Sheehan, D.V., Lecrubier, Y., & Sheehan, K.H. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *PubMed, 59*(20), 22-23.

Sheehan, D. V., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A.,Schinka, J., Knapp, E., Sheehan, M. F., Dunbar, G.C. (1997). The validity of the Mini International Neuropsychiatric Interview (M.I.N.I.) according to the SCID-P and its reliability. *Eur Psychiatry*, 12, 232-241.

Simson, U., Nawarotzky, U., Friese, G., Porck, W., Schottenfeld-Naor, Y., & Hahn, S. (2008). Psychotherapy intervention to reduce depressive symptoms in patients with diabetic foot syndrome. *Diabet Med 25*(2), 206-212.

Singh, N. , Armstrong, D.G., & Lipsky, B.A. (2005). Preventing foot ulcers in patients with diabetes. *JAMA., 293*(2), 217-228.

Strine, T. W., Okoro, D.P., Chapman, G.L.A., Beckles, L., Balluz, & Mokdad, A.H. (2005). The impact of formal diabetes education on the preventive health practices and behaviours of persons with type 2 diabetes. *Preventive Medicine, 41*(1), 79-84.

Tarsitani, L., & Bertolote, J. M. (2006). Major Depressive co-morbidity in epilepsy as a reactive process to a chronic condition. *Epilepsy & Behaviour, 8*, 343-344.

Tennvall, G.R., Apelqvist, J., & Eneroth, M. (2000). Costs of foot infections in patients with diabetes mellitus. *Pharmacoeconomics, 18*, 225-238.

Thomas, J., Jones, G. , Scarinci, I. , & Brantley, P. (2003). A Descriptive and Comparative Study of the Prevalence of Depressive and Anxiety Disorders in Low-Income Adults With Type 2 Diabetes and Other Chronic Illnesses. *Diabetes Care, 26*(8), 2311-2317.

Toni, N., Vanessa, I., & Sue, P. (2013). Assessment of depression in people with diabetes attending outpatient clinics for the treatment of foot ulceration. *Journal of Foot and Ankle Research, 6*(1).

Torquato, M.T., Montenegro, J.R.M. , Viana, L.A., de Souza, R.A., Lanna, C.M., & Lucas, J.C. (2003). Prevalence of diabetes mellitus and impaired glucose tolerance in the urban population aged 30-69 years in Ribeirão Preto (São Paulo), Brazil. *São Paulo Med J 121*(6), 224-230.

Uchimoto, S., Tsumura, K., Hayashi, T., Suematsu, C., Endo, G., & Fujii, S. et al. (1999). Impact of cigarette smokingg on the incidence of Type 2 diabetes mellitus in middle-aged Japanese men: the Osaka Health Survey. *Diabet Med, 16*(11), 951-955.

Upton, D., Solowiej, K. L., Woo, K. Y. (2014). A multinational health professional perspective of the prevalence of mood disorders in patients with acute and chronic wounds. *International Wound Journal*, 11(6), 625-635.

van Dam, H.A., van der Horst, F.G., Knoops, L., Ryckman, R.M., Crebolder, H.F., & van den Borne, B.H. (2005). Social support in diabetes: a systematic review of controlled intervention studies. Comprehensive systematic review of social support in diabetes using controlled intervention studies from 1980 to 2003. *Patient Educ. Couns., 59*(1), 1-12.

van der Feltz-Cornelis, C. M., Nuyen, J., Stoop, C. (2010). Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. *Gen Hosp Psychiatry,* 32, 380–395.

van Dooren, F., Nefs, G. , Schram, M. , Verhey, F. , & Denollet, J. et al. (2013). Depression and Risk of Mortality in People with Diabetes Mellitus: A Systematic Review and Meta-Analysis. *PubMed, 8*(10), 65-71.

Vedhara, K., Miles, J.N. , Wetherell, M.A., Dawe, K., Searle, A. , & Tallon, D. (2010). Coping style and depression influence the healing of diabetic foot ulcers: observational and mechanistic evidence. *Diabetologia 53*(8).

Von Korff, M., Scott, K.M., & Gureje, O. (2009). *Global Perspectives on MentalPhysical Comorbidity in the WHO World Mental Health Surveys*. New York: Cambridge University Press.

Wayne, J. , & Katon. (2011). Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues Clinical Neuroscience, 13*(1), 7-23.

Weijman, I., Kant, I. , Swaen, G. M., Ros, W. J. G. , Rutten, G. E. H. M. , Schaufeli, W. B., Winnubst, J. A.M. (2004). Diabetes, Employment and Fatigue-Related Complaints: A Comparison Between Diabetic Employees, "Healthy" Employees, and Employees With Other Chronic Diseases. *J Occup Environ Med, 46*, 828-836.

Wells, K.B., Stewart, A., & Hays, R.D. (1989). The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA, 262*, 914-919.

World Health Organization. (2013). Diabetes Mellitus (6th ed.). Geneva.

World Health Organization. (2015). Diabetes Mellitus (7th ed.). Geneva.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global Prevalence of Diabetes. Estimates for the year 2000 and projections for 2030. *Diabetes Care, 27*, 1047-1053.

Williams, L. H., Rutter, C. M., Katon, W. J., Reiber, G. E., Ciechanowski P., Heckbert S. R., ..., Von Korff M. (2010). Depression and incident diabetic foot ulcers: A prospective cohort study. *American Journal of Medicine*, 123(8), 748-754.

Willrich, A., Pinzur, M., McNeil, M. , Juknelis, D., & Lavery, L. (2005). Health related quality of life, cognitive function and depression in diabetic patients with foot ulcer or amputation. A preliminary study. *Foot Ankle International., 26*, 128-134.

Zahra, C., Charles, M.J.S. , & Jörg, W.H. (2014). High levels of anxiety and depression in diabetic patients with Charcot foot. *J Foot Ankle Res., 7*(22).

Zigmond, A.S., Snaith, R.P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand, 67*, 361-370.

Zimet, G.D., Dahlem, N.W., Zimet, S.G., & Farley, G.K. (1988). The Multidimensional Scale of Perceived Social Support. *Journal of Personality Assessment, 52*, 30-41.

Zimmet, P.Z., & Alberti, K.G. (2006). Introduction: Globalization and the non-communicable disease epidemic. *Obesity (Silver Spring), 14*(1), 1-3.