Hochschule für Angewandte Wissenschaften Hamburg
Hamburg University of Applied Sciences

Hamburg University of Applied Sciences

Faculty of Life Sciences

Master in Public Health degree

Economics of the Diabetic Foot: A Cost-Of-Illness Study in Saudi Arabia

Master Thesis

Date of submission: **12.09.2016**

Submitted by: Turki Bafaraj

Matriculation number: 2232574

Examination supervisor: Prof. Dr. York F. Zöllner

Secondary supervisor: Prof. Dr. med. Hasan A. Alzahrani,

ACKNOWLEDGEMENTS

First of all, I'm grateful to THE ALMIGHTY ALLAH for establishing me to complete this project.

I give all my success and achievement to my parents, Ghazi Bafaraj and Amnah Alahdal. Also to my wife Nidaa Zawawi, supportive brothers and lovely sisters for their unceasing encouragement.

Thank you Prof. Dr. York F. Zöllner and Prof. Dr. med. Hasan A. Alzahrani who were more than generous with their expertise and precious time.

A special thanks to Dr. Hani Jokhdar for his countless hours of helping to access the data, and most of all patience throughout the entire process.

I would like to acknowledge and thank the Faculty of Life science, Hamburg University of Applied Sciences for allowing me to conduct my research and providing any assistance requested.

Finally, I would like to thank all teachers and administrators in my Faculty that assisted me during my studying of MPH.

Abstract

Background: Diabetes mellitus (DM) is a chronic disease today's societies encounter. Diabetes symptomatology implies a definitive hormonal background involving insulin production, or its tissue uptake (types 1 and 2 diabetes, respectively); however its exact etiology is still unknown. Diabetes is a disease of complications, e.g., angiopathy, neuropathy; particularly diabetic foot disorders (DFDs) which can be devastating. Amputation, especially following ulceration is a catastrophic endpoint of DFDs. Saudi Arabia suffers a terrifying DM situation (>20% adults), aggravated by high obesity rates and modernized way of living. Above 25% Saudi diabetics develop DFDs, >25% of whom end up with amputation. "Cost of illness" (COI) can be used to estimate the economic burden of DFDs. This work focuses on COI in DFDs in Saudi; identifying risks affecting this cost.

Methodology: Records of adult diabetics with DFDs enrolled with a major insurance agency in Jeddah, KSA were reviewed. Studied data included demographics, intervention options, and reimbursement as a COI measurement during fiscal year (FY) 2015. A quota sample of 60 diabetics was recruited; their risk factors for developed DFDs and COI analyzed.

Results: The median age of participants was 58y (IQR 3y). Male: female 2.53:1; and Saudi: non-Saudi 4:1. Most subjects (43.3%) needed debridement, 35% minor amputation, 15% major amputation, and 6.7% conservative treatment for their DFDs episodes. Age≥55 significantly required more intensive intervention compared to younger age (minor amputation 35% vs. 0%, major amputation 15% vs. 0%, respectively; Fisher's exact 8.567, p=0.011). Age significantly impacted COI [r(df=58) =0.333, p=0.009]. Saudis significantly experienced amputation more frequently than non-Saudis (33.3% vs. 1.7% major amputation, 15.0% vs. 0.0% minor amputation, respectively; Fisher's exact 11.98, p=0.004). They also bear higher COI [t(df 55.6= 4.7, p<0.0001). Mean COI significantly varied by intervention option [F (df 3, 56) =101.3, p<0.0001]. Age could predict change in COI (Exp B = 1.84, 95% 1.2 - 2.74. Although COI varied by type of intervention, the latter could not predict such change in COI.

Conclusion: Age is risk for a worsened DFDs prognosis and higher costs. Saudis are at risk of more costly DFs. The change in COI could be predicted by studied risks. Findings from this work can be used in developing an integrated DFDs database, planning to alleviate DFDs burden and improve the health related quality of life Saudi diabetic patients.

Keywords: Diabetic foot, cost of illness, Saudi Arabia

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AGES	Advanced Glycation End-Products
CVD	Cardiovascular Disease
CBA	Cost-Benefit Analysis
CDA	Canadian Diabetes Association
CEA	Cost-Effectiveness Analysis
CI	Confidence interval
COI	Cost of Illness
CUA	Cost-Utility Analysis
DALYs	Disability Adjusted Life Years
DFDs	Diabetic Foot Disorders
DPP	Diabetes Prevention Program
DM	Diabetes Mellitus
FPG	Fasting Plasma Glucose
GP	General Practitioner
GDP	Gross Domestic Product
GDM	Gestational Diabetes Mellitus
GLP-1	Glucagon-Like Peptides 1 Receptor Agonists
HRQOL	Health Related Quality of Life
ICD-10-CM	International Classification of Diseases-Version 10 Coding Manual
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glycaemia
IHD	Ischemic Heart Disease
LICs	Low Income Countries
LMICs	Low and Middle Income Countries
LYG	Life Year Gain
MI	Myocardial Infarction

NCDs	Non-Communicable Diseases
OGTT	Oral Glucose Tolerance Test
PHC	Primary Health Care
PVD	Peripheral Vascular Disease
QALYs	Quality Adjusted Life Years
QOL	Quality of Life
USD	United States Dollar
WHO	World Health Organization

1. Introduction

Diabetes mellitus (DM) is a serious disease that occurs either when the pancreas does not produce enough insulin (type 1 diabetes), or when the body cannot effectively utilize the insulin it produces (type 2 DM) (WHO, 1999). Generally, the majority of diabetic patients are affected by type 2 diabetes. The age predominance of type 2 diabetes traditionally used to occur almost entirely among adult populations; but now it occurs in children too (WHO, 2013a). A sharp demarcation in the global prevalence of the two types thereby barely exists. Diabetes literally represents a major concern for healthcare systems, globally, given the increase in incidence rates among almost all population subsets, disregarding the variability in the demographic or socio-economic status. Despite the higher opportunity for building up sound health culture aided by a wider span of health education and the accessibility to quality health services many developed countries enjoy, such merits failed to halt the alarming statistics of diabetes and its complications in these countries. The prevalence of diabetes competes with other non-communicable diseases (NCDs) which attract an utmost public health's attention, such as cardiovascular disease (CVD), cancer, and chronic respiratory disorders. In spite of the presence of cost-effective interventions, NCDs, including DM receive less than 3% of annual development assistance for health to low and middle income countries (LMIC), offered by top donors in global health (e.g., Bill and Melinda Gates Foundation and the World Bank) (Risko, et al., 2011). Undoubtedly, no significant change in DM situation could be felt in the presence of this modest budgeting. And whether such meager funding would be kept on the table for the prevention and control of NCDs and whether a global plan of action to mitigate their ongoing spread will be achieved in the foreseen future are questionable.

The global burden of DM is overwhelming. As of 2014, trends suggested the rate of diabetes in the general populations would continue to rise (IDF, 2014). For instance, in 2015, an estimated 415 million people had diabetes worldwide, with type 2 DM making about 90% of the cases. This represents 8.3% of the adult population (Yuankai & Hu, 2014), and with nearly equal rates in both women and men (Vost, et al., 2012). Importantly, the current epidemiological profile of DM probably reflects a universally escalating tendency for risk factors, such as being overweight or obese. Mortality-wise, too, diabetes occupies the 8th

position among causes of death due to NCDs (WHO, 2014) e.g., accounting up to 1.5 million deaths in 2012. Higher-than-optimal blood glucose caused an additional 2.2 million deaths by increasing the risks of cardiovascular and other diseases. Forty-three percent of these 3.7 million deaths occur before the age of 70. The toll of diabetes and elevated blood glucose in those under 70 is now higher in low- and middle-income countries than in high-income countries (150 million vs. 0.3 million respectively) (WHO, 2016). Factoring the relatively limited healthcare resources and support these countries might be suffering (Risko, et al., 2011), an unfavorable health and economic outcome is justified.

In Saudi Arabia, the overall epidemiologic picture of diabetes with its risks and consequences is no departure from the global situation. Like most oil-rich countries, leaving behind the physically demanding life of the desert for air-conditioned comfort, servants, and fast food and meat based dishes replacing fiber rich food**,** Saudi Arabia does struggle with obesity and diabetes (Jalboukh, 2008). The prevalence of DM among adult Saudis has reached 23.7%, a proportion that is one of the highest in the world (Alwakeel, et al., 2009). The burden of diabetes upon the Saudi society continues to be on the rise. Diabetes negatively impacts the health standard of the Saudi populations and causes a considerable source of drainage in national health funds in terms of the costs associated with treating affected cases and treating the disability and losses incurred due to lost wages and hampered productivity.

Complications, risks, and burden of diabetes are increasingly stressing to medical, social, economic and healthcare planners. The issue is that if not well controlled, diabetes can possibly lead to those complications affecting almost all body systems. Knowledge and awareness about DM, its risk factors, complications, and successful management plan requirements are important aspects for a better control and a better health-related quality of life (HRQOL) (Wild et al., 2004). Frequently, by the time people are diagnosed, they have developed severe complications, e.g., microangiopathic processes (as in retinopathy), or macroangiopathic processes [as in ischemic heart disease (IHD)]. Other body organs affected as diabetes and more-than optimum blood glucose progress to complications include central nervous system (e.g., stroke), peripheral nerves (e.g., diabetic neuropathy), kidney (diabetic nephropathy), eye (diabetic retinopathy), and DFDs.

The cost of case negligence and the benefit of prevention and early intervention in diabetes is a notion that is well addressed by the diabetes care providers' community and stakeholders. If

not well controlled, diabetes may cause blindness, kidney failure, lower limb amputation and long-term disabilities that impact significantly on the patients' QOL. Although many people living with diabetes are prone to developing foot complications, there are no exact global estimates regarding the particularly lower extremity amputations (Moxey, et al., 2011). Moreover, diabetes, and its subsequent complications bring about substantial economic losses to patients and their families. These losses involve direct medical costs and loss of work and wages, as seen by the global economic cost of diabetes in 2014 estimated totaling a staggering $612 billion (International Diabetes Federation- IDF, 2013). While the major cost drivers are hospital and outpatient care, a contributing factor is the rise in cost for analogue insulins (derived from human insulin by modifying its structure to change the pharmacokinetic profile), which are increasingly prescribed, despite little evidence that they provide significant advantages over cheaper human insulins (NCD Risk Factor Collaboration, 2007).

The facts that certain risks, (e.g., lifestyle, medical, and environmental factors), may precipitate diabetes, especially in the genetically predisposed, and that diabetes itself leads to consequences, some of which, are underlying disease triggers, e.g., hypertension, warrant early intervention to interrupt the circle, and hence control the diabetes problem in the community. Because blood glucose levels can rise to diabetic levels with little or nothing in the way of symptoms, early detection of diabetes would lead to measures to reduce the risk of heart disease, e.g., the use of statins to lower cholesterol, the reduction of blood glucose levels initially by diet and exercise, supplemented with hypoglycemic drugs, as necessary (Waugh, et al., 2007). The costs of case finding, e.g., through community screening programs for diabetes are quite reasonable and are balanced in relation to health expenditures as a whole, and facilities and resources available to treat newly diagnosed cases (Engelgau, et al., 2000). Although type 1 diabetes cannot be prevented with current knowledge (World Health Organization, 2014), effective approaches are available to prevent type 2 diabetes and to prevent the complications and premature death that can result from all types of diabetes. These include policies and practices across whole populations and within specific settings (school, home, and workplace) that contribute to good health for everyone, regardless of whether they have diabetes, such as exercising regularly, eating healthily, avoiding smoking, and controlling blood pressure and lipids. That the starting point for living well with diabetes is

early diagnosis; the longer a person lives with undiagnosed and untreated diabetes, the worse their health outcomes are likely to be. For those who are diagnosed with diabetes, all types, a series of cost-effective interventions can improve their outcomes, such as blood glucose control, through a combination of diet, physical activity and, if necessary, medication; to reduce the risk for complications; and regular screening for organs vulnerable to these complications, including eyes, kidneys, nerves, and feet, to facilitate early treatment.

Especially foot in diabetics is seat for a sequence of insults due to multiple pathological risks involving vascular changes, immune system integrity, neurological impairment, and deranged cell metabolism; all intervene, particularly uncontrolled diabetes. In fact, DFDs are among the most feared complications of DM Clinically, DFDs may present in the form of foot ulceration, infection, neuropathy, deformity, gangrene and/or ischemia. (A combination of any of DFDs symptoms may occur simultaneously, and both feet may be affected). Infected foot ulcers can progress to gangrene and lower limb amputation. Diabetics are 10-20 times more likely to experience amputation than normal population. Recently, a few high-income countries have documented a reduction in amputation rates in people with diabetes (Roglic, 2016). The derangement in the social, psychological, and QOL inflecting diabetics with foot ulceration is truly painful. Cost- wise, the expenditure against caring for diabetics with foot ulceration is five-times greater than that for no-ulcerative peers a year-time after the first diabetic ulcer episode (Driver, et al., 2010). All health economies suffer from such costs, e.g., account between 15% up to 40% of the of the world's total healthcare expenditure, (being highest in developing countries) (Boulton, et al., 2005). In practice, patients with DF ulcers have a higher demand for health care at all settings, inpatient, emergency or outpatient follow up services. The costs of such services should be endorsed in the cost accounting for any ulcer episodes a diabetic patient may have gone through (Ali, et al., 2008).

Despite the seriousness of DFDs there is limited research investigating the impact of this group of diabetic health problems on the economic status of the Gulf countries, in general, and Saudi Arabia, in particular. The scanty research on DFDs in Saudi Arabia has been undertaken in hospital setting (Alzahrani, et al., 2013). The majority of other hospital-based researcher done elsewhere used quantitative measures of HRQOL, such as, the Nottingham health profile and the Diabetes QOL measure. From the societal perspective, too, it is

therefore necessary to consider the economic impacts of DFDs, and identify interventions that can reduce the burden of these health problems. Studying COI is an essential evaluation technique in our attempts to measure and compare the economic burden of DFDs to society (Jo, 2014). Findings from this work help healthcare decision-makers in setting up and prioritize healthcare policies and interventions to improve diabetes outcomes in the community.

1.1.Rationale

The major part of the burden of people with diabetes is their impaired HRQOL, largely due the liability to chronic complications which DFDs take the greatest toll. Among those, distressing DFDs, especially ulcers are common and often progress to lower extremity amputation. Comprehensive data about the epidemiological characteristics, including disease distribution and determinants, and scale of DFDs problem in Saudi Arabia are lacking. Sources for gaining evidence-based information, especially about complicated DM, such as diabetes national registry or large-scale systematic reviews, are either scarce or incomplete. On the other hand, the prevalence of DM problem and subsequent risk of developing DFDs among affected individuals is paramount. Likewise, the impact of DFDs problem per se upon the diabetics' QOL and the economic loss incurred are stressing. Even with recent emergence of sporadic attempts to approach the burden of the DFDs problem in Saudi Arabia, little research managed to embrace an integrated economic evaluation plan, using standardized health economic outcome measures, such as COI. Adopting recognized economic evaluation tools, such as the COI method helps understand the economic outcome of DFDs problem in Saudi Arabia and hence enable integrating this understanding in designing and evaluating intervention plans for preventing and managing DFDs and diabetes problem in Saudi Arabia on sound scientific basis.

Only recently, a number of reports with various economic approaches have been published from different countries addressing the economic impact of foot complications in patients with diabetes. Relatively few studies discuss health economics, especially related to foot ulceration, the severest and most devastating DFs complications of DM. The interest in investigating the cost issues of DFDs is gaining momentum, perhaps due to increased suffering societies started to experience from such health challenge. The disorders affect an

increasingly large number of people around the world, putting them at risk for disability and diminished QOL. The strains on the health care budget occur at the same time that newly expensive technologies and treatment options have become available. Here, we analyze the economic consequences of diabetic foot lesions among diabetic patients in Saudi Arabia, as expressed by means of COI, where all DFDs types would be covered.

1.2 Aim and Questions of Thesis

1.2.1. General aim

This study aimed to explore and quantify the current economic burden associated with diabetic foot disorders in Saudi Arabia.

1.2.2. Specific aims

1. To identify the distribution pattern of demographic criteria associated with DFDs.
2. To determine the prevalence of DFDs intervention options in reflection of these disorders' severity upon affected individuals.
3. To identify COI distribution pattern among different DFD intervention groups.
4. To realize and measure the impact of demographic and DFDs determinants upon COI in the study population.
5. To predict the probability of change in COI of DFDs in response to a unit change in selected predictors.

The research questions are as follows:

1. What is the distribution pattern of intervention options among the study's DFDs population?
2. Is there a significant relationship between demographic criteria and the prevalence of the intervention options used for treating DFDs?
3. What is the distribution pattern of the COI among different DFDs groups?
4. Is there a significant relationship between COI and DFD intervention options?
5. Can selected study determinants predict the change in COI of DFDs?

1.3 Thesis Structure

The thesis is structured in six parts: First, the introduction and outline of the research project, second, the theoretical background that gives an overview of the project's background, third, the methodological framework, fourth, the presentation of the results, fifth, a subsequent discussion of the findings, and sixth, a short conclusion.

2. Theoretical Background

This investigator has conducted a thorough and meticulous search, considering reliable and evidence-based sources available, in order to explore all what has is known up to date relevant to diabetic foot disorders, their epidemiology, presentation, burden, economics, particularly cost of illness, and apply these information to the Saudi Arabian populations. Based on the comprehensive literature review done, the theoretical background of the researched subject will be outlined in this section.

2.1 Literature Review

2.1.1 Definition and Description of Diabetes Mellitus

"Diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both" (World Health organization, 1999). Other definitions for diabetes given by several scientific and professional diabetes concerned organizations exist. All these definitions mainly focus on the state chronicity of high blood glucose and the endocrinal background of the disorder where problems with insulin and its role in cell metabolism is incriminated. In their description of diabetes, too, concerned researches address the complexity of DM; its close association with underlying risk factors on the one hand, and close association with detrimental consequences upon the body systems if not adequately controlled, on the other. For instance, the American Diabetes Association (ADA) (2004) endorses DM as a *"group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both."* The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and

failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels." The Canadian Diabetes Association (CDA) (2013) envisions diabetes as being *a "metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both."* In diabetes, ongoing patient self-management education and support are critical to prevent acute complications and reducing the risk of long-term complications. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for CVD. The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy. On the other hand, there is a large body of evidence in support of a range of interventions to significantly mitigate the occurrence of these complications and hence improve diabetes outcomes. (American Diabetes Association, 2015; Griffth, et al., 2011; Khan, et al., 2010).

In essence, diabetes as also defined in surveys as those having fasting plasma glucose (FPG) value of greater than- or equal to- 7.0 mmol/L or on medication for diabetes/raised blood glucose, involves a myriad of etiologic, deterministic, physiological, clinical, and prognostic characteristics, many of which can be crippling. For instance, it has been postulated that due to population growth and the increase in longevity, the prevalence of diabetes has considerably risen at each age of human population. In parallel, a plenty of medical advances, new health education, quality assurance measures, and health legislative actions have been sustained and showed significant success in decreasing the prevalence and load of many health challenges in a variety of regions, worldwide. Whether these advances would be able to counteract or neutralize the impact of overpopulation alongside with other risks on the growth of the diabetes rates then boost the opportunity of an improved HRQOL of diabetics is still questionable. Since 1965 the WHO has published guidelines for the diagnosis and classification of diabetes. These were reviewed in 1998 and periodically thereafter, and were published as the guidelines for the "Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications" (World Health Organization, 1999). Ever since, more information relevant to the diagnosis of diabetes has become available. In November 2005 a joint WHO and International Diabetes Federation (IDF) Technical Advisory Group met in Geneva to review and update the current WHO guidelines (World Health Organization, 2006).

Diabetes mellitus poses a considerable burden upon the public health systems and national economies, especially being one of the ten leading causes of all deaths, worldwide (World Health Organization, 2014). The disease is recognized as one of the most important causes of premature death and disability, the reason why it has been among four priority NCDs targeted by world leaders in the 2011 Political Declaration on the Prevention and Control of NCDs (United Nations, 2011). Again, despite the remarkable advance in the healthcare research which has brought about innovative diagnostic and therapeutic solutions to a large number of ailments like never before, diabetes with its immense challenge as a complex community health problem remains on the rise. In the past three decades the prevalence (age-standardized) of diabetes has increased substantially in countries of all income levels, (probably mirroring the global increase in populations' tendency for increased weight problems and unhealthy diet and lifestyle). For instance, the prevalence of diabetes has grown from 108 million (4.7% of the world's population) in 1980 to 422 million (8.5% of the world population) in 2014, during which time prevalence has increased; or at best remained unchanged, in every country (NCD Risk Factor Collaboration, 2016).

2.1.2 Classification and Types of Diabetes Mellitus

According to the WHO guidelines for the classification and diagnosis of diabetes (World Health Organization, 2015), which came into effect in June 2000, diabetes mellitus is separated into four subcategories: type 1 diabetes, type 2 diabetes, gestational diabetes (GDM) and other specific types of DM (e.g., drug induced or DM due to other endocrine diseases such as Cushing's' disease). Type 1 DM (where the pancreas fails to produce enough insulin), which was formerly known as "insulin-dependent diabetes mellitus" or "juvenile diabetes"). The condition can occur at any age but presents mainly in childhood and early adult life and accounts for around 10% of all cases of diabetes. The main cause of type 1 diabetes is autoimmune destruction of the islet beta cells of the pancreas. The etiology is complex and is still not fully understood. The role of genetic predisposition in type 1 diabetes has not been proven, but increased susceptibility to the disease may be inherited. Environmental factors may trigger the auto-immune response in predisposed individuals. With type 1 diabetes insulin replacement is a necessity, a lack of insulin results in hyperglycemia and ketoacidosis [International Diabetes Federation (IDF), 2014].

Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop (World Health Organization, 2014). (This form was previously referred to as "non-insulin-dependent DM" or "adult-onset diabetes"), and the primary cause is excessive body weight and not enough exercise. Type 2 diabetes is more common, and unlike type 1 diabetes, usually begins in middle age or in the elderly, but can begin at any age. Type 2 diabetes accounts for 80% of cases of diabetes. The cause of Type 2 diabetes is thought to be primarily due to resistance to the action of insulin at its target cells. A genetic factor has also been implicated and many patients have a family history of diabetes. The majority of people with type 2 diabetes are obese as this in itself causes or aggravates insulin resistance. Unlike people with type 1 diabetes, people with type 2 diabetes produce insulin; however, the insulin their pancreas secretes is either insufficient (reduced insulin production) to maintain normal blood glucose levels or the body tissues is unable to recognize the insulin and utilize in cell metabolism (insulin resistance) (Kumar, et al., 2005). Symptoms may be similar to those of type 1 diabetes, but are often less marked or absent. As a result, the disease may go undiagnosed for several years, until complications have already arisen (World health Organization, 1999). Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate conditions in the transition between normal blood glucose levels and diabetes (especially type 2), though the transition is not inevitable (World Health Organization, 2014).

The term "prediabetes" indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes (Afifi, et al., 2015). The cutoff for considering prediabetes as described by the American Diabetes Association (ADA) is ≥200 mg/dl (=11.1 mmol/l) with or without symptoms of diabetes, and without regard to time of last meal (American Diabetes Association-AMA, 2003). As such, IFG is considered a pre-diabetic state. The condition is associated with insulin resistance and increased risk of cardiovascular pathology, although of lesser risk than impaired glucose tolerance (IGT). There is a 50% risk over 10 years of progressing to overt diabetes. In fact, many newly identified IFG patients progress to diabetes in less than three years (Nicolas, et al., 2007). Further, IFG is also a risk factor for mortality (Barr, et al., 2007). "Type 3

diabetes" has been suggested as a term for Alzheimer's disease as the underlying processes may involve insulin resistance by the brain (de la Monte, 2014).

2.1.3 Pathophysiology of Diabetes Mellitus

Carbohydrates are the front-line source for energy in the body. Glucose is a "monosaccharide" (the simplest carbohydrates form; also called single sugar) hexose (6-carbon atom sugar molecule), which constitutes the most important source of carbohydrate energy in human cells. (Monosaccharides are the building blocks from which all bigger carbohydrates are made). Glucose is normally freely found in a concentration of an about 100mg/dl in the blood (Tawar, et al., 2016). Due to its small size and water solubility, glucose molecules can pass through the cell membrane into the cell. Energy is released when glucose molecules are metabolized ($C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$), (and this is part of the internal cell respiration). Principally, it is insulin which is the hormone responsible for regulating the uptake of glucose from blood into the body cells. Some tissues, particularly liver, muscle, and adipose tissue have higher reliance on insulin with respect to the glucose regulatory process. Therefore, deficiency of insulin or the diminished sensitivity of cell receptors to it plays a central role in all forms of diabetes mellitus (American Diabetes Association, 2015). The body maintains a continuous supply of glucose from three main places: the intestinal absorption of food, the breakdown of glycogen (glycogenolysis), the storage form of glucose found in the liver, and the generation of glucose from non-carbohydrate substrates in the body (gluconeogenesis).

Insulin plays a key role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen. (Dolores & Gardner, 2011). Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and stimulates glycogenolysis. This process is mainly controlled by hormone glucagon, which acts in the opposite manner to insulin (Kim, et al., 2012). If the amount of insulin available is

insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistent hyperglycemia (high levels of blood glucose), poor protein synthesis, and other metabolic derangements, such as acidosis (Dolores & Gardner, 2011). When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine (glycosuria) (Murray, et al., 2012). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia). All those processes resulting from impaired insulin secretion and/or action mimic the pathologic mechanisms occurring as part of the natural history of diabetes, (i.e., pathologic sequence when the disease is not treated). The sequelae of chronic hyperglycemia in diabetes largely involves the vascular bed, both small vessels and larger vessels. Small vessel insult (microvasculopathy) affects tissues, namely eye, kidney, and nerves, ending up with blindness, renal failure, and neuropathy, respectively. Larger vessels are also affected by time and drive to a peripheral vascular disease (PVD) pathway leading to accelerated vessel injury (macrovasculopathy) (Al-Rubeaan, et al., 2015; Boulton, et al., 2008). This type of vessel injury in turn leads to an increased risk for myocardial infarction (MI), stroke, and lower limb amputation. In diabetic vasculopathiesy, some biochemical pathways are abnormally hyper-activated [e.g., polyol pathway flux, advanced glycation end-products (AGEs) formation, protein kinase C (PKC) activation, and hexosamine pathway flux]. These enhanced pathways lead to an overproduction of oxidants ("superoxide" by the mitochondrial electron transport chain). The latter partially inhibits some glucose-utilization cycles (glycolysis) enzymes (e.g., glyceraldehyde-3-phosphate dehydrogenase- G3PH); decreased G3PH) leads to its limited capacity to divert sustained substrate flux from glycolysis to pathways of glucose overutilization, and thereby blood glucose build up) (Hammes, 2003). Preliminary experimental evidence in vivo suggests that this new paradigm provides a novel basis for research and drug development.

2.1.4 Categories of Increased Risk for Diabetes (Prediabetes)

Prediabetes is a practical and convenient term referring to IFG**,** IGT or a glycated hemoglobin (A1C) of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications (Canadian Diabetes Association, 20013). In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (Expert Committee, 1997). defined IFG as FPG levels 100–125 mg/dL (5.6–6.9 mmol/L) and IGT as 2-h PG after 75-g oral glucose tolerance (OGTT) levels 140–199 mg/dL (7.8–11.0 mmol/L). It should be noted that the WHO and numerous diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L). As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from sixteen cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with an A1C between 5.5–6.0% had a substantially increased risk of diabetes (5-year incidence from 9 to 25%). An A1C range of 6.0–6.5% had a 5-year risk of developing diabetes between 25–50% and a relative risk 20 times higher compared with an A1C of 5.0% (Zhang et al., 2010). In a community-based study of African American and non-Hispanic white adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (Selvin, et al., 2010). Other analyses suggest that an A1C of 5.7% is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (Ackermann, et al., 2011). Hence, it is reasonable to consider an A1C range of 5.7–6.4% as identifying individuals with prediabetes. As with those with IFG and/or IGT, individuals with an A1C of 5.7–6.4% should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks. Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (Zhang, et al., 2010). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C .6.0%).

2.1.5 Signs and Symptoms of Diabetes Mellitus

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). Symptoms may

develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 DM. Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes (Naidu, 2006). A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes (James, et al., 2006).

2.2 Complications of Diabetes Mellitus

Uncontrolled diabetes leads to complications in many organs and tissues of human body. All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels (diabetic angiopathy) (Hammes, 2003). For instance, diabetes doubles the risk of CVD and about 75% of deaths in diabetics are due to coronary artery disease (O'Gara, et al., 2013). Other macrovascular diseases are stroke, and PVD of lower extremities, as addressed elsewhere in this report (Al-Rubeaanet al., 2015; Boulton et al., 2008;). The primary complications of diabetes due to damage in small blood vessels, include damage to the eye, kidneys, and nerves. Damage to the eyes (diabetic retinopathy) is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness (World Health Organization, 2014). Damage to the kidneys (diabetic nephropathy) can lead to renal scarring, proteinuria, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplant. Damage to the nerves of the body (diabetic neuropathy) is the most common complication of diabetes, too (World Health Organization, 2016). Symptoms include numbness, tingling, pain, and altered pain sensation, which especially leads to damage to the skin. If the foot is inflected by such progressive skin damage, a chain of events may find its way with the foot, including ulcer formation. The latter may be difficult to treat until occasionally ends up with amputation (see later). Additionally, proximal diabetic neuropathy causes painful muscle wasting and weakness.

2.3 Diabetic Foot Disorders (DFDs)

Foot complications are among the most harmful and costly disorders diabetics may be affected with (Al-Wahbi, et al., 2006; Tashkandi, et al., 2011). Estimates indicate that every 20 seconds a limb is lost to diabetes somewhere in the world. Particularly in the developing world, it is associated with high morbidity and mortality rates (International Diabetes Federation, 2014). The "term diabetic foot disorders" refers to a group of disorders which clinically present with one or more of the following clinical manifestations: foot ulceration, infection, neuropathy, deformity, gangrene and/or ischemia (Tashkandi, et al., 2011). All or some of these clinical presentations may overlap in same patients and frequently affect the feet. The annual incidence of diabetic foot ulceration varies between 2.1 to 7.4%, and the lifetime risk of developing a diabetic foot ulcer has been estimated to be as high as 25% (Alzahrani HA, et al., 2013). If not timely and properly managed, the ultimate endpoint of diabetic foot ulcer is amputation in 15% – 27%. Furthermore, when amputation happens, it is usually associated with significant morbidity and mortality in addition to immense emotional, social, psychological and financial consequences (Al-Tawfiq, et al., 2009; Alzahrani, et al., 2013; Boutoille, et al., 2008; Kalish & Hamdan, 2010;).

2.4 Pathophysiology of Diabetic Foot Disorders

Diabetic foot problems most often develop due to a combination of reasons and mechanisms, important of which are peripheral neuropathy changes of the nerve supply to the foot, augmented by ischemia (impoverished circulation) as a result of PVD due to the macroangiopathic changes of the foot vasculature. Neuropathy and resulting parasthesia (impaired sensations) is particularly dangerous as these patients are at great risk of painless injury to their feet. However, neuropathy or PVD alone does not cause spontaneous ulceration of the foot; mechanical factors coupled with these pathologies lead to ulceration. Extrinsic ulceration is a result of trauma to the soft tissues from an extrinsic source such as tight fitting footwear or a lack of cushioning. In contrast, intrinsic ulceration is a result of abnormalities in the structure of the neuropathic foot which lead to deformities such as clawing of the lesser digits that increases the pressure on the metatarsal heads and dorsal inter-phalangeal joints (Green et al., 2002). This altered mechanics of the foot results in excessive pressures on the exposed plantar aspect of the foot which when walking causes formation of callous that in

itself may cause high pressure (Young et al., 1992), and ultimately leads to tissue damage and ulceration (see Appendix E). Autonomic neuropathy can also lead to diabetic foot complications as it causes reduced sweating. This results in dry skin that is prone to cracks and fissures which then allows portal of entry for infection. The role of maintained hyperglycemia in the causation of PVD and peripheral neuropathy in diabetes and hence accelerates foot ulceration is evident. The DFDs vary in size and severity, ranging from superficial abrasions, peeled dry skin, callus formation, and infection. Tissue breakdown together with poor healing capacity of the injured tissue due to poor blood supply and diminished immune response can turn quickly into an ulcer formation. And foot ulceration is one of the most distressing complications of diabetes, the implication of which is witnessed daily within the clinical setting (Reiber et al., 1998) defined foot ulceration as *"A cutaneous erosion characterized by a loss of epithelium that extends into or through the dermis to deeper tissues."* Foot infections are the commonest cause of hospital admission in patients with diabetes and in many cases is the cause of lower limb amputation. There is no compelling evidence that ulceration is directly caused by infection. It is likely that once the skin surface has been breached the infection then establishes.

2.5 The Saudi Healthcare System

Health care services in K.S.A. have been given a high priority by the government. During the past few decades, health and health services have improved greatly in terms of quantity and quality (Almalki, et al., 2011). The Saudi society spending on health comes from four main sources: government-funded services, including ministry of health (MOH) auspices which undertakes 59.5% of the service volume, other governmental health agencies which undertakes 19.3% of the service volume, [including armed forces health services, security forces medical services, health services in the Royal Commission premises, and health services in the oil industry (run by the sole national oil industry owner in the country called Arab American Oil Company - ARAMCO)] , and the private sector, which shares up to 21.2% of the overall spending on health (Health Statistical Year Book, 2009). The health care movement in Saudi Arabia sees a fast development in all health sectors, striving to catch up with the updated international quality standards. In 2002, Gallagher stated:

"Although many nations have seen sizable growth in their health care systems, probably no other nation other than Saudi Arabia of large geographic expanse and population has, in comparable time, achieved so much on a broad national scale with a relatively high level of care made available to virtually all segments of the population)."

The Saudi health system is ranked 26th among 190 of the world's health systems, ranking before many international health systems such as Canada and other systems in the region (World Health Organization, 2013b). As a result, health of the Saudi population has markedly improved in recent decades. However, a number of issues remained challenging the health system, such as shortage of Saudi health professionals, recently shrinking financial resources, changing patterns of disease and the eruption of NCD epidemic of the time, particularly obesity and diabetes. Meanwhile, the Saudi citizens have their high expectations toward their government, demanding deployment of cutting edge technologies to cover up a full spectrum of care for health services, all subsidized and free of charge. This perspective puts clinicians, health professionals, and decision makers under pressure to live up to their expectations and meet the people's health demands, meanwhile contain cost and slow the flowing drainage of resources in an all-out fee healthcare service.

2.5.1 Health insurance system in Saudi Arabia. Funding health services is becoming a major challenge faced by the Saudi government. Since the total expenditure on public health services comes from the government and the services are free-of-charge, this led to considerable cost pressure on the government, particularly in view of the rapid growth in the population, the high price of new technology and the growing awareness about health and disease among the community. To meet the growing population demands for health care and to ensure the quality of services provided, the Council for Cooperative Health Insurance (CCHI) was established by the government in 1999. (Council of Health Services, http://shc.gov.sa/En/default.htm). The main role of this Council is to regulate a health insurance strategy for the Saudi health care market. The implementation of a cooperative health insurance scheme was planned over three stages. In the first stage, cooperative health insurance was applied for non-Saudis and Saudis in the private sector, in which their employers have to pay for health cover costs. In the second stage, the cooperative health insurance is to be applied for Saudis and non-Saudis working in the government sector. The

government pays the cooperative health insurance costs for this category of employee. In the third stage, the cooperative health insurance would be applied to employees of all companies in Saudi Arabia, domestic workers, and other groups, such as pilgrims. (The implementation of this phase is in progress). The first phase covered companies with 500 or more employees, while the second phase applied to employers with more than 100 workers. (No information is available yet regarding the cooperative health insurance scheme for the population of Saudi Arabia other than employees and expatriates). While the market for cooperative health insurance in Saudi Arabia started with only 1 company in 2004, it currently involves about 25 companies. The introduction of the scheme is intended to decrease the financial burden on Saudi Arabia due to the costs associated with providing health services free of charge. It also gives people more opportunity to choose the health services they require (Walston, et al., 2008). The real challenge for policymakers in Saudi Arabia always remains is to introduce a comprehensive, fair, and affordable service for the whole population.

2.5.2 Diabetes in Saudi Arabia. Within a changing economic environment in Saudi Arabia, diabetes is a progressive challenge all stakeholders are facing. Figures on prevalence rates and risks are alarming. Out of 35.4 million people who in 2015 had DM in the 19-country "Middle East and North Africa" (MENA) region, almost 10% (n=3.4million) of them where in Saudi Arabia. This diabetes population accounts over 17.5% of the adult (20-79 years) population in Saudi Arabia (International Diabetes Federation, 2015). The cost per person with diabetes in the country mounts up to $1,145.3. Further, the number of undiagnosed diabetics had been estimated at 1.2243 million; adding another dimension to the challenge and raises resource issues, such as the need for more preventive support, screening programs, health education, and innovative strategies to integrate these tactics into a common diabetes management plan. Part of a broad community screening program to identify risks and rates of some NCDs in Saudi, an enlisted population was interviewed and examined to determine the prevalence rates of prediabetes and diabetes among this population stratum (Afifi, et al., 2015). Afifi et al., indicated in that research that 21.4% of all screened persons had random plasma glucose (RPG) $\geq$ 200 mg%, who were either uncontrolled diabetics (56% of high RBG and 12% of the study population) or undiagnosed (prediabetic) (44% of high RBG, and 9.4% of the study population). The participants had risk of high weight problems

(mean BMI was 28.9 ± 4.1 kg/m2 = first degree obesity, 43.6% were overweight, and 41.8% were obese). The study indicates that prediabetes and diabetes are prevalent in Saudi Arabia, albeit between groups who supposedly should sustain a healthier fitness profile. A preventive approach to control the diabetes-prediabetes problem was a top priority in this population group, too.

The burden of diabetes upon the Saudi society is escalating; the more newly diagnosed diabetes the more populations at risk for developing diabetic complications, including DFDs (Al-Wakeel, et al., 2009). Knowledge and awareness about DM, its risk factors, complications and management requirements are important aspects of a better control and a better QOL. Saudi Arabia is at the heart of such region (MENA) which is already one of the highest rates of diabetes, worldwide. The MENA diabetes problem is going to increase substantially over the next few years, (e.g., from 32.8 million people in 2011 to 59.7 million people in 2030) (International Diabetes Federation, 2015). The WHO expected that diabetes in Saudi Arabia would grow 283% between 2000 and 2030, due to the changes in lifestyle and diet described earlier leading to enhanced levels of obesity. Therefore, Saudi Arabia is the highest end of the spectrum of diabetes prevalence in the MENA region with 21.8%. The diabetes problem is more prevalent in urban Saudi (25.5%) compared to the rural (19.5%), same as commonly met with other MENA populations. Despite the readily available access to healthcare facilities, a large number of Saudi diabetics (27.9%) are unaware of having diabetes (Al-Nozha, et al., 2015). Data from the Saudi National Diabetes Registry (SNDR) by Alrubean, et al. (2015) were collected and analyzed to DFDs trends and risk factors among the Saudi populations. A sample frame of anonymous 65,534 SNDR registered diabetics between 2000 till December 2012 was collected, out of which a cohort of 62,681 diabetic patients aged ≥25 years were admitted to the study. Interestingly, the prevalence of DFDs in Saudi from this database largely sets within what was reported internationally. For instance, the overall prevalence of DFDs was estimated at 3.3%; 2.05% was foot ulcer and 1.14% was gangrene. Out of the total 2,071 registered DFD cases, 1285 (62.05%) had foot ulcers divided into 505 (39.30% of ulcers and 24.4% of all DFDs) with past history of ulcer, and 780 (60.70% of ulcers and 75.6% of all DFDs) with current ulcer. Further, 119 (5.75%) and 667 (32.20%) had foot gangrene and amputation, respectively. Age, sex, and diabetes duration were consistently risk factors for worse diagnoses. Moreover, DFDs were significantly associated with other chronic

complications, especially neuropathy (61.98% of foot ulcer cases). Likewise, PVD contributed to one third of foot ulcer development in the studied cohort, a finding which was similar to what has been previously reported (Boulton, et al., 2008). More importantly, the ulcers were responsible for more than 50% of the amputation cases. Peripheral neuropathy was one of the strongest risk factors for all the foot complications amongst the studied cohort, with this association also being significant in age and gender adjusted and multivariate logistic regression models as having found in Danish and Saudi populations (Abolfotouh, et al., 2011; Bruun, et al., 2013). This strong association of the PVD and peripheral neuropathy with DFDs could reflect the high prevalence of peripheral nerve decompression to alleviate the probability of DFDs in Saudi Arabia. Perhaps in support of this connotation is what has been reported that 33% of diabetic patients are suffering from chronic nerve compression (SharHashemi, et al., 2013). In fact, this observation emphasizes the role of screening for lower extremities nerve compression in diabetics and advocating, e.g., the surgical nerve decompression at lower extremities. (This intervention has been recently proven to significantly prevent new ulcers and amputations through improving nerve function and increasing microcirculation).

2.6 Economic Burden in Diabetic Foot Disorders

Diabetic foot is one of the most costly complications of diabetes. In 2007, the treatment of diabetes and its complications in the U.S. involved at least $116 billion in direct costs; at least 33% of these costs were linked to the treatment of foot ulcers (Driver, et al., 2010). Therefore, diabetic foot complications result in large economic consequences, utilizing up to 15% of healthcare spending in industrial economies, and as much as 40% spending in developing countries. Diabetic foot individuals require more visits to healthcare facilities, and when admitted to hospital for inpatient care or surgery they tend to stay longer (Alzahrani, et al., 2013). In an Algerian study, nearly 80% of the financial expenditure on DFDs management was on patients' hospitalization (Lamri, et al., 2014). Diabetic foot complications ending with lower extremity amputation, due mostly to limb ischemia have been major drivers of diabetes-related direct health care costs. In the U.S.A. the direct costs of inpatient care and prostheses for estimated 42,424 DFDs patients undergoing amputation totaled $1.65 billion in annual total direct health care cost of DFDs (Davis et al, 2006). Ultimately, the high liability for complications renders people with diagnosed diabetes to have medical expenditures almost

2.3 times higher than those without diabetes (American Diabetes Association, 2007). Total expenditure on diabetes, as well as DFDs includes direct and indirect costs. In the U.S.A. too, indirect costs include increased absenteeism ($2.6 billion) and reduced productivity while at work ($20.0 billion) for the employed population, reduced productivity for those not in the labor force ($0.8 billion), unemployment from disease-related disability ($7.9 billion), and lost productive capacity due to early mortality ($26.9 billion) (American Diabetes Association, 2007).

2.6.1 Cost of illness in DFDs. Cost of illness is a measurement tool used for economic evaluation of a disease burden upon the patient, health system, and the society. So doing, economists and researchers want to consider and prioritize financial, economic and social inputs of interest to help develop healthcare policies aiming to minimize cost and disease burden, and maximize saving and favorable social outcomes. Within the resourcing stream, Jefferson et al. (2000) describes the economic nature of COI studies as that *"they aim to itemize, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden."* A basic assumption here is that COI represents the potential benefits of a health care intervention if it had eradicated the illness. Thereby, COI analysis includes some metric of "health loss" and it also attempts to measure the costs incurred, e.g., in treating DFDs. The issue is that in economic decision making, "cost" should be considered, e.g., in contrast with benefit [as in cost-benefit analysis (CBA)], with effectiveness [as cost-effectiveness analysis (CEA)], with QALYs or latent utility assessment [as in cost-utility analysis (CUA)]. Determining COI is eventually essential for selecting the most appropriate intervention option, and then we become able to economically furnish appropriate required resources, especially in the presence of budgetary constraints or shrinking resources many healthcare environments are encountering (Jo, 2014).

Technically, several COI analysis methods are known; each can serve several certain purposes. For instance, "cost estimates" may be used to argue if a disease should be given a priority in the healthcare policy agenda; how much the society is "willing to pay" in medical spending to obtain certain amount of social and economic savings. In comparison, disease burden analysis counts on squeezing the postulated burden items into only the "number of years of life lost" (YLL) due to premature death or the number of years lost due to disability

(YLD). From the previous two health outcome measures, the concept of "disability-adjusted life years" (DALYs) emerges, which involves costing of the disease management process, e.g., in terms of lost economic or societal contribution as a result of disability. With the same token, QALYs assesses the quantity of lost economic and societal contribution but due to premature death from the disease under investigation.

2.6.1.1 Types of costs in DM and DFDs economic evaluation. In COI analysis, cost is split into the traditional cost categories, direct – and – indirect costs. (The intangible costs category is seldom applicable to COI due to controversies and difficulties in its quantification and the weight they account).

2.6.1.1.1 Direct costs. All stakeholders of the healthcare process, including the individual patient, family, society and the health system can be affected by direct cost accounting. Direct costs also come from healthcare-related sources and non-healthcare related sources. As with diabetic DFDs, direct costs include medical expenditures, (importantly, hospitalization, physician office visits, prescription medications, laboratory works, surgeries, hypoglycemic agents, insulins, disposables, devices, supplies, prosthetics, rehabilitation), and any other expenditures going directly toward caring for the condition.

2.6.1.1.2 Indirect cost. Indirect costs in COI of DFDs mostly refer to productivity losses due to morbidity and mortality, borne by the individual, family, society, or the employer, (compared to supporting and overhead activities shared among the users in non-healthcare businesses). Other indirect costs include cost of ambulatory or home care and rehabilitation. Traditionally, there is little literature on the non-health related costs of DM or its complications, but targeted literature searches could identify some data that had been used to provide some estimates (Hex, et al., 2012). A number of methods for calculating indirect costs in healthcare economics are known. These include: a) human capital method (HCM), b) friction cost method (FCM), and c) willingness to pay method (WTP). The HCM is based on recognizing human as one of the production inputs that can generate additional values by employing it into a production process (van den Hout, 2010), whereas FCM estimates the value of human productivity when another person (from the unemployment pool) replaces the present value of a worker's future earnings until the incapacitated worker returns or is eventually replaced. In other words, HCM takes the patient's perspective and counts any hour

not worked as an hour lost, and FCM takes the employer's perspective, and only counts as lost those hours not worked until another employee takes over the patient's work. The WTP method measures the amount that an individual is eager to pay in order to reduce the probability of illness or mortality (Hodgson & Meiner, 1982). Each one of these method has its own advantages and disadvantages; usages and eventual criticism. Detailed information about how these methods work, how to calculate, and technical differences between them are beyond the scope of this work. However, generally, HCM is criticized that because it depends on current socioeconomic status, certain groups are assigned a higher value than others, which may cause a statistical bias that leads to spurious estimation results (Hodgson & Meiner, 1982). The WTP approach is thought to be giving higher estimates of the value of life than the HCM attempts to ameliorate these problems. The FCM approach is favored over HCM by some for overvaluing the indirect costs, claiming that the productivity losses are often eliminated after a new employee is well-trained enough to replace the former sick one. However many claim that the FCM itself is rarely used because it requires extensive data to estimate only the losses during the friction period (Rothermich & Pathak, 1999).

2.6.1.2 Calculating COI. Computing for COI to describe and analyze the desired economic consequence of DFDs, a clear discrimination between costs associated with DM itself and costs related to the studied foot complication should be established. Naturally, no such distinction can always be made because often the same medication, laboratory test or procedure used in routine follow up of DM might have to be utilized to evaluate the degree and severity of the diabetic foot problem studied (Tennvall & Apelqvist, 2004). The same discrimination must be done to verify costs referable to the studied foot complication and other types of DM complications. This differentiation is especially important in the use of secondary data sources. For instance, one recent Swedish study showed that other conditions were reported as the primary diagnosis in >80% of the discharges, when DFDs were actually the main reason for inpatient treatment (Tennvall & Apelqvist, 2004). This demonstrates the risk of underestimation of the costs of DFDs when analyses are based on primary diagnosis from secondary data sources. Underestimation of costs for diabetes based on inpatient statistics or secondary databases has been observed in the U.K., as well (Masson, et al., 2009). This malpractice probably occurs in health care systems without a direct connection between

the diagnosis and economic compensation and may be less likely to occur in such countries as the U.S., where the reimbursement system provides incentives for more accurately coded diagnoses.

In a retrospective study in Belarus (Kozhanova, et al., 2015), to describe costs and outcomes pursuant to innovative techniques experimented to improve the health and economic outcomes among DFD patients, the COI of diabetic foot ulcers and that of amputations were compared. Both direct and indirect costs and also inpatient - and outpatient care financial data were admitted. It was found that direct outpatient medical cost averaged $572 (78 - 636), and indirect cost averaged $2604 (1042 – 4357), all per patient per year. Also, the cost of a major amputation on average was $10976 (643 – 13,556) per hospitalization and $2404 (282 – 3702) for a small amputation. Indirect cost averaged $368 (352 – 978) through the treatment duration (Kozhanova, et al., 2015). These figures constitute a huge proportion of health spending; probably why investing in exploring opportunities of expansive outpatient medical technology use should be prioritized in enthusiastic DFDs care policies. Without careful COI assessment, no valid conclusions about the value of adopting promising techniques for effective and economic management of DM and its foot complications could have been made. Likewise, high risk diabetics were studied in Peru (Cardenas, et al., 2015). to estimate the economic costs of diabetic foot ulcers, and how they may be influenced by adopting secondary prevention techniques (baseline care, standard care as per IDF recommendations, standard care plus daily self-monitoring of foot temperature). The average direct cost per patient was $5,153 for healing with a minor amputation and $7,360 for healing with a major amputation. Healing with only debridement cost $1,022, and healing with outpatient visit was $79. Ultimately, the implementation of a standard care strategy would avert 791 deaths and is cost-saving in comparison to baseline care (Cardenas, et al., 2015). Regarding the total outcomes averted and cost-effectiveness estimates modeled, the study it was concluded that the more comprehensive the preventive strategy was the greater the number of deaths that were averted. (Out of 1,757 predicted deaths from foot ulceration while on basic care, 791 would be averted by standard care and 1,385 by standard care plus temperature monitoring strategy).

2.7 Diagnosis of Diabetes Mellitus

The diagnosis of DM is readily entertained when a patient presents with classic symptoms, i.e., polyuria, polydipsia, polyphagia, weight loss. Other symptoms that may suggest hyperglycemia include blurred vision, lower extremity paresthesias, or yeast infections, particularly balanitis in men (Khardori, 2016). However, many patients with type 2 diabetes are asymptomatic, and their disease remains undiagnosed for many years. In older studies, the typical patient with type 2 diabetes had diabetes for at least 4-7 years at the time of diagnosis. Among patients with type 2 diabetes, 25% had retinopathy; 9%, neuropathy; and 8%, nephropathy at the time of diagnosis (King, et al., 1999).

2.7.1 Basis for testing for diabetes in asymptomatic adults. According to the American Diabetes Association (2015), testing to detect type 2 diabetes in asymptomatic people and prediabetics should be considered in adults of any age who are overweight or obese [body mass index (BMI) $\geq$25 kg/m^2] and who have one or more additional risk factors for diabetes. For all patients, particularly those who are overweight or obese, testing should begin at age 45 years. If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. To test for diabetes, hemoglobin A1C (simply called A1C), FPG, and 2-h PG after 75-g OGTT are appropriate.

2.7.2 What are additional risk factors for testing asymptomatic adults for DM? As above, overweight people should be tested for DM if they have additional risk factors including: a) physical inactivity, b) first-degree relative with diabetes, c) high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American), d) women who delivered a baby weighing 0.9 lb or were diagnosed with GDM, e) hypertension (140/90 mmHg or on therapy for hypertension), f) HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level 0.250 mg/dL (2.82 mmol/L), g) women with polycystic ovary syndrome, h) A1C 5.7%, IGT, or IFG on previous testing, i) other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans), j) history of CVD (American Diabetes Association, 2015). Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic patients include age which is a major risk factor for diabetes. Testing should begin at age 45 years for all patients, particularly those who

are overweight or obese. BMI and ethnicity testing should be considered in adults of any age with BMI 25 kg/m^2 and one or more additional risk factors for diabetes (Afifi, et al., 2015). (However, recent data suggest that the BMI cut point should be lower, i.e., 23 kg/m^2 for some ethnic groups, e.g., Asian American population). Also some medications, such as glucocorticoids, thiazide diuretics, and atypical antipsychotics (Erickson, et al., 2012) are risk factors for diabetes and should be considered when ascertaining a diagnosis.

2.7.3 Diagnostic tests for DM. The A1C, FPG, and 2-h PG after 75-g OGTT are appropriate for testing. It should be noted that the tests do not necessarily detect diabetes in the same individuals. The efficacy of interventions for primary prevention of type 2 diabetes has primarily been demonstrated among individuals with IGT, not for individuals with isolated IFG or for those with prediabetes defined by A1C criteria. The appropriate interval between tests is not known. The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced and individuals with false-negative tests will be retested before substantial time elapses and complications develop (Johnson & Tabaei, 2005). (That is why in determining risk measurement such as BMI cut point in screening for diabetes, it is important to balance sensitivity and specificity so as to provide a valuable screening tool without numerous false positives).

2.7.4 Community screening for detecting prediabetes and undiagnosed diabetes. Diabetes and prediabetes meet criteria for conditions in which early detection is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical diabetes are readily available. The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes and reduce the risk of diabetes complications. Approximately one-quarter of people with diabetes in the U.S. are undiagnosed. Although screening of asymptomatic individuals to identify those with prediabetes or diabetes might seem reasonable, rigorous clinical trials to prove the effectiveness of such screening have not been conducted and are unlikely to occur. A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of

screening and routine care (Griffin, et al., 2011). General practice patients between the ages of 40–69 years were screened for diabetes and randomized by practice to intensive treatment of multiple risk factors or routine diabetes care. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment compared with routine care, but the incidence of first CVD events or mortality was not significantly different between the groups (Griffin, et al., 2011). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limit our ability to prove that screening and early intensive treatment impact outcomes. Mathematical modeling studies suggest that screening, beginning at age 30 or 45 years and independent of risk factors, may be cost-effective [<$11,000 per quality-adjusted life-year (QALY) gained] (Kahn, et al., 2010). Ideally, testing should be carried out within a health care setting because of the need for follow-up and treatment. Community testing outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. Community testing may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed.

2.7.5 Criteria for diagnostic tests of hyperglycemic states. Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following: a) FPG level $\geq$ 7.0 mmol/l (126 mg/dl), b) PG $\geq$ 11.1 mmol/l (200 mg/dl) two hours after a 75-g oral glucose load as in GTT, c) symptoms of high blood sugar and casual plasma glucose $\geq$ 11.1 mmol/l (200 mg/dl), d) A1C $\geq$ 48 mmol/mol (American Diabetes Association, 2010; World health organization, 1999). A positive result, in the absence of unequivocal high blood sugar, should be confirmed by a repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test.

According to the current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) is considered diagnostic for diabetes mellitus; and people with FPG

levels from 6.1 to 6.9 mmol/l (110 to 125 mg/dl) are considered to have IFG, people with PG at or above 7.8 mmol/l (140 mg/dl) but not over 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load are considered to have IGT (World health organization, 2006). Of the two prediabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus, as well as CVD. Glycated hemoglobin is better than FPG for determining risks of CVD and death from any cause (Selven, et al., 2010).

2.8 Risk Factors for Type 2 Diabetes

The risk of type 2 diabetes is determined by interplay of genetic and metabolic factors. Ethnicity, family history of diabetes and previous gestational combine with older age, obesity, unhealthy diet, physical inactivity, and smoking increase the disease risk (Global Burden Disease Risk Factor Collaborators, 2015). Excess body fat, a summary measure of several aspects of diet and physical activity, is the strongest risk factor for type 2 diabetes both in terms of clearest evidence base and largest relative risk. Overweight and obesity, together with physical inactivity, are estimated to cause a large proportion of the global diabetes burden. Especially higher waist circumference and higher BMI are associated with increased risk of type 2 diabetes (Afifi, et al., 2015; Hu, et al., 2001), though the relationship may vary in different populations. Populations in South-East Asia, for example, develop diabetes at a lower level of BMI than populations of European origin. Several dietary practices are linked to unhealthy body weight and/or type 2 diabetes risk, including high intake of saturated fatty acids, high total fat intake and inadequate consumption of dietary fiber.

2.9 Prevention of DM

Even in presence of a genetic background for DM, the development to an overt disease can largely be prevented, (however, there is no known preventive measure for type 1 diabetes). Type 2 diabetes can be prevented by maintaining a normal body weight, engaging in physical exercise, and consuming a healthful diet. Evidently, a well-managed and complied with prevention plan adjusted to identify and abolish such risk factors in susceptible candidates can postpone diabetes mellitus (Afifi, et al., 2015, Alrubean, e al., 2015). Data from the Nurses' health study suggest that 90% of type 2 diabetes in women can be attributed to five such factors: excess weight, lack of exercise, a less-than-healthy diet, smoking, and

abstaining from alcohol (Hu, et al., 2001). Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as the polyunsaturated fats found in nuts, vegetable oils, and fish. The "Diabetes Prevention Program" examined the effect of weight loss and increased exercise on the development of type 2 diabetes among men and women with high blood sugar readings that had not yet crossed the line to diabetes. In the group assigned to weight loss and exercise, there were 58% fewer cases of diabetes after almost three years than in the group assigned to usual care. Even after the program to promote lifestyle changes ended, the benefits persisted. Active smoking is also associated with an increased risk of diabetes, so smoking cessation can be an important preventive measure as well (Hu, et al., 2001).

2.10 Management of DM

Diabetes mellitus is a chronic disease, for which there is no known cure except in very specific situations. Management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually be accomplished with a healthy diet, exercise, weight loss, and use of appropriate medications (insulin in the case of type 1 diabetes; oral medications, as well as possibly insulin, in type 2 diabetes). Learning about the disease and actively participating in the treatment is important, since complications are far less common and less severe in people who have well-managed blood sugar levels. The goal of treatment is an HbA1C level of 6.5%, but should not be lower than that, and may be set higher. Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise. Specialized footwear is widely used to reduce the risk of ulceration, or re-ulceration, in at-risk diabetic feet. Evidence for the efficacy of this remains equivocal, however (Cavanagh, 2004).

2.10.1 Lifestyle. People with diabetes can benefit from education about the disease and treatment, good nutrition to achieve a normal body weight, and exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds (Adler, et al., 2000). In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.

2.10.2 Medications. There is a number of medications used to lower blood sugar levels; some are available by mouth, such as metformin, and others are only via parenteral route, such as glucagon-like peptides 1 receptor (GLP-1) agonists. Type 1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin, or synthetic insulin analogs. Metformin is generally recommended as a first line treatment for type 2 diabetes, as there is good evidence that it decreases mortality (Ripsin, et al., 2009). It works by decreasing the liver's production of glucose. Several other oral hypoglycemic medications include agents that increase insulin release, agents that decrease absorption of sugar from the intestines, and agents that make the body more sensitive to insulin. If insulin would be needed in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications. Doses of insulin are then increased to yield the desired effect (Ripsin, et al., 2009). Since CVD is a serious complication associated with diabetes, blood pressure levels below 130/80 mmHg may be advisable (Kumar, et al., 2005). Also, among medications that lower blood pressure, angiotensin converting enzyme inhibitors (ACEIs) improve outcomes in those with DM while the similar medications angiotensin receptor blockers (ARBs) do not (Cheng, et al., 2014).

2.10.3 Surgery. A pancreas transplant is occasionally considered for people with type 1 diabetes who have severe complications of their disease, including renal failure requiring kidney transplantation. Weight loss surgery in those with obesity and type 2 diabetes is often an effective measure. Many are able to maintain normal blood sugar levels with little or no medications following surgery and long-term mortality is decreased (Schulman, et al., 2009).

2.10.4 Support. In countries using a general practitioner (GP) system, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications or difficult blood sugar control (Polisena, et al., 2009). In other circumstances, GP and specialists share care in a team approach. Home "telehealth" support can be an effective management technique.

3. Methods

3.1 Study Setting

This study was conducted in Jeddah; K.S.A. Jeddah is a coastal city on the western bank of the Red sea in the western region of the KSA. The city has around 3.4 million populations, representing almost 13% of the total population of the kingdom (which is estimated at 27,136,977: 18,707,576 Saudi nationals and 8,429,401 non-nationals, as in 2010 census, with a national growth rate around 1.49%), (Saudi Arabia Population Clock). Over the last few decades, Jeddah has grown progressively until it became second largest city in the country and center for money and business, and a major port for exporting non-oil related goods, as well as importing domestic needs in the country. Jeddah is also considered the touristic capital of Saudi Arabia especially that it is the main gateway for millions of pilgrimages and visitors from all over the world to the Islamic holy cities Mecca and Medina. The commercial and diversified nature of Jeddah gives room for private health care business for a shared responsibility of community health in a rivalry-motivated environment, which can be positively reflected upon the clienteles and the providers. Further, business organizations in Jeddah compete in retaining good human resources base through securing health insurance for staff and their families [Council of Cooperative health Insurance (CCHI), 2016]. The critical nature of the disease under study, DM, necessitated resorting to a reliable source of health and economic information in order to assure highest degree of validity and representativeness of the study results to the general population. Our systematic search in the health insurance marketplace in Jeddah led to a short list of reputed health insurance rivals. Bupa Arabia (BA) (http://www.bupa.com.sa), a division of the international Bupa group, is one of the largest health insurance corporations working in Saudi Arabia, since 1997. Official information shows that over 3 million members are enrolled with this company up to date.

3.2 Study Design

As per the study plan, diabetic patients' information congruent with the study objectives would be outreached. Accordingly, BA had been selected and to whom the research idea was conveyed, aiming to gain access to patient information which would serve the study goal. A medical liaison from BA was assigned to cooperate in providing the dataset permitted to us by the company's authority. Patient records with type 2 diabetes mellitus since 2007 or

earlier have been identified. Out of these records, patients who show history of DFDs and were reimbursed for any DFDs care during 2015 were reviewed. Authorization to access patient data with specific restrictions and fulfilling a series of confidentiality requirements on the part of patients and BA had to be acknowledged and applied.

3.2.1 The study participants. According to the study design, a subject is labeled as "type 2 diabetes mellitus" if she or he met the International Classification-9- Coding Manual (ICD-9-CM) criteria for type 2 DM diagnosis (ICD-9-CM, 2011), ICD-9: 250.00 refers to diabetes mellitus without mention of complication. As per ICD-9, any disease is given a 5-digit number, the last pair of digits of which is left for complication coding. For instance, 250.70 is the code given to type 2 DM with peripheral circulatory disorders not stated as uncontrolled and 250.72 is the code given to type 2 DM with peripheral circulatory disorders stated uncontrolled, and so forth. (ICD-9-CM 250.80 is a billable medical code that can be used to indicate a diagnosis on a reimbursement claim. (However, 250.80 should only be used for claims with a date of service on or before September 30, 2015; and for claims with a date of service on or after October 1, 2015, ICD-10-CM code equivalent can be used). (See Appendix-B for DM ICD-9 coding).

According to ICD-9-CM, DFDs are coded as 250.00 which implies either diabetes with other specified manifestations, type II or unspecified type, diabetes not stated as uncontrolled plus codes for systemic diseases compatible with the DFDs. [Diabetic foot disorder include, ulcer of heel and mid foot include carbuncle and furuncle of foot, heel, toe (680.7), cellulitis and abscess of toe (681.1), cellulitis or abscess of foot(707.14), chronic osteomyelitis of ankle and foot (730.17), unspecified infection of bone of ankle and foot (730.97), atherosclerosis of the extremities with ulceration (440.23)]. (See Appendix B). The insurer uses industry standard codes developed by "Clinical Coding & Schedule Development Group" (CCSD) (CCSD, http://www.ccsd.org.uk/), which contain codes for produces guidance to enable accurate coding of clinical activity in independent healthcare. Each ICD-9 diagnosis code of participants and its CCSD equivalent used by BA were matched for accurate admission to the study. (See Appendix C).

Cost information was based on the reimbursement schedules provided by BA and according to the billing and reimbursement system in action the time of the study. The insurer

uses a billing system which utilizes electronic submission of invoices for accurate reimbursement. [The system is derived from the original International Classification of health Interventions-ICHI- coding system (ICD-9-CM, 2011)], (Reimbursement policy information is displayed in Appendix C).

3.2.2 Inclusion criteria. Patients included in the study if they fulfilled ICD-9-CM diagnosis of type 2 DM, has been enrolled with BA and developed and received medical and / or surgical care for any DFDs which have been reimbursed for during 2015. As such, only direct costs for the DFD incidents covered from 2015 budget was analyzed. Patients should also be adults who stay in Jeddah, as the place of permanent residence the time of the study. Otherwise, no patient would be excluded from the study because of sex, marital status, socioeconomic status or underlying health condition. Also all types of insurance policies were allowed, whether part of a group insurance policy by the employer or individual and private insurance policies.

3.3 Sampling Technique and Sample Size

A sample frame containing enrollees diagnosed with diabetes and who had developed any DFD episode which was reimbursed in 2015 were identified. A quota sample of 60 patients had been permitted by BA to be included in the study.

3.4 Data Collection

A data collection form was predesigned by this researcher in order to administer the required patient information. (See in Appendix A; spreadsheet). The form includes five major fields, case and disease coding, demographic, clinical and procedural, as well as direct cost data fields. At the beginning of this project, there was a sincere desire to gather a full scope of demographic and clinical information to be used as potential risks of a hypothesized influence on the development of DFDs in the study participants. However, restrictions imposed on information pertinent with the patients' socioeconomic status, education, underlying health status and comorbidities, and also health care costs during enrollment other than those for DFDs reimbursed in 2015 were not given. The rationale by BA was not to jeopardize patients' confidentiality and not to breach the company's billing and financial secrecy policy.

3.5 The Study Variables

Demographic variables include age in years [an interval ratio scale (IRS) variable], sex (male or female), and nationality (Saudi or non-Saudi), both of which are dichotomous. Clinical variables include types of diabetic foot complication, as well as the specific medical and/or surgical intervention applied to each condition. Intervention data consist of five categories: a) conservative only, b) debridement, c) minor amputation, and d) major amputation. (Appendix A). Eventually, two sets of risk variables are studied, demographic criteria and intervention type. The terms "risk factor", "risk", "input", "correlate" "dependent variable", all can be used exchangeable for these risk variables above. Cost data (expressed here as an IRS variable) indicate cost of DFDs illness per diabetic foot disorder incident each participant had encountered and led to one of the treatment procedures described above. The COI accounting was based on the following financial information:

a) Subtotal direct medical costs, such as doctor's fee, outpatient visits, medicines, devices, hospital stay, and surgery.

b) Subtotal non-medical costs, such as transportation, communications, extra accommodation or room accommodation and the likes.

c) COI = subtotal direct medical/surgical costs + subtotal direct medical/surgical costs, less deducible and copayment, (i.e., deductibles and copayment are not included in COI); all in Saudi Riyal (approximate transfer rate: $0.267).

NB. Indirect costs, such as employee time, rehabilitation or home care costs all were not included in the study, since they are not covered by the insurance plan. Also, extra medical charges paid at the patient's expense or outside the insurance plan were not be included.

Eventually, two outcome (dependent) variables would be deployed for this study, type of intervention (an intermediary outcome), and COI as the final outcome of interest.

3.6 Statistical Analysis

First, obtained data were entered into a Microsoft system with adequate back up. Statistical analysis included both descriptive statics and analytical statistics. For instance, IRS variables, such as COI and age would be described in terms of the mean ± standard deviation (SD) or the median ± interquartile range (IQR), where appropriate. [Selecting either the mean or the median as a most appropriate measure of central tendency depends on assumptions

relevant to parametric techniques (PMTs), important of which are normality and sample size]. Categorical variables, such as sex and nationality would be described in count and percentage. As far as inferential statistics, the influence of the study correlates, e.g., the difference in the level of COI among the study's gender groups could be measured using student t- test, or Mann Whitney-*U* test, where appropriate (i.e., based on normality distribution of COI variable, as well as other PMT assumptions, as applicable). Likewise, the influence of the type of intervention upon COI may be measured using one-way analysis of variance (ANOVA) test or its nonparametric alternative Kruskal Wallis test, where appropriate (based on PMT assumptions fulfillment). Importantly, normality of the study's interval scale data could be assessed using one of the normality measuring techniques, such as the one-ample Kolmogorov Smirnov (K-S) test. In this research we tended as a rule in analyzing the impact of the study correlates on the study outcomes to run both PMT and non-PMTs for the same relationship. Should there was a difference in the significance result between the two approaches the non-PMT would be prioritized (not to violate the normality assumption for PMT calculation). If the two approaches yielded significant results, PMT could be adopted and safely discussed. [This strategy, for instance applies to t-test vs. Mann-Whitney-*U* test, ANOVA vs. Kruskal Wallis test, linear regression vs. logistic regression analyses, and Pearson correlation vs. Spearman rho techniques (see later)]. Also, the association between any of the demographic categorical variables such as nationality and the type of DFD intervention could be assessed using chi square test of independence, and either Pearson chi-square or Fisher's exact test for significance, where appropriate. (The latter is used if ≥25% of cells in cross-tabulation contains less than 5 expected count). In case we wished to measure the relationship between age and COI (both are IRS continuous variables), correlation analysis could be calculated. (Both Pearson's correlation and Spearman rho would be calculated, according to the PMT/non-PMT testing policy above, and either of them is selected for display, where appropriate). Finally, a model to predict the probability of the change in the dependent variable "COI" as a result of a unit change in each predictor would be constructed. (Both multivariate linear regression and logistic regression analysis would be tried, as per the PMT/non-PMT policy). In case COI was skewed, the differences in the levels of COI among sex, nationality, and intervention groups would be attempted both utilizing PMT and non-PMTs alternatives, as above. Also COI may be transformed into a binary variable, namely

SR<35,000 and ≥SR35,000 to calculate the logistic regression test of interest. The statistical analysis plan would be set forth so that the influence of the independent variables may be tested both upon the type of intervention and COI. Intervention, as an intermediary variable may be tested against COI as the final outcome variable. Eventually, two phases of statistical analyses would be conducted; each encompasses a set of tests. In the first phase, we will measure the effect of selected study determinants upon the type of intervention. In the second phase, the effect of selected determinants as well as the type of intervention upon COI will be measured. The study findings would be displayed summarized as tables and graph charts, such as histograms, bar graphs or pie charts, as appropriate. Besides, a brief narrative comment opposite each finding would be added. The Statistical package for social sciences version 18 (SPSS Inc., Chicago, IL, USA) was used in the analysis. Our tolerable alpha error is 0.05 and results with p-value <0.05 would be considered significant. Also the 95% confidence interval (CI) of the odds ratio (OR) may be used to assess the significance of the strength of association between risks and dependent variables measured by OR as in chi square or regression analysis tests.

3.7 Ethical Considerations

Early in this work, it was quite expected to face difficulty in gaining access to patient records, especially in a disease such as DM. This disease condition implies many personal and moral concerns to individual patients, and thereby it was well-understood to abide by confidentiality standards applicable to the selected data source, such as the selected insurance agency. Especially the latter holds high accountability and liability for personal information confidentiality. It was also understood that only anonymous patient data may be accessed and utmost insured information confidentiality ascertained. On our part, we declared and acknowledged before the insurer that the obtained information would remain anonymous by de-personalizing names and places in the transcriptions and ascertained that only grouped information would be disclosed to the public at scientific and research settings.

3.8 The Role of the Researcher

The idea of this research arose from the desire of this researcher to apply some valuable public health and health economics expertise acquired while in direct contact with renowned public health sources in Germany and Europe to the quest of healthcare of Saudi Arabia. Diabetes in particular was selected to study because of the tremendous impact upon the Saudi Arabia, homeland for this investigator. During medical training in Saudi Arabia before joining the master program of public health in Hamburg University, this researcher realized the enormous burden of diabetes, especially associated with underlying comorbidities, such as obesity and unhealthy nutritional habits widespread in today's Saudi community. Thereby, there was a wish to address diabetes from the angle of one of its severest complications, which is DFDs. Thereby, this researcher was adamant to tackle all possible sources of DM and DFDs data and could conclude this research plan with one of the largest and most reputed insurance agencies in the country.

This researcher has developed the study's goal and objectives plan, bearing in mind highlighting objectives that are reproducible and measurable, using the available set of data. Handled by this researcher, too, but not limited to, were data entry, coding, preliminary handling, and conducting thorough literature review from best evidence resources relevant to the topic, interpretation and discussion of the research findings, timeline setting (see appendix F), write-up formatting, referencing, appendix arrangement, and abstract transcription. Help was sought with respect to the statistical analysis which needed more specialized experience, particularly deciding about most appropriate statistical techniques.

4. Results

4.1 Descriptive Statistics Results

(Table 1, Table 2, Figure 1a, Figure 1b, Figure 2, Figure 3)

Variable			
Age (year)			
Mean	57.28±2.65		
Median	58.00		
Mode	60.00		
Range	13 (Min 47; Max 60)		
25th percentile	56.00		
75th Percentile	59.00		
Interquartile Range (IQR)	3.00		
COI (SR)			
Mean	33622.08±26067.073		
Median	27817.50		
Mode	9859		
Range	131527 (Min 9859; Max 141386)		
25th percentile	14582.75		
75th Percentile	38916.00		
Interquartile Range (IQR)	24333.25		
		n	%
Sex			
Male		43	71.7
Female		17	28.3
Nationality			
Saudi		48	80.00
Non-Saudi		12	20.00

Table 1 Descriptive Criteria of Study Group: Age, Sex, Nationality, COI (n = 60)

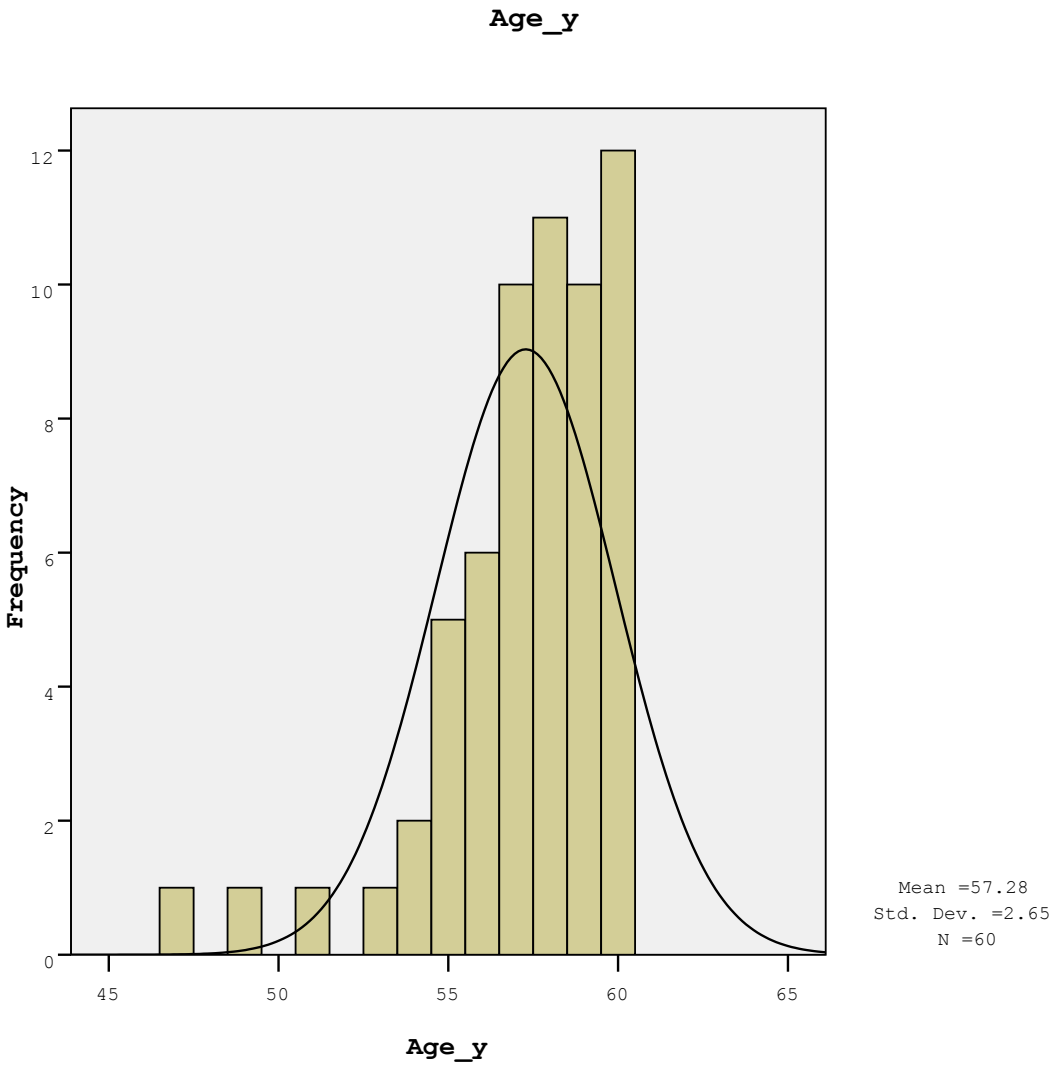


Figure 1a Histogram: Age Distribution Pattern of the Study Group

Figure 1a shows that age apparently looks rather left-sided skewed; however, K-S test suggested a normal distribution (Z=1.384, p=0.053). In contrast, COI was not normally distributed (Z=1.47, p=0.027), (Figure 1b). (See Appendix D for K-S output).

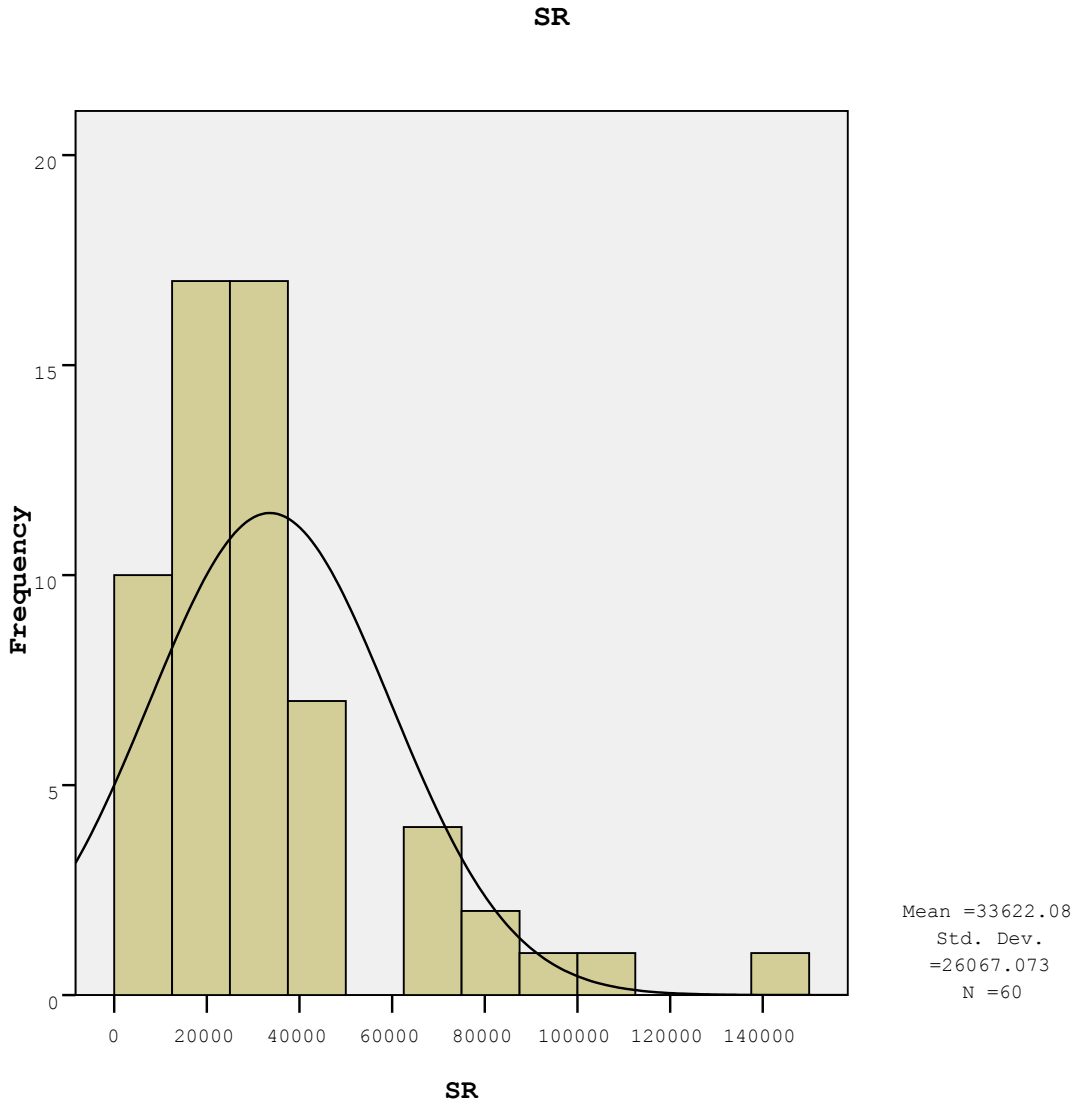


Figure 1b Histogram: Cost of Illness (COI) Distribution Pattern of the Study Group

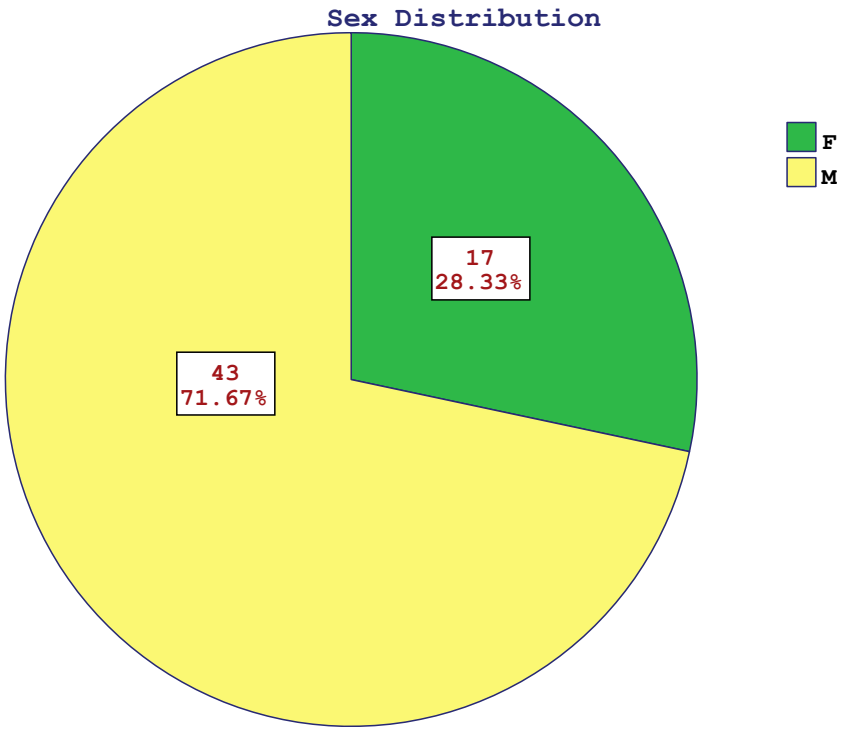


Figure 2 Sex Distribution Pattern of the Study Group

Intervention	N	%
Conservative treatment only	4	6.70
Debridement	26	43.3
Minor amputation	21	35.00
Major amputation	9	15.00
Total	60	100.00

Table 2 Distribution of the Study Group by Type of DFD Intervention (n = 60)

As in Table 2, the majority (43.3%, n=26) of the study group had debridement as the first line of treatment for their DFD episode. Second to debridement was minor amputation in the frequency of 21 (35%) incidents. Major amputations affected 15.0% (n=9) of the study population. Least occurring was conservative treatment alone (6.7%, n=4 cases). (See also Figure 3).

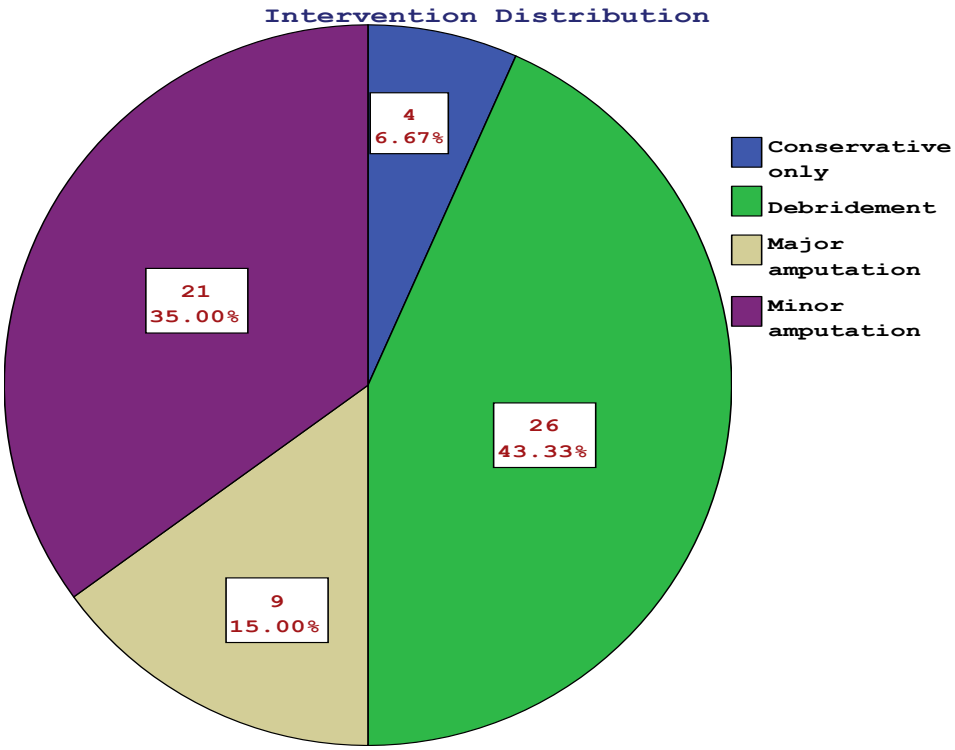


Figure 3 Intervention Options Distribution Pattern of the Study Group

---

4.2 Analytical Statistics Results

4.2.1 Phase 1: Influence of the Study Determinants upon Type of Intervention

Age category		Intervention				Total	Test statistic (p-value) (2-tailed)
	n	Conservative only	Debridement	Minor amputation	Major amputation		
<55y	Count	2 (3.3%)	4 (6.7%)	0 (0.0%)	0 (0.0%)	6 (10.0%)	Fisher's exact =8.567 (p=0.011)
	Expected	0.4	2.6	2.1	0.9	6.0	
≥55y	Count	2 (3.3%)	22 (36.7%)	21 (35.0%)	9 (15.0%)	54 (90.0%)	
	Expected	3.6	23.4	18.9	8.1	54.0	
Total		4 (6.7%)	26 (43.3%)	21 (35.0%)	9 (15.0%)	9 (15.0%)	

Table 3 Influence of Age upon the Prevalence of Specific DFDs Interventions: Cross tabulation

4.2.1.1 The relationship between age and type of intervention (Table 3, Figure 4). As in Table 3, the effect of age (binary: <55y and ≥55y) was examined as a risk factor for the type of intervention. a chi-square technique calculation shows that patients with DFDs who were 55-years old or higher are significantly at greater risk of requiring lower extremity amputation whether minor (35.0%) or major (15%) ones (Table 3). (See also Figure 4 for comparative distribution). Among the non-amputation categories, diabetics ≥55 were also more likely to need debridement (36.7%) compared to the <55y counterparts (6.7%); however both age group did not differ in the need for frequency of conservative treatment alone (Fisher's exact 8.567, p=0.011).

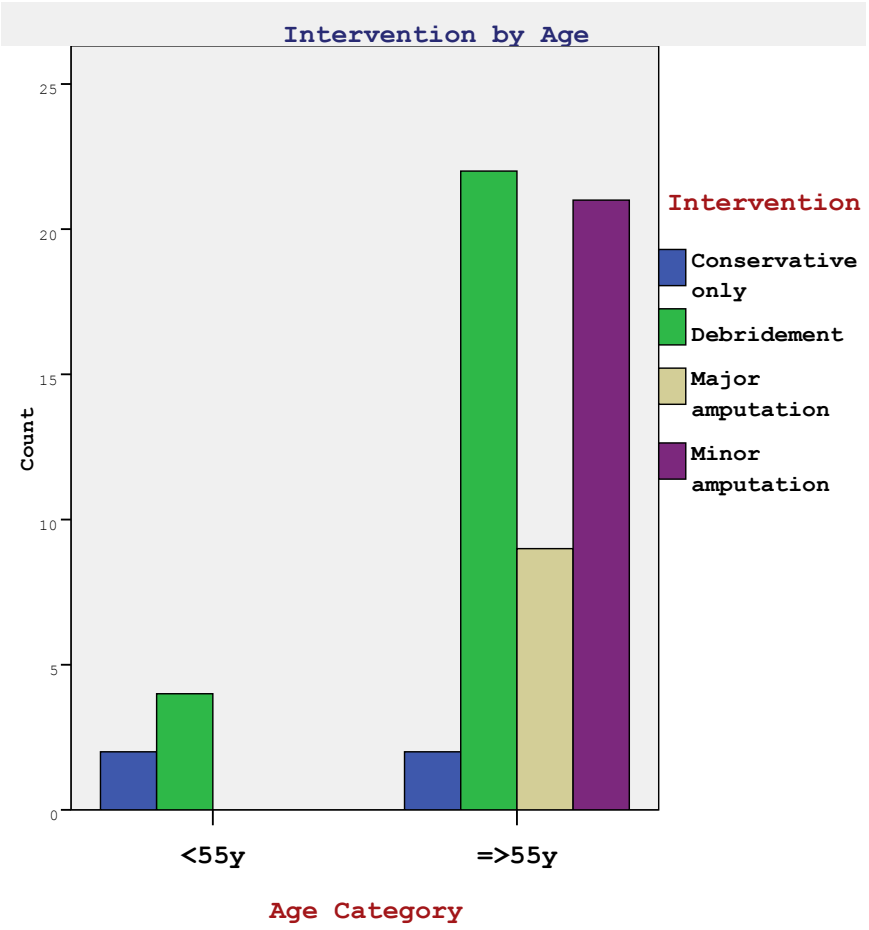


Figure 4 Distribution of the study DFDs Intervention Groups by Age Category

4.2.1.2 The relationship between sex and type of intervention (Table 4). In another cross tabulation to evaluate the influence of sex upon the type of intervention, no significant effect has been found (Fisher's exact 0.427, p=0.968)), (Table 4).

Sex category		Intervention				Total	Test statistic (p-value) (2-tailed)
	n	Conservative only	Debridement	Minor amputation	Major amputation		
Male	Count	3 (5.0%)	19 (31.7%)	15 (25.0%)	6 (10.0%)	42 (71.7%)	Fisher's exact = 0.427 (p=0.968)
	Expected	2.9	18.6	15.1	6.5	43	
Female	Count	1 (1.7%)	7 (5.7%)	6 (10.0%)	3 (5.0%)	17 (28.3%)	
	Expected	1.1	7.4	6.0	2.6	17.0	
Total		4 (6.7%)	26 (43.3%)	21 (35.00%)	9 (15.9%)	9 (15.9%)	

Table 4 Influence of Sex upon the Prevalence of Specific DFDs Interventions: Cross-tabulation

---

4.2.1.3 The relationship between nationality and type of intervention (Table 5, Figure 5).

Nationality		Intervention				Total	Test statistic (p-value) (2-tailed)
	n	Conservative only	Debridement	Minor amputation	Major amputation		
Saudi	Count	3 (5.0%)	15 (25.0%)	9 (15.0%)	20 (33.3%)	47 (78.3%)	Fisher's exact = 11.98 (p=0.004)
	Expected	3.1	20.4	7.1	16.5	47.0	
Non-Saudi	Count	1 (1.7.0%)	11 18.3(%)	0 (0.0%)	1 (1.7%)	13 (21.7%)	
	Expected	0.9	5.6	2.0	4.6	13.0	
Total		4 (6.7%)	31 (43.3%)	9 (15.0%)	21 (35.0%)	21 (35.0%)	

Table 5 Influence of Nationality upon the Prevalence of Specific DFDs Interventions: Cross tabulation

Evaluating the relationship between nationality and type of intervention among our DFDs group, chi-square testing showed that the prevalence of amputation incidents (both major and minor) among Saudi diabetics significantly exceeds that among the non-Saudi counterparts [33.3% vs. 1.7% major amputation, and 15.0% vs. 0.0% minor amputation, respectively) (Table 5). The same trend is observed in regard to debridement and conservative treatment [25.0% vs. 11.8%, and 5.0% vs. 1.7%, respectively], (Fisher's exact 11.98, p=0.004) (Table 5). (Also see Figure 5 for a comparative distribution).

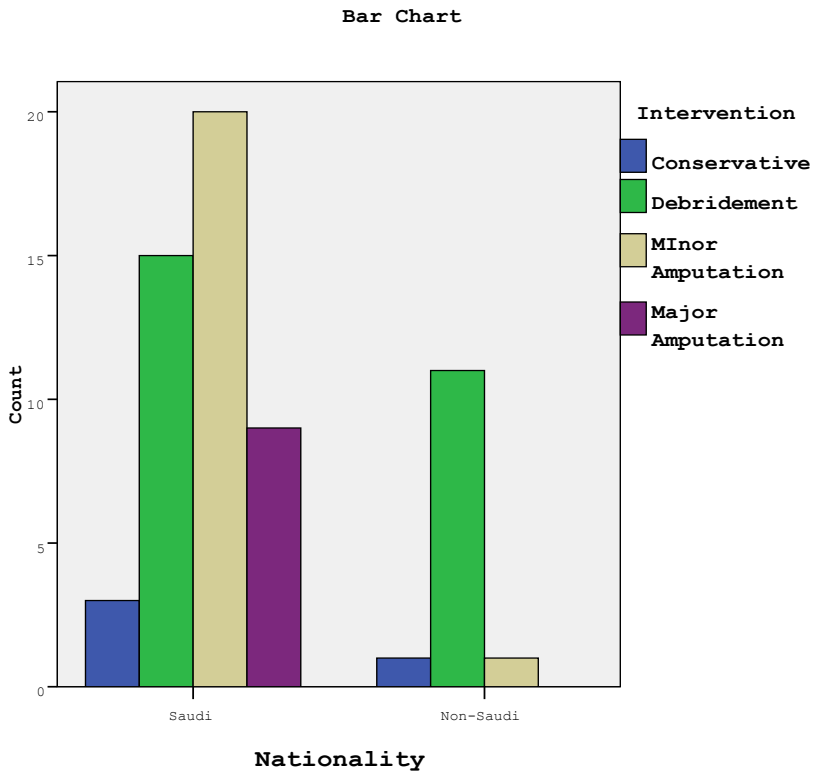


Figure 5 Distribution of the study DFDs Intervention Groups by Nationality: Saudi vs. Non-Saudi

---

4.2.2 Phase 2: Influence of the Study Determinants upon COI

4.2.2.1 The relationship between age and COI: correlation analysis. (Table 6)

	Correlation	COI (SR)
Age (y)	Pearson Correlation	0.333
	p-value	0.009
	n	60

Table 6 The Relationship between Age and COI: Correlations Analysis

As in Table 6, there is a week (33.33%) but highly significantly correlation between age and COI [r(df=58) =0.333, p=0.009]. [In a Spearman's correlation test rho calculation, correlation was as higher as moderate (Spearman's rho= 0.467, p<0.0001]. (Appendix D).

4.2.2.2 The Relationship between sex and COI: student t-test. (Tables 7)

	Levene's test (equality of Variances			t-test for Equality of Means					95% CI of the difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Diff.	SE Diff.	Lower	Upper
COI (SR)	Equal variances assumed	0.122	0.728	0.075	58	0.941	562.78 *	7531.83	-14513.8	15639.4
	Equal variances not assumed			0.082	36.53	.935	562.78	6838.78	-13299.9	14425.5

* Mean COI male= 33462.63 (SD 27696.2). Mean COI female = 34028.4 (SD 22176.7)

Table 7 The Relationship between Sex and COI: Two Independent Samples t-Test

In Table 7 above, the mean COI did not significantly differ between the two gender groups (Mean COI male = SR33462.63± 27696.2, mean COI female = SR34025.41 ±22176.7) (Table 8 footnote) (difference = SR562.78) (Table 8) [t(df = 0.075, p=0.941).

4.2.2.3 The relationship between nationality & COI: student t-test. (Tables 8)

	Levene's test (equality of Variances			t-test for Equality of Means					95% CI of the difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	SE Diff.	Lower	Upper
COI	Equal variances assumed	8.23	0.006	2.62	58	0.011	20383.2	7791.8	4786.1	35980.3
	Equal variances not assumed			4.7	55.6	<0.0001	20383.2	4324.3	11719.1	29047.4

* Mean COI Saudi= SR38038.5 (SD 27781.7). Mean COI non-Saudi = SR17,655.2 (SD 5441.6)

Table 8 The Relationship between Nationality and COI: Two Independent Samples t-Test

In Table 8 above, the mean COI significantly differed between Saudi and non-Saudi groups. Saudis incur average SR38038.5 (SD 27781.7) while non-Saudis incur average SR17,655.2 (SD 5441.6) in COI (Table 8, footnote). The difference in the mean COI between the two nationalities (SR20383.2) (Table 8) was statistically significant [t (df 55.6) = 4.7, p<0.0001). (Mann-Whitney-*U* test also gave significant difference). (Appendix D).

4.2.2.4 The relationship between type of intervention and COI: one-way ANOVA. (Tables 9a, 9b)

Intervention Category	N	Mean COI (SR)	SD	Std. error	95% CI of the difference	
					Lower	Upper
Conservative Only	4	10278.75	480.68	240.34	9513.88	11043.62
Debridement	26	17276.00	5396.72	1058.38	15096.22	19455.78
Minor amputation	21	35892.33	6109.51	1333.20	33111.32	38673.35
Major amputation	9	85921.67	24399.18	8133.06	67166.79	104676.54
Total	60	33622.08	26067.07	3365.25	26888.24	40355.92

Table 9a Difference in the Mean COI of the Four Intervention Group Options among the Study Population: ANOVA Test

	Sum of Squares	df	Mean square	F	p-value
Between Groups	33852152781.167	3	11284050927.056	101.301	<0.0001
Within Groups	6237893043.417	56	111390947.204		
Total	40090045824.583	59			

Table 9b ANOVA Analysis: Mean Difference among DFDs Groups

As in Table 9b above, the mean COI increases gradually by the intensiveness of the intervention procedure: The mean ± SD COI (SR) for the procedures are as follows: conservative treatment only = 10278.75± 480.68; debridement = 17276.00± 5396.72; minor amputation = 35892.33± 6109.51; and major amputation = 85921.67± 24399.18. The difference in these means was statistically significant [F(df 3, 56)=101.301, p<0.0001] (Table8b). A post-hoc test [least square difference (LSD)] was also conducted to measure the

"within-groups" difference in COI. Most comparisons were significantly different. (See Appendix D). (Kruskal Wallis test also gave significant difference). (Appendix D).

4.2.2.5 Predicting the change in COI to changes in selected outputs (Table 10)

Independent variable	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Sex(1)	– 0.141	0.667	0.045	1	0.832	0.868	0.235	3.209
Age	0.596	0.210	8.003	1	0.005	1.814	1.201	2.740
Constant	– 35.221	12.262	8.250	1	0.004	0.000		

Table 10 Predictability of Independent Variables Age and Sex on the Chnge in COI: Logistc Rgerssion Analysis

Near the end of the analysis, a multiple logistic regression model was fitted to measure whether the selected independent variables could predict change in COI due to a unit change in each independent variable. The COI was first modified as <SR35,000 and ≥SR35,000 as the binary independent varlable for the model. In Table 9, the regression coefficint (B) for age is positive 0.596. Exponent B for age (column 7, Table 9) is the odds ratio (OR) (which is anti-log of B) of the impact of age upon COI. It indicates that a higher COI is 1.814 times significantly more likely to be associated with higher age [ExpB=1.81, 95% confidence interval (CI) 1.201 – 2.74]. Interpreting output Table 9, too, the fitted regression model for the included variables would be constucted in the for of the following formula:

$$[P/1 - P] \text{ Change in COI} = \frac{e^{-35.221 + 0.596\,(\text{Age}) - 0.141\,(\text{Female})}}{1+e^{-35.221 + 0.596\,(\text{Age}) - 0.141\,(\text{Female})}}$$

5. Discussion

The cornerstone of mitigating diabetes complications and alleviate its burden is to control blood glucose level and guard a higher than optimum glucose levels by all means and under all circumstances. The longer the normalization of PG levels the farther postponement of developing diabetic macrovasculopathy, neuropathy and impaired immune response to infectious agents (Hammes, 2003; O'Gara, et al., 2013). These disorders endanger foot tissue health and integrity and if not controlled DFDs of variable severity and implications are precipitated (Macleod et al., 1996; Tashkandi, et al.,2011). Although many diabetics are at risk of developing DFDs the exact estimate of DFDs and hence exact economic burden and COI attributed to them are lacking, globally (Moxey, et al., 2011), and locally (Alzahrani, et al., 2013).

5.1 Interpreting Demographic Findings in Relation to DFDs Intervention Outcome

We first found that both age and Saudi nationality were risk for a severer DFD prognosis. On the other hand, sex had no influence upon our study outcomes. In Saudi Arabia, too, Alrubean, et al. (2015) found that age, male sex, and diabetes duration were risk factors for worse diabetes diagnoses. Alrubean and collaborates' work was based on reviewing the Saudi National Diabetes Registry (SNDR), whereas it was claimed that only a total 2,071 DFD cases were registered with SNDR, and 32.20% of those who sustained worst diagnoses (ulcer and gangrene) had major amputation. The amputation frequency in Alrubean, et al., also closely compares to ours (35.0%). In our study we would be concerned about such high amputation rate in a population who is fully covered and supposedly having access to good medical care. Alrubean and colleagues' finding that 2071 subjects with DFDs all through 2000 till 2012, raises another concern about DFDs situation in Saudi Arabia. Assuming the least estimate of 3.3% DFDs in KSA, as in Alrubean et al., this should account to not less than 100,000 cases [considering 3.4 million with diabetes in KSA (International Diabetes Federation, 2015) and that 90% of them are type 2 (International Diabetes Federation, 2014)]. The large difference in DFDs rates between the two reports warrants further inquiry about the true reason for under-reporting diabetes disorders and the reluctance to administer DFDs incidents in the SNDR.

While between 15% and 35% of our DFD patients were victimized with amputation, this rate also conforms to what has been speculated elsewhere that severer DFDs not timely and properly managed might end up with amputation in 15%-27% of cases (Alzahrani, et al., 2013). The issue is that Saudi Arabia envisions a progressive medical, strategic, and administrative advance in health services (Almalki, et al., 2011; Walston, et al. 2008; World Health Organization-WHO, 2013) including diabetes care capabilities. Therefore, the discouraging DFDs outcome reported in our study perhaps fails our expectation of a better outcome in a community that is well-served and driven by market economy such as Jeddah. Many factors could be incriminated in our attempt to understand the mismatch between this unfavorable health outcome and the reasonably good financial and health system inputs.

Little studies addressed the prevalence and risks of DFDs among Saudi Arabian citizens (Alrubean, et al., 2015; Alzahrai, et al., 2013) in agreement with our instinct with this regard. Instead, the prevalence of diabetes itself in Saudis compared with other nations has been documented by many other studies (Afifi, et al., Al-Nozha, et al., 2015; Alrubean, et al., 2015; Al-Wakeel, et al. 2009; IDF, 2015). Diabetes in Saudi Arabia reached 23.7% (Alwakeel, et al., 2009) a proportion that is one of the highest not only in MENA zone but in the world (Alwakeel, et al., 2009), and that is prone to grow to astronomical numbers, e.g., 283% by 2030, (International Diabetes Federation, 2015) if the Saudi diet style and physical inactivity persist and no radical intervention plan has been enforced. In diabetes, early detection of clinical and pathological risks for DFDs, namely vacuities, neuropathy and skin infection of the foot, is critical (American Diabetes Association, 2015; Canadian Diabetes Association, 20013; Griffth, et al., 2010; Hammes, 2003; Khan, et al., 2010; Zhang, et al., 2010). These pathologies frequently overlap in the same DFD episode and progress to resistant foot ulcer and then amputation (Al-Rubeaan, et al., 2015; Boulton, et al., 2008). A radical strategy to handle diabetes problem in Saudi should rest on prevention, early detection of prediabetes and uncontrolled diabetes cases and continuous monitoring of A1C in known diabetics (Afifi, et al., 2015). Especially the high risk, diabetics should be given specific consideration at family medicine and primary healthcare setting. There should be also an emphasis on a combined screening strategy for high risk groups, including the obese, less served communities, and the low socioeconomic class (Ackermann, et al., 2011). Even the high socioeconomic class should be considered in risk detection and prevention of DM. The two socioeconomic classes have

reasons to an exaggerated diabetes opportunity. The unfortunates lack access health care both in quantity and quality (Selvin, et al., 2010). The less educated may not have the enthusiasm for health education and realizing its role in preventing chronic diseases that impact health, survivability and QOL (Alzahrani, et al. 2013; American Diabetes Association- ADA, 2015; Griffth, et al. 2011; Khan, et al., 2010; Moxey, et al., 2011; Tashkandi, et al. 2011; Wild et al., 2004). The rich are often intimidated by easy life and often unhealthy diet (Jalboukh, 2008), as well as technologies which bring the plenty of life utilities at their fingertips and persuade physical inactivity.

5.2 Discussing COI Findings

I literature, the cost per person with diabetes in Saudi Arabia mounts up to $1,145.3 (IDF, 2015). This implies that the Saudi society spends over $15 billion on DM [$1145.3 * 3.4 million estimated diabetics, (IDF, 2015)], while the outcome, e.g., 15%-35% amputation as in this study and 27.9% - 44% individuals with undiagnosed DM (Afifi, et al., 2015; Al-Nozha, et al., 2015) does not live up to what was expected from such investment. The median COI for DFDs care in our study was SR27,817.50 ($7,418 equivalent) (IQR= SR 24,333.25); the mean COI was SR33,622.08 ± 26,067.073 (= $8965.9 ± 6951.2); and a range of SR131,527 (minimum SR9859 and maximum SR141,386). Data from a recent sample-based study on the cost of DFD illnesses in Saudi Arabia by Alzahrani, et al. (2013) showed that the median COI totaled SR12,819.5. The median COI of Alzahrani et al., is less than half that in our work. Both Alzahrani et al., and our study share a common setting and some clinical criteria. For instance, the two studies were conducted on Jeddah diabetic patients, and also the broad clinical intervention categories were almost identical (conservative treatment alone, debridement, minor amputation, major amputation). Other studies elsewhere on DFDs also tended to use the same clinical intervention classification (Boulton, et al. 2005). According to Alzahrani et al., study design, recruitment was limited to DFD patients upon a single hospital admission to receive inpatient care for their stressing DFD condition. Further, the length of hospital stay only averaged 9 days (compared to similar studies with longer hospital stay, Benotmane, et al., 2008. In practice, however, patients with DFDs tend to require more frequent emergency department visits and outpatient appointments, and probably other follow up procedures in-between visits, Boulton, et al., 2005). Therefore, a larger-scale costing

studies for DFDs not only included the immediate DFDs episode costs but other costs, such as Benotmane, et al. (2008) and Boulton, et al. (2005) are often be required. Needless to say, indirect cost items may also be calculated. However the estimation of these costs is not always possible, especially in the presence of obstacles that limit the allocation of resources for a comprehensive COI study. The frequency of debridement intervention in Alzahrani et al. and us was highest among all DFDs procedures (48.8% vs. 43.3%) (See Appendix D for comparative tables between the two studies developed by this researcher).

Findings from western DFDs costing research report variable median costs for DFDs care. The trend was that lower limb amputations usually cost higher than non-surgical care. The median cost in Australia for lower extremity amputation was A$12,485, (range 6,037-24,415) (Davis, et al. 2006), i.e., compared to $9,288 – $20,569 median COI for minor amputation and major amputation, respectively in our study) (see Appendix D for detailed comparative COI Table). Highest among all, $32,129 is the median cost in admission for ischemic limb ambulation in U.S.A. (Peacock, et al. 2008). The differences in study designs, procedures, length of hospital stay, as well as the variability in health benefits and billing systems alongside with the variability in each country's economics and living expenses all can cause variability in COI of DFDs care.

As in the type of intervention analyses, age and nationality were risks for incremental COI. Comparable results have been reported by other COI in DFDs studies (Afifi, et al., 2015; Alrubean, et al., 2015). Typically, diabetes complications develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. As such, older diabetics are at greater risk of suffering a complicated disease (Abulfotouh, et al., 2011; Alrubean, et al., 2015; Reiber, et al., 1998).

5.3 Discussing the Regression Analysis

Multiple linear regression analyses were first attepted and no significant predictibilities by the entered predictots for the change in COI were found. Alternatively, logistic regression would be conducted; in which case COI would be transformed into the binary dependent variable for conducting the logistic regression technique. First a cutoff point at around the median COI was selected (<SR60,000 and ≥60,000) but the model could not preict the change in the COI. When the cutoff point was decreased gradually until 35,000, significant effect was

obtained. Although type of DFDs care did impact the level of COI (ANOVA analysis), its effect as a dummy variable on the change in COI was not significantly receognized wnen first entered to the logistic model, thereby they were removed. Fnally, age only could predictor for COI change. For instance, if a 60 year old (male) diabetic dveleoped DFDs (any type), the probability for a change in COI because of age, (sex is not significant), will be:

$$[P/1 - P] \text{ Change in COI} = \frac{e^{-35.221 + 0.596\,(60) - 0.141\,(\text{Zero})}}{1 + e^{-35.221 + 0.596\,(60) - 0.141\,(\text{Zero})}} = \frac{1.71}{2.71} = 0.633$$

Abulfotouh, et al (2011) conducted a case-control study on 50 diabetic patients attending outpatient diabetes clinic in King Abdulaziz Medical City (KAMC) in Riyadh, who had DFD episodes between January 2009 and July 2010. The study methodology was based on testing the impact of some predictors assembled in a multiple logistic regression model on DFDs type and severity. Diabetic foot disorders studied included infection, ulceration, neuropathy, and vascular insufficiency. Significant risk factors in individual chi-square tests included male gender, age ≥40, illiteracy, DM durationn≥20y, peripheral neuropathy, PVD, IHD, and erythrocyte sedimentation rate (ESR). Applying the logistic regression with the presence of DF as the dependent variable, only neuropathy, DM duration and ESR were significant predictors for DFDs. Other variables which were significant determinants on DFDs development in separate chi square analyses were not significant predictors, in resemblance with our findings profile.

A large-scale research from Denmark by Bruun and collaborates (2013) was conducted to analyze the prevalence and determinants of diabetic foot ulcers and amputation rate in adult diabetics observed over 19 years of disease diagnosis (at 6 year and 14 year observation points). Age, gender, and co-morbidities were independent variables studied. Significant predictors of any amputation were peripheral neuropathy (OR 2.09; 95% CI 1.19-3.69), vasculopathy (OR 3.43; 95% CI 1.65-7.12), male gender (OR 2.40; 95% CI 1.31-4.41). Age in women was risk of amputation, but men were at higher risk when they get DM at a younger age. In other words, age here revolve around the number of years lived with diabetes until DFDs has developed. For this very relationship, we were curious to invite to this study

patients who had more eight years of enrollment with this insurer (since 2007), first to remove the confounding effect of the difference in insurance package (e.g., health benefits, preferred provider organization provision, billing and disease coding), and fluctuation on the quality of the offered health service. Second, to incorporate disease duration issue in the study background, which researchers now agreed on its role in provoking DFDs complications (Abulfotouh, et al.. 2011; Alrubean, et al., 2015; Bruun, et al., 2013; Reiber, et al.. 1998). With that in mind, we first tried to admit subjects with longer duration of enrollment with the insurer (10-15y). However, this was not guaranteed owing to the relative newness of this insurer in the Jeddah market (since 1997) and the restriction terms forced on release of patient information to unauthorized persons or for research purpose.

5.4 Study Aims and Answering the Research Questions

The economic burden associated with DFDs in the study population could be quantified using the dataset collected and analyzed. Results from this research, if related to the scientific and healthcare policy maker community could be of an added value in understanding and planning for improving DM the economic outcomes of diabetes and DFDs in Saudi Arabia. Likewise, the research objectives have been achieved. For instance, the distribution pattern of the study subjects' demographic traits, as well as the prevalence of DFDs intervention options have been identified and evaluated. The distribution pattern of these DFDs reflects the severity of DFDs problem in the studied population, for further action by interested healthcare planners. Specifically, the cost trends and levels linked to DFDs episodes have been thoroughly examined and quantified.

The implications of the demographic and intervention correlates upon the COI have been identified and measured and inferences from the studied relationships could be concluded. Further, the predictability potential of the study variables to the change in COI could be identified and interpreted. The obtained logistic model formula enables predicting what COI category to expect (<SR35,000 or ≥SR35,000) if a diabetic patient would go through a diabetic foot experience at a certain age. Inability of the type of intervention to predict COI change does not mean they are ineffective because their effect on COI has already been shown in a separate analysis. Probably including intervention type in a larger sample size

study replicating the same methodological technique of this research may well generate a significant result.

The research questions have been all answered, following the same logic advocated in achieving the research objectives, as above. We now realize that 43.3% of DFDs could be treated by simple surgical intervention in the form of debridement. Less likely, meanwhile still concerning, are those who experience minor amputations (35%). This specific DFD stratum should be given top priority in the form of close follow up and observation to retain them into the less invasive DFD treatment groups. Better care and closer follow up can further improve the outcome of the two amputation groups and raise the prevalence of conservative treatment from 6.7% to tangibly higher levels in particular.

Answering question about how significant the impact of demographic criteria on the prevalence of intervention options, both age and Saudi nationality have been of a significant impact with this respect (Tables 3 and 5, respectively). Inquiring about the pattern of the COI and whether there was a significant relationship between it and type of intervention, we found that COI varies significantly by intervention type, a result that can explain the most part of this research and can be used for estimating the economic burden of DFDs in the studied population. Similarly, the prediction function for COI change by any significantly included predictor was assessed using the multiple logistic technique approach, as in the methodology plan.

5.5 Strengths and Limitations

This work has a number of strengths adding to the validity and reliability of the obtained findings, e.g., planning for improved diabetes management in Saudi Arabia. The source the information was gained from is a reputed agency working in the Saudi healthcare market. From the methodology viewpoint, data entry and the sophisticated statistical analysis approach, e.g., strict adherence to PMT technique assumptions before attempting any of these techniques, enhance the validity of the study results and importantly depreciate the probability of systematic or misclassification bias. Also, in our risk-outcome analysis plan, the deployment of DFDs both as potential risk for COI and then as an intermediary outcome enabled conducting a larger number of comparisons and helped us envisage DFDs from a broader risk-outcome angle.

On the other hand, some limitations, which are mostly related to access to the amount of released patient data had been encountered. First it was not possible to get the exact duration of diabetes of the recruited patients or when it had started. Had disease duration been obtained it could have been added to the study correlates and a broader picture of the epidemiology of DFDs in Jeddah could have been drawn. The sample size we were permitted was rather small. Statistically-speaking sample size generally affects the study power due to inflating type-two error (β- error). This may often limit generalizability of studies' results. However, the quota sampling approach, which involves a nonprobability technique, could have some effect in offsetting type-2 error inflation and maintaining a better generalizability potential on the population.

6. Conclusion

Despite good access to health care and coverage, the incidence of amputations among our study population is worrying. Older age diabetic patients particularly the Saudis are at a greater risk for complicated DFDs and amputation. These concerns warrant developing more efficient and effective follow up policy on regular base for diabetic patients in general and DFD patients in particular. High risk patients, e.g., the obese or those with CVD and other comorbidities worth a closer follow up. The findings of this research emphasize the stressing need to keep diabetic patients under continuous glycemic control to delay the occurrence of ischemic vascular and neurological complications which in turn have serious implications upon the diabetic patient's foot wellbeing. When neglected, deranged foot vasculature and peripheral nerves act as precursors for DFDs. A preventive approach both to minimize the number of new diabetics and creating an unfavorable environment for developing complications are mostly recommended. Improving the primary prevention programs, adopting a multidisciplinary collaboration in delivering holistic healthcare service package in Saudi Arabia is critical for alleviating diabetes problems burden upon the Saudi community and the national economy. Further larger scale research highlighting other economic aspects of DFDs and utilizing evaluation techniques enabling addressing indirect costs of lost productivity, moral hazard, and impaired QOL due to loosing limbs to diabetes, is warranted particularly in population with an exceptionally high rates of diabetes, such as Saudi Arabia.

References

Abolfotouh, M. A., Alfaifi, S. A., & Al-Gannas, A. S. (2011). Risk factors of diabetic foot in central. *Saudi Arabia. Saudi Medical Journal, 32,* 708–713.

Adler, A.I., Stratton, I. M., Neil, H. A., Yudkin, J. S., Matthews, D. R., Cull, C. A., et al. (2000). "Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study". *British Medical Journal, 321*(7258), 412–9.

Ackermann, R. T., Cheng, Y. J., Williamson, D. F., & Gregg, E.W. (2011). Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1C. *American journal of Preventive Machine, 40*(1):11-7.

Afifi, R., Omar, S., & El Raggal, A. (2015). A community screening plan for the prevalence of some chronic diseases in specified adult populations: pre-diabetes and diabetes mellitus. *International Journal of Diabetes in Developing Countries. 35*(3), 149-156.

Al-Nozha, M. M, Al-Maatouq, M. A., Al-Mazrou, Y. Y., Al-Harthi, S. S., Arafah, M. R., Khalil, M., Z. et al. (2004). *Diabetes mellitus in Saudi Arabia. Saudi Medica; Journal, 25,* 1603–1610.

Ali, S. M., Fareed, A., Humail, S. M., Basit, A., Ahmedani, M. Y., Fawwad, A., & Miyan Z. (2008). The personal cost of diabetic foot disease in the developing world–a study from Pakistan. *Diabetes Medicine, 25,* 1231–3.

Almalki, M., Fitzgerald, G., & Clark, M. (2011). Health care system in Saudi Arabia: an overview. *Eastern Mediterranean Health Journal,17*(10), 784-93.

Al-Rubeaan, K. H., Al Derwish, M., Ouizi, S., Youssef, A. M., Subhani, S. N., Ibrahim, H. M., et al. (2015). Diabetic foot complications and their risk factors from a large retrospective cohort study. *PLoS One, 10*(5): e0124446. doi: 10.1371/journal.pone.0124446

Al-Tawfiq, J. A., & Johndrow, & J. A. (2009). Presentation and outcome of diabetic foot ulcers in Saudi Arabian patients. *Advances in Skin Wound Care, 22,* 119–21.

Al-Wahbi, & A. M. (2006). The diabetic foot in Arab world. *Saudi Medical Journal*. *27,* 147–53.

Alwakeel, J. S., Al-Suwaida, A,, Isnani, A. C, Al-Harbi, A., & Alam, A. (2009). Concomitant macro and micro-vascular complications in Diabetic nephropathy. *Saudi Journal of Kidney Disease Transplantation, 20,* 402–9.

Alzahrani, & A. H. (2013). The direct cost of diabetic foot management in some of private hospitals in Jeddah, Saudi Arabia. *International Journal of Diabetes in Developing Countries, 33*(1), 34–39. doi: 10.1007/s13410-012-0107-x.

Alzahrani, H. A., Hitos, K., Fletcher, & J. P. (2011). *The diabetic foot.* (1st ed.). Sydney: Hemi Australian Pty Ltd.

American Diabetes Association (AMA). (2003). Screening for Type 2 Diabetes. *Diabetes Care; 26*(suppl 1): s21-s24. Retrieved from: http://dx.doi.org/10.2337/diacare.26.2007.S21

American Diabetes Association (ADA). (2004). Diagnosis and classification of diabetes mellitus. *Diabetes Care; 27*(suppl 1): s5-s10. http://dx.doi.org/10.2337/diacare.27.2007.S5

American Diabetes Association (ADA). (2008). Economic costs of diabetes in the U. S. in 2007. *Diabetes Care, 31,* 596–615.

American Diabetes Association (ADA). (2010). "Diabetes Care". Summary of Revisions for the 2010 Clinical Practice Recommendations". *Diabetes Care, 33*(Supplement 1),S33.

American Diabetes Association (ADA). (2015). American Diabetes Association's "Standards of Medical Care in Diabetes" *Summary of Revisions Diabetes Care, 38*(Suppl. 1):S4. doi: 10.2337/dc15-S003.

Barr, E. L., Zimmet, P. Z., Welborn, T. A., Jolley, D., Magliano, D. J., Dunstan, D. W., et al. (2007). Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian diabetes, obesity, and lifestyle study (AusDiab). *Circulation, 116*(2), 151–7.

Benotmane, A., Mohammedi, F., Ayad, F., Kadi, K., & Azzouz, A. (2001). Management of diabetic foot lesions in hospital: costs and benefits. *Diabetes Medicine, 27,* 688–94.

Boulton, A. J, Vileikyte, L., Ragnarson-Tennvall, G., & Apelqvist, J. (2005). The global burden of diabetic foot disease. *The Lancet, 366,* 1719–24.

Boulton, A. J. M., Armstrong, D. G., Albert, S. F., Frykberg, R. G., Hellman, R., Kirkman, M.S., et al. (2008). Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care, 31, 1679–1685. doi: 10.2337/dc08-9021Brown, A. F., Mangione, C. M., Saliba, D., & Sarkisian, C. A. (2003). California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *Journal of the American Geriatric Society, 51*(Suppl. Guidelines), S265–S280. doi: 10.1046/j.1532-5415.51.5s.1.x

Bruun, C., Siersma, V., Guassora, A. D., Holstein, P., de Fine- & Olivarius N, (2013). Amputations and foot ulcers in patients newly diagnosed with type 2 diabetes mellitus and observed for 19 years. The role of age, gender and co-morbidity. *Diabetes Medicine, 30,* 964–972. doi: 10.1111/dme.12196

Canadian Diabetes Association (CDA). (2013). Canadian diabetes association clinical practice guidelines expert committee. Clinical practice guidelines for the prevention and management of diabetes in Canada. *Canadian Journal of Diabetes, 37*(suppl 1):S1-S212. Retrieved from: http://guidelines.diabetes.ca/app_themes/cdacpg/resources/cpg_2013_full_en.pdf

Cardenas, M. K., Mirelman, A. J., Galvin, C. J., Lazo-Porras, M., Pinto M., Jaime, J., et al. (2015). The cost of illness attributable to diabetic foot and cost-effectiveness of secondary prevention in Peru. Biomed Central (BMC) Health Services Research, 15, 483. doi: 10.1186/s12913-015-1141-4

Cavanagh, P. R. (2004). Therapeutic footwear for people with diabetes. Diabetes *Metabolism and Research Reviews, 20*(Suppl 1), S51–5. doi:10.1002/dmrr.435.

Cheng, J., Zhang, W., Zhang, X., Han, F., Li X,, He. X., & Li, Q. (2014). Effect of angiotensin-converting enzyme inhibitors and angiotensin ii receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. *Journal of American Medical Association, 174*(5), 773–85. doi:10.1001/jamainternmed.2014.348.

Clinical Coding and Schedule Development Group (CCSD). Retrieved from: http://www.ccsd.org.uk/

Council of Cooperative Health Insurance (CCHI). (2016). http://www.cchi.gov.sa/en/InsuranceCompanies/Pages/Companies.aspx

Council of Health Services. Vision and tasks of the Council of Health Services in Saudi Arabia. Retrieved from: http://shc.gov.sa/En/default.htm

Davis, W. A., Norman, P. E., Bruce, D. G., Davis, & T. M. Predictors. (2006). Consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: The Fremantle diabetes study. Diabetologia, 6(49), 2634–41.

De la Monte, S. M. (2014). Type 3 diabetes is sporadic Alzheimer′s disease: mini-review". European neuropsychopharmacology: *the journal of the European College of Neuropsychopharmacology, 24*(12), 1954–60. doi:10.1016/j.euroneuro.2014.06.008.

Dellon, A. L., Muse, V. L., Nickerson, D. S., Akre, T., Anderson, S. R., Barrett, S. L., et al. (2012). Prevention of ulceration, amputation, and reduction of hospitalization: outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. *Journal of Reconstructive Microsurgery, 28*(4):241-6. doi: 10.1055/s-0032-1306372

Dolores, S., & Gardner, D. G. (2011). *Greenspan's basic and clinical endocrinology*. (9th ed.). New York: McGraw-Hill. ISBN 9780071622431.

Driver, V. R., Fabbi, M., Lavery, L. A., & Gibbons, G. (2011). The costs of diabetic foot: the economic case for the limb salvage team. *Journal of Vascular Surgery, 52*(3 Suppl), 17S–22S. Retrieved form: http://www.ncbi.nlm.nih.gov/pubmed/20804928

Engelgau, M. M., Narayan, K. M. V., Herman, & W. H. (2000). Screening for Type 2 *Diabetes. Diabetes Care, 23*(10), 1563-80.

Erickson, S. C., Le, L., Zakharyan, A., Stockl, K. M., Harada, A.S., Borson, S., et al. (2012). Newonset treatment-dependent diabetes mellitus and hyperlipidemia associated with atypical antipsychotic use in older adults without schizophrenia or bipolar disorder. *Journal of the American Geriatrics Society, 60,* 474–479

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. (2007). *Diabetes Care, 20,* 1183–1197

Gallagher, EB. (2002). Modernization and health reform in Saudi Arabia, Chapter 4. In: Twaddle, A. C. ed. *Health care reform around the world.* London: Auburn House. P.181–197.

Global Burden Disease Risk Factors Collaborators (GBD). (2015). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the GBD Study 2013. The Lancet, 386(10010), 2287–323. doi: http://dx.doi.org/10.1016/S0140-6736(15)00128-2

Green, M. F., Aliabadi, P. T. Z., & Green, B. T., (2002). Diabetic foot: Evaluation and management. *Southern Medical Journal, 95*(1), 95-101.

Griffin, S. J., Borch-Johnsen, K., Davies, M. J., Khunti, K., Rutten, G. E., Sandbæk, A., et al. (2011). Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (addition-Europe): a cluster-randomised trial. *The Lancet, 378,* 156–167.

Hammes, H. P. (2003). Pathophysiological mechanisms of diabetic angiopathy. *Journal of Diabetes Complications, 17*(2 Suppl), 16-9.

Health Statistical Year Book. (2009). Ministry of Health (MOH), Riyadh, Saudi Arabia, Retrieved from: http://www.moh.gov.sa/Ministry/MediaCenter/News/Documents/healthybook.pdf

Hex, N., Bartlett C., Wright, D., Taylor, M., & Varley, D. (2012). Health Economics Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. York Health Economics Consortium Ltd, University of York, York, UK. doi: 10.1111/j.1464-5491.2012.03698 x.

Hodgson, TA, & Meiners, MR. (1982). Cost of illness methodology: a guide to current practices and procedures. Milbank memorial fund quarterly. *Health and Society, 60,* 429–462. doi: 10.2307/3349801. Retrieved from: http://www.jstor.org/stable/3349801

Hu, F. B., Manson, J. E., Stampfer, M. J., Colditz, G., Liu, S., Solomon, C. G., & Willett, W. C. (2001). Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *New England Journal of Medicine, 345,* 790-7.

International Diabetes Federation (IDF). (2013). *Diabetes atlas*, (6th ed.) p. 7. ISBN 2930229853.

International Diabetes Federation (IDF). (2014). Annual report 2014. Retrieved from: http://www.idf.org/sites/default/files/IDF-2014-Annual-Report-final.pdf

International Diabetes Federation (IDF). (2015). Middle East and North Africa. Diabetes in Saudi Arabia-2015. Retrieved from: http://www.idf.org/membership/mena/saudi-arabia

International Classification-9- Coding Manual (ICD-9-CM). (2011). ICD-9-CM official guidelines for coding and reporting effective October 1, 2011. Retrieved from: https://www.cdc.gov/nchs/data/icd/icd9cm_guidelines_2011.pdf

Jalboukh, T. (2008). Health report on Saudi Arabia. Available from: http://www.ameinfo.com/136229.html

James, W. D., Berger, T., & Elston, D. (2006). *Andrews' diseases of the skin: clinical dermatology.* (12th ed.) Philadelphia: Saunders Elsevier. ISBN 0-7216-2921-0.

Jo C. (2014). Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. 20(4): 327–337. doi: 10.3350/cmh.2014.20.4.327

Jefferson, T., Demicheli, V, & Mugford, M. (2000). *Cost-of-illness studies, elementary economic evaluation in health care.* 2nd ed. London: British medical Journal Publishing Group; 2000. pp. 17–29.

Jo, C. (2014). Cost-of-illness studies: concepts, scopes, and methods. *Clinical and Molecular Hepatololgy, 20*(4), 327–337. doi: 10.3350/cmh.2014.20.4.327

Johnson, S. L., Tabaei, B. P., & Herman, W. H. (2005). The efficacy and cost of alternative strategies for systematic screening for type 2 diabetes in the U.S. population 45-74 years of age. *Diabetes Care, 28,* 307–311.

Kahn, R., Alperin, P., Eddy, D., Borch-Johnsen, K., Buse, J., Feigelman, J., et al. (2010). Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *The Lancet, 375,* 1365–1374

Khardori, R. (2016). Medscape. Type 2 diabetes mellitus clinical presentation. Retrieved from: http://emedicine.medscape.com/article/117853-clinical

Kim, E., Barrett, K. Barman, E., S. M., Boitano, S., & Brooks, H. (2012). *Ganong's review of medical physiology.* 24th ed. New York: McGraw-Hill. ISBN 0071780033.

King, P., Peacock, I., & Donnelly, R. (1999). The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *British Journal of Clinical Pharmacology, 48*(5), 643–648. doi: 10.1046/j.1365-2125.1999.00092.x

Knowler, W. C., Fowler, S. E, Hamman, R. F., Christophi, C. A., Hoffman, H. J. Brenneman, A. T, et al. (2009). 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. The Lancet. 374, 1677-86.

Kozhanova, I., Romanova, I., Gavrilenko, L., Sachek, L., Shepelkevich, A., Artsiomenka, A., et al. (2015). Cost of illness analysis in patients with diabetic foot syndrome in health care of republic of Belarus. *Value Health, 18*(7): A604. doi: http://dx.doi.org/10.1016/j.jval.2015.09.2078

Kumar, V., Fausto, N., Abbas, A. K., Cotran R. S, & Robbins, S. L. (2005). *Robbins and Cotran pathologic basis of disease* 7th ed. Philadelphia, Pa.: Saunders. pp. 1194–1195.

Lamri, L., Gripiotis, S., & Ferrario, A. (2014). Diabetes in Algeria and challenges for health policy: a literature review of prevalence, cost, management and outcomes of diabetes and its complications. Global Health. 2014; 10: 11. doi: 10.1186/1744-8603-10-11

Masson, E. A., MacFarlane, I. A., Power, E., & Wallymahmed, M. (2009). An audit of the management and outcome of hospital inpatients with diabetes: resource planning implications for diabetes care team. *Diabetes Medicine, 9*, 753-5.

Moxey, P. W., Gogalniceanu, P., Hinchliffe, R. J., Loftus, I. M., Jones, K. J., Thompson, M. M., et al. (2011). Lower extremity amputations – a review of global variability in incidence. *Diabetic Medicine, 28*(10), 1144–1153.

Murray, R. M., Bender, D. A., Botham, D. M., Kennelly, P. J., Rodwell, V. W., & Weil, P. A.https://en.wikipedia.org/wiki/Diabetes_mellitus - cite_ref-46 (2012). *Harper's illustrated biochemistry*. 29th ed. New York: McGraw-Hill. ISBN 007176576X.

Naidu, K. M. (2006). *Community health pursing*. New Delhi: Gennext Publication. ISBN 978-81-908675-1-1. p. 314.

NCD Risk Factor Collaboration (NCD-RisC). (2007). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4*4 million participants. *The Lancet, 387,* 1513–1530. doi: http://dx.doi.org/10.1016/S0140-6736(16)00618-8

Nichols, G. A., Hillier, T. A., & Brown, J. B. (2007). Progression from newly acquired impaired fasting glucose to type 2 diabetes. *Diabetes Care. 30*(2): 228–233. doi:10.2337/dc06-1392.

O'Gara, P. T., Kushner, F. G., Ascheim, D. D, Casey, D. E, Chung, M. K., de Lemos, J.A., et al. (2013). 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines." *Circulation, 127*(4): e362–425. doi:10.1161/CIR.0b013e3182742cf6.

Peacock, J., M., Keo H. H, Duval, S., Baumgartner, I., Oldenburg, N. C, Jaff, M., R., et al. (2011). The incidence and health economic burden of ischemic amputation in Minnesota, 2005–2008. *Preventing Chronic Disease, 8*, A141. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22005634

Polisena, J., Tran, K., Cimon, K., Hutton, B., McGill, S., & Palmer, K. (2009). Home telehealth for diabetes management: a systematic review and meta-analysis. *Diabetes Obesity and Metabolism Journal, 11*(10), 913–30.

Reiber, G. E., Lipsky, B. A., & Gibbons, G. W. (1998). The burden of diabetic foot ulcers. *American Journal of Surgery, 176*(suppl 2A): 5S-10S. :Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9777967.

Ripsin, C. M., Kang, H., & Urban, R. J. (2009). "Management of blood glucose in type 2 diabetes mellitus" *American Family Physician, 79*(1), 29–36.

Risko, N., Calvello, E. J. B, de Ramirez, S. S., Narayan, M., & Hirshon, J. M. (2011). Including emergency and acute care as a global health priority. *International Journal of Emergency Medicine, 12*(4), 75. doi: 10.1186/1865-1380-4-75.

Roglic, G. (2016). WHO global report on diabetes. *A summary review article, 1*(1): 3-8. Retrieved from: http://www.ijncd.org/article.asp?issn=WKMP-0120;year=2016;volume=1;issue=1;spage=3;epage=8;aulast=Roglic

Rothermich, E. A., & Pathak, D. S. (1999). Productivity-cost controversies in cost-effectiveness analysis: review and research agenda. *Clinical Therapeutics, 21*, 255–267.

Selvin, E., Steffes, M. W., Zhu, H., Matsushita, K., Wagenknecht, L., Pankow, J., et al. (2010). Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *New England Journal of Medicine, 362*(9), 800–11. doi:10.1056/NEJMoa0908359.PMC 2872990.

United Nations (UN). (2011). Resolution adopted by the general assembly. 66/2. political declaration of the high-level meeting of the general assembly on the prevention and control of noncommunicable diseases. Retrieved from: http://www.who.int/nmh/events/un_ncd_summit2011/political_declaration_en.pdf

Saudi Arabia Population Clock. Retrieved from: http://countrymeters.info/en/Saudi_Arabia

Schulman, A. P, del Genio, F., Sinha, N., & Rubino, F. (2009). Metabolic surgery for treatment of type 2 diabetes mellitus. *Endocrine Practice, 15*(6): 624–31. doi:10.4158/EP09170.RAR.

SharHashemi, S., Cheikh, I., & Dellon, A. L. (2013). Prevalence of upper and lower extremity tinel signs in diabetics: cross-sectional study from a United States, urban hospital-based population. *Journal of Diabetes and Metabolism, 4,* 2. Retrieved from: http://www.omicsonline.org/prevalence-of-upper-and-lower-extremity-tinel-signs-in-diabetics-crosssectional-study-from-a-united-states-urban-hospital-based-population-2155-6156.1000245.php?aid=10898

Tashkandi, W. A., Badri, M. M., Badawood, S. M., Ghandoura, N. A., & Alzahrani, H. A. (2011). Lower limb amputation among diabetics in three major hospitals in Jeddah, *Saudi Arabia. Saudi Medical Journal.18*, 23–35.

Tawar, G. P., Hasnain, S. E., & Sarin, S. K. (Eds.). (2016). *Textbook of biochemistry, biotechnology, allied and nuclear medicine.* (4th ed.). Delhi: PHI Learning Private Limited. ISBN 9788120351257. p. 142.

Tennvall, R. G., & Apelqvist, J. (2004). Health-economic consequences of diabetic foot lesions. Clinical Infectious Diseases, 39(Supplement 2), S132-S139. doi: 10.1086/383275

van den Hout, W. B. (1982). The value of productivity: human-capital versus friction-cost method. *Annals of Rheumatology Diseases,* 69, i89-i91 doi:10.1136/ard.2009.117150

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., et al. (2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the global burden of disease study 2010." *The Lancet. 380*(9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2.

Waugh, N., Scotland, G., McNamee, P., Gillett, M., Brennan, A., Goyder, E., Williams, R., & John, A. (2007). Screening for type 2 diabetes: literature review and economic modeling." *Health Technology Assessment, 11*(17). Retrieved from: from: www.hta.ac.uk/execsumm/summ1117.htm.

Walston, S., Al-Harbi, Y., & Al-Omar, B. (2008). The changing face of healthcare in Saudi Arabia. *Annals of Saudi Medicine, 28,* 243– 250.

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,* 1047-53.

World health Organization (WHO). (1999). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus (WHO/NCD/NCS/99.2). Geneva: WHO. Retrieved from: http://apps.who.int/iris/bitstream/10665/66040/1/WHO_NCD_NCS_99.2.pdf

World Health Organization (WHO). (2006). Diabetes programme. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF consultation. Retrieved from: http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

World Health organization (WHO). (2013a). Diabetes fact sheet N°312". WHO. October 2013. Retrieved from: https://web.archive.org/web/20130826174444/http://www.who.int/mediacentre/factsheets/fs312/en/

World Health Organization (WHO). (2013b). Saudi Arabia. Country cooperation strategy. Health and development. Retrieved from: http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_sau_en.pdf

World Health Organization (WHO). (2014). Media Center. Diabetes. "The top 10 causes of death Fact sheet. N°310". May 2014. Retrieved from: http://www.who.int/mediacentre/factsheets/fs310/en/

World Health Organization (WHO). (2015). Classification and *Diagnosis of Diabetes. Diabetes Care,* 38(Suppl. 1):S8–S16. doi: 10.2337/dc15-S005.

World Health Organization (WHO). (2016). Global report on diabetes. Retrieved from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf

Young, M.J., Cavanagh, P.R., & Thomas, G. (1992) The effect of callous removal on dynamic plantar foot pressure in diabetic patients. Diabetic Medicine. 9: 75 – 77.

Yuankai, S., & Hu, F. B. (2014). The global implications of diabetes and cancer. *The Lancet. 383*(9933): 1947–8. doi: 10.1016/S0140-6736(14)60886-2

Zhang, X., Gregg, E. W., Williamson, D. F., Barker, L. E., Thomas, W., Bullard, K. M,, et al. (2010). A1C level and future risk of diabetes: a systematic review. Diabetes Care, 33, 1665–1673.

Declaration:

I hereby confirm that I am the author of the thesis presented. I have written the thesis as applied for previously unassisted by others; using only the sources and references stated in the text.

Turki Bafaraj

Date: 12.09.2016

Appendix A

Study Population Dataset: Spreadsheet

#	COI (SR)	Sex	Age (y)	Treatment	Gender	Interven.	Age <55- >55	Cost <75- >75	Cost <35- >35	Saudi-Non	Conserv	Debrid	Minor Amp	Major Amp
1	141386	M	57	MJAmp ǂ	1	3	2	2	2	1	0	0	0	1
2	107402	M	60	MJAmp	1	3	2	2	2	1	0	0	0	1
3	89913	M	58	MJAmp	1	3	2	2	2	1	0	0	0	1
4	79930	F	60	MJAmp	0	3	2	2	2	1	0	0	0	1
5	77133	F	60	MJAmp	0	3	2	2	2	1	0	0	0	1
6	70026	M	60	MJAmp	1	3	2	2	2	1	0	0	0	1
7	69710	F	59	MJAmp	0	3	2	2	2	1	0	0	0	1
8	69471	M	55	MJAmp	1	3	2	2	2	1	0	0	0	1
9	68324	M	57	MJAmp	1	3	2	2	2	1	0	0	0	1
10	48090	F	58	MNAmp†	0	2	2	1	2	1	0	0	1	0
11	47775	M	60	MNAmp	1	2	2	1	2	1	0	0	1	0
12	46033	M	59	MNAmp	1	2	2	1	2	1	0	0	1	0
13	41118	M	59	MNAmp	1	2	2	1	2	1	0	0	1	0
14	40551	M	57	MNAmp	1	2	2	1	2	1	0	0	1	0
15	39364	M	59	MNAmp	1	2	2	1	2	1	0	0	1	0
16	37572	M	58	MNAmp	1	2	2	1	2	1	0	0	1	0
17	36683	F	60	MNAmp	0	2	2	1	2	1	0	0	1	0
18	36302	M	60	MNAmp	1	2	2	1	2	1	0	0	1	0
19	36039	F	60	MNAmp	0	2	2	1	2	1	0	0	1	0
20	34828	M	59	MNAmp	1	2	2	1	1	1	0	0	1	0
21	34646	M	56	MNAmp	1	2	2	1	1	1	0	0	1	0
22	33633	M	59	MNAmp	1	2	2	1	1	1	0	0	1	0
23	32577	M	57	MNAmp	1	2	2	1	1	1	0	0	1	0
24	32116	M	60	MNAmp	1	2	2	1	1	1	0	0	1	0
25	30681	F	58	MNAmp	0	2	2	1	1	1	0	0	1	0
26	29786	F	60	MNAmp	0	2	2	1	1	1	0	0	1	0
27	29472	F	57	MNAmp	0	2	2	1	1	1	0	0	1	0
28	29123	M	56	MNAmp	1	2	2	1	1	1	0	0	1	0

29	29061	M	58	MNAmp	1	2	2	1	1	2	0	0	1	0
30	28289	M	55	MNAmp	1	2	2	1	1	1	0	0	1	0
31	27346	M	57	Debrid	1	1	2	1	1	1	0	1	0	0
32	26382	M	58	Debrid	1	1	2	1	1	1	0	1	0	0
33	25798	M	59	Debrid	1	1	2	1	1	1	0	1	0	0
34	24649	M	56	Debrid	1	1	2	1	1	2	0	1	0	0
35	24477	F	58	Debrid	0	1	2	1	1	1	0	1	0	0
36	23493	F	59	Debrid	0	1	2	1	1	2	0	1	0	0
37	22861	F	57	Debrid	0	1	2	1	1	1	0	1	0	0
38	20528	M	60	Debrid	1	1	2	1	1	2	0	1	0	0
39	18670	M	55	Debrid	1	1	2	1	1	1	0	1	0	0
40	18253	F	57	Debrid	0	1	2	1	1	2	0	1	0	0
41	18216	M	56	Debrid	1	1	2	1	1	2	0	1	0	0
42	15688	M	49	Debrid	1	1	1	1	1	2	0	1	0	0
43	15522	M	58	Debrid	1	1	2	1	1	1	0	1	0	0
44	15125	F	58	Debrid	0	1	2	1	1	2	0	1	0	0
45	15047	F	57	Debrid	0	1	2	1	1	2	0	1	0	0
46	14428	M	58	Debrid	1	1	2	1	1	1	0	1	0	0
47	13456	M	54	Debrid	1	1	1	1	1	2	0	1	0	0
48	13266	M	55	Debrid	1	1	2	1	1	1	0	1	0	0
49	13252	M	56	Debrid	1	1	2	1	1	2	0	1	0	0
50	12576	M	53	Debrid	1	1	1	1	1	1	0	1	0	0
51	12373	M	57	Debrid	1	1	2	1	1	1	0	1	0	0
52	12057	M	58	Debrid	1	1	2	1	1	1	0	1	0	0
53	11793	F	56	Debrid	0	1	2	1	1	2	0	1	0	0
54	11714	M	47	Debrid**	1	1	1	1	1	1	0	1	0	0
55	11141	M	59	Debrid	1	1	2	1	1	1	0	1	0	0
56	11065	M	55	Debrid	1	1	2	1	1	1	0	1	0	0
57	10957	M	60	Conserv*	1	0	2	1	1	2	1	0	0	0
58	10258	M	51	Conserv	1	0	1	1	1	1	1	0	0	0
59	10041	M	59	Conserv	1	0	2	1	1	1	1	0	0	0
60	9859	F	54	Conserv	0	0	1	1	1	1	1	0	0	0

* Conservative treatment only
** Debridement
† Minimal amputation
† Major amputation

Appendix B

ICD-9_CM Coding Guidelines for DM and DFDs

Codes for amputation involving the lower extremity

Current amputations (ICD-9 procedure codes):84.11-17
Past amputations (ICD-9-CM codes): V49.71-77; V52.1 (CPT-4 codes): 27888, 28800, 28801, 28802, 27803, 28804, 28805, 27290, 27598, 27880, 27881, 27882, 27884, 27885, 27886, 27590, 27591, 27592, 27290, 27291, 27292, 27293, 27294, 27295, 27594, 27595, 27596, 26910, 28810, 28811, 28812, 28813, 28814, 28815, 28816, 28817, 28818, 28819, 28820, 28821, 28822, 28823, 28824, 28825

Final set of ICD-9-CM codes for foot infection

Gangrene
040.0 Gas Gangrene
440.24 Atherosclerosis of the extremities with gangrene
785.4 Gangrene but only if any one of the following is also present:
250.7 Diabetes with peripheral circulatory disorders
440.2 Atherosclerosis of native arteries of the extremities
Any condition classifiable to 440.21, 440.22, and 440.23

Osteomyelitis
730.07 Acute osteomyelitis of ankle and foot
730.17 Chronic osteomyelitis of ankle and foot
730.27 Unspecified osteomyelitis of ankle and foot
730.97 Unspecified infection of bone of ankle and foot

Ulcer
440.23 Atherosclerosis of the extremities with ulceration
707.14 Ulcer of heel and mid foot
707.15 Ulcer of other part of foot
707.1 Ulcer of lower limbs

Cellulitis or abscess of foot
680.7 Carbuncle and furuncle of foot, heel, toe
682.7 Cellulitis and abscess of foot, except toes
Cellulitis or abscess of toe
681.1 Cellulitis and abscess of toe
681.10 Cellulitis, toe NOS

Paronychia
681.11 Onychia and paronychia of toe

ICD-9-CM codes for complications of diabetes
Peripheral vascular disease: 250.7, 440, 443.8, 443.9, 785.4, 997.2
Peripheral neuropathy: 250.6, 357.2
Diabetic eye disease: 250.5, 362.0, 379.23
Cerebrovascular disease: 435 or [primary diagnosis = 430-432, 434, 436] OR
[V57.xx (rehab) AND secondary diagnosis = 342 (hemiparesis), 430-438] OR
[Primary diagnosis = 433, 435 AND secondary diagnosis = 342, 430-432, 434, 436]
Myocardial infarction: 410, 411.0, 427.5
Renal disease: 585, 586, 996.73, 996.81, V42.0, V45.1

Benjamin G, Fincke, BG, Miller DR, Turpin R. (2010). A classification of diabetic foot infections using ICD-9-CM codes: application to a large computerized medical database. BMC Health Serv Res.; 10: 192. Published online 2010 Jul 6. doi: 10.1186/1472-6963-10-192. Retrieved from:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2914721/

Appendix C

Insurer Schedule of Diagnostic Tests

List of industry standard investigations including pathology, medical specialty and imaging tests used to find or help to find the cause of symptoms of a disease, illness or injury that are eligible for funding by Bupa.

Vascular system

https://bupa.secure.force.com/procedures?chapter=9

1. If a procedure is marked with an (i) Bupa's policy on intensive therapy applies (see note 7 in the Essential Notes to the Schedule and Appendix A).

2. The surgeon's benefit entitlement for complex vascular surgery includes fees for pre-operative/peri-operative/post-operative management including intensive therapy up to 72 hours.

3. The anaesthetist's benefit entitlement for complex vascular surgery includes fees for pre-operative/peri-operative/post-operative management including intensive therapy/ventilation for up to 72 hours.

4. In circumstances where the intensive therapy exceeds 72 hours, further benefit may be considered on a case by case basis.

5. We will not pay additional benefits if a procedure is unbundled. To find out more about unbundling, please refer to note 6 of the Essential Notes to the Schedule.

6. No additional benefit is available for the harvesting of the vein graft as it is considered to be an integral part of the overall procedure and is reflected in the classification of the main procedure.

7. All varicose vein procedures include pre-operative marking of varicosities.

Appendix D

SPSS Output

A- Descriptive Statistics

Frequencies

Statistics

		Age_y	SR
N	Valid	60	60
	Missing	0	0
Mean		57.28	33622.08
Std. Error of Mean		.342	3365.245
Median		58.00	27817.50
Mode		60	9859(a)
Std. Deviation		2.650	26067.073
Variance		7.020	679492302.112
Skewness		-1.725	1.986
Std. Error of Skewness		.309	.309
Kurtosis		4.043	4.705
Std. Error of Kurtosis		.608	.608
Range		13	131527
Minimum		47	9859
Maximum		60	141386
Sum		3437	2017325
Percentiles	25	56.00	14582.75
	50	58.00	27817.50
	75	59.00	38916.00

a Multiple modes exist. The smallest value is shown

Normality Distribution Testing: Age and COI (SR)
NPar Tests

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Age_y	60	57.28	2.650	47	60	56.00	58.00	59.00
SR	60	33622.08	26067.073	9859	141386	14582.75	27817.50	38916.00

One-Sample Kolmogorov-Smirnov Test

		Age_y	SR
N		60	60
Normal Parameters [a,b]	Mean	57.28	33622.08
	Std. Deviation	2.650	26067.073
Most Extreme Differences	Absolute	.174	.190
	Positive	.153	.190
	Negative	-.174	-.181
Kolmogorov-Smirnov Z		1.348	1.470
Asymp. Sig. (2-tailed)		.053	.027

a. Test distribution is Normal.

b. Calculated from data.

Comparative Descriptive COI Statistics: Alzahrani et al. (2013) vs. This Work

DFD category	**This thesis**		**Alzahrani et al**		**This thesis**	**Alzahrani et al**
	N 1	**% 1**	**N2***	**% 2***	**Median-1**	**Median-2**
Conservative only	4	15.0	10	11.4	SR10,149.5 ($2707)**	SD4,746.5 ($12732)**
Debridement	26	43.3	43	48.8	SR15,323.5 ($4,086)	SD12,207.0 ($3255)
Minor amputation	21	35.0	5	5.7	SR34,828.0 ($9,288)	SD15,337.0 ($4,090)
Major amputation	9	21.0	30	34.1	SR77,133.0 (20,569)	SD17,884.5 ($4,769)
	N 1*	**%1***	**N2***	**%2***	**Mean-1***	**Mean-2***
Conservative only	4	15.0	10	11.4	SR10,278.75	SD2,666.1
Debridement	26	43.3	43	48.8	SR17,276.00	SD3,443.2
Minor amputation	21	35.0	5	5.7	SR35,892.33	SD2,629.8
Major amputation	9	21.0	30	34.1	SR85,921.67	SD3,753.9

* 2 Data retrieved from findings of Alzahrani et al, 2013). ** SR = $0.267; or $ = 3.75

B- Analytical Statistics

Phase 1: The Relationship between Determinants & Intervention Types

Correlations

		Age_y	SR
	Correlation Coefficient	1.000	.467(**)
	Sig. (2-tailed)	.	0.000
	N	60	60
	Correlation Coefficient	.467(**)	1.000
	Sig. (2-tailed)	0.000	.
	N	60	60

** Correlation is significant at the 0.01 level (2-tailed).

Frequency Distribution: Sex

Sex Nominal

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	f	17	28.3	28.3	28.3
	m	43	71.7	71.7	100.0
	Total	60	100.0	100.0	

Frequency Distribution: Type of Intervention

Intervention

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Conservative only	4	6.7	6.7	6.7
	debridement	26	43.3	43.3	50.0
	major amputation	9	15.0	15.0	65.0
	minor amputation	21	35.0	35.0	100.0
	Total	60	100.0	100.0	

Cross Tabulation-1: Age vs. Intervention

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Age_Cat * Intervention	60	100.0%	0	.0%	60	100.0%

Age_Cat * Intervention Crosstabulation

			Intervention				
			Conservative only	debridement	major amputation	minor amputation	Total
Age_Cat	1	Count	2	4	0	0	6
		Expected Count	.4	2.6	.9	2.1	6.0
		% within Age_Cat	33.3%	66.7%	.0%	.0%	100.0%
		% within Intervention	50.0%	15.4%	.0%	.0%	10.0%
		% of Total	3.3%	6.7%	.0%	.0%	10.0%
	2	Count	2	22	9	21	54
		Expected Count	3.6	23.4	8.1	18.9	54.0
		% within Age_Cat	3.7%	40.7%	16.7%	38.9%	100.0%
		% within Intervention	50.0%	84.6%	100.0%	100.0%	90.0%
		% of Total	3.3%	36.7%	15.0%	35.0%	90.0%
Total		Count	4	26	9	21	60
		Expected Count	4.0	26.0	9.0	21.0	60.0
		% within Age_Cat	6.7%	43.3%	15.0%	35.0%	100.0%
		% within Intervention	100.0%	100.0%	100.0%	100.0%	100.0%
		% of Total	6.7%	43.3%	15.0%	35.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	11.282[a]	3	.010	.011
Likelihood Ratio	11.140	3	.011	.010
Fisher's Exact Test	8.568			.016
McNemar-Bowker Test	.	.	.[b]	
N of Valid Cases	60			

a. 5 cells (62.5%) have expected count less than 5. The minimum expected count is .40.

b. Computed only for a PxP table, where P must be greater than 1.

Cross Tabulation-2: Sex vs. Intervention

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Sex Nominal * Intervention	60	100.0%	0	.0%	60	100.0%

Sex Nominal * Intervention Crosstabulation

			Intervention				
			Conservative only	debridement	major amputation	minor amputation	Total
Sex Nominal	m	Count	3	19	6	15	43
		Expected Count	2.9	18.6	6.5	15.1	43.0
		% within Sex Nominal	7.0%	44.2%	14.0%	34.9%	100.0%
		% within Intervention	75.0%	73.1%	66.7%	71.4%	71.7%
		% of Total	5.0%	31.7%	10.0%	25.0%	71.7%
	f	Count	1	7	3	6	17
		Expected Count	1.1	7.4	2.6	6.0	17.0
		% within Sex Nominal	5.9%	41.2%	17.6%	35.3%	100.0%
		% within Intervention	25.0%	26.9%	33.3%	28.6%	28.3%
		% of Total	1.7%	11.7%	5.0%	10.0%	28.3%
Total		Count	4	26	9	21	60
		Expected Count	4.0	26.0	9.0	21.0	60.0
		% within Sex Nominal	6.7%	43.3%	15.0%	35.0%	100.0%
		% within Intervention	100.0%	100.0%	100.0%	100.0%	100.0%
		% of Total	6.7%	43.3%	15.0%	35.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	.159[a]	3	.984	1.000
Likelihood Ratio	.156	3	.984	1.000
Fisher's Exact Test	.427			.968
McNemar-Bowker Test	.	.	.[b]	
N of Valid Cases	60			

a. 3 cells (37.5%) have expected count less than 5. The minimum expected count is 1.13.

b. Computed only for a PxP table, where P must be greater than 1.

Cross Tabulation-3: Nationlity vs. Intervention

Nationality * Intervention Cross-tabulation

Total	Intervention						
	3	2	1	0			
13	0	1	11	1	Count	2.00	Nationality
13.0	2.0	4.6	5.6	.9	Expected Count		
100.0%	.0%	7.7%	84.6%	7.7%	% within Nationality		
21.7%	.0%	4.8%	42.3%	25.0%	% within Intervention		
21.7%	.0%	1.7%	18.3%	1.7%	% of Total		
47	9	20	15	3	Count	1.00	
47.0	7.1	16.5	20.4	3.1	Expected Count		
100.0%	19.1%	42.6%	31.9%	6.4%	% within Nationality		
78.3%	100.0%	95.2%	57.7%	75.0%	% within Intervention		
78.3%	15.0%	33.3%	25.0%	5.0%	% of Total		
60	9	21	26	4	Count	Total	
60.0	9.0	21.0	26.0	4.0	Expected Count		
100.0%	15.0%	35.0%	43.3%	6.7%	% within Nationality		
100.0%	100.0%	100.0%	100.0%	100.0%	% within Intervention		
100.0%	15.0%	35.0%	43.3%	6.7%	% of Total		

Chi-Square Tests

Point Probability	Exact Sig. (1-sided)	Exact Sig. (2-sided)	Asymp. Sig. (2-sided)	df	Value	
		.006	.006	3	12.578(a)	Pearson Chi-Square
		.003	.002	3	14.754	Likelihood Ratio
		.004			11.980	Fisher's Exact Test
.002	.003	.004	.004	1	8.210(b)	Linear-by-Linear Association
					60	N of Valid Cases

a 4 cells (50.0%) have expected count less than 5. The minimum expected count is .87.
b The standardized statistic is -2.865.

Phase 2: The Relationship between Determinants & COI

Age vs. COI: Correlation Analysis

Correlations

			Age_y	SR
Spearman's rho	Age_y	Correlation Coefficient	1.000	.467(**)
		Sig. (2-tailed)	.	.000
		N	60	60
	SR	Correlation Coefficient	.467(**)	1.000
		Sig. (2-tailed)	.000	.
		N	60	60

** Correlation is significant at the 0.01 level (2-tailed).

Nationality vs. COI: Mann-Whitney Test

Ranks

	Nationality	N	Mean Rank	Sum of Ranks
SR	1.00	47	33.87	1592.00
	2.00	13	18.31	238.00
	Total	60		

Test Statistics(a)

	SR
Mann-Whitney U	147.000
Wilcoxon W	238.000
Z	-2.844
Asymp. Sig. (2-tailed)	.004

a Grouping Variable: Nationality

Difference in COI Means in DFDs Groups:

One-Way ANOVA Test:

1- One way

Descriptives

SR

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
0	4	10278.75	480.683	240.342	9513.88	11043.62
1	26	17276.00	5396.722	1058.384	15096.22	19455.78
2	21	35892.33	6109.515	1333.205	33111.32	38673.35
3	9	85921.67	24399.183	8133.061	67166.79	104676.54
Total	60	33622.08	26067.073	3365.245	26888.24	40355.92

Test of Homogeneity of Variances

SR

Levene Statistic	df1	df2	Sig.
12.204	3	56	.000

ANOVA

SR

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	33852152781.167	3	11284050927.056	101.301	.000
Within Groups	62378930043.417	56	111390947.204		
Total	40090045824.583	59			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: SR
LSD

(I) Intervention	(J) Intervention	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Upper Bound	Lower Bound
0	1	-6997.250	5668.510	0.222	-18352.64	4358.14
	2	-25613.583(*)	5757.783	0.000	-37147.81	-14079.36
	3	-75642.917(*)	6342.279	0.000	-88348.03	-62937.80
1	0	6997.250	5668.510	0.222	-4358.14	18352.64
	2	-18616.333(*)	3096.546	0.000	-24819.46	-12413.21
	3	-68645.667(*)	4081.794	0.000	-76822.48	-60468.85
2	0	25613.583(*)	5757.783	0.000	14079.36	37147.81
	1	18616.333(*)	3096.546	0.000	12413.21	24819.46
	3	-50029.333(*)	4204.890	0.000	-58452.74	-41605.93
3	0	75642.917(*)	6342.279	0.000	62937.80	88348.03
	1	68645.667(*)	4081.794	0.000	60468.85	76822.48
	2	50029.333(*)	4204.890	0.000	41605.93	58452.74

* The mean difference is significant at the .05 level.

2- Kruskal Wallis Test

NPar Tests

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
SR	60	33622.08	26067.073	9859	141386	14582.75	27817.50	38916.00
Intervention	60	1.58	.829	0	3	1.00	1.50	2.00

Ranks

	Intervention	N	Mean Rank
SR	0	4	2.50
	1	26	17.50
	2	21	41.00
	3	9	56.00
	Total	60	

Test Statistics[a,b]

	SR
Chi-Square	51.467
df	3
Asymp. Sig.	.000

a. Kruskal Wallis Test

b. Grouping Variable: Intervention

Test Statistics[b]

	SR
N	60
Median	27817.50
Chi-Square	60.000[a]
df	3
Asymp. Sig.	.000

a. 4 cells (50.0%) have expected frequencies less than 5. The minimum expected cell frequency is 2.0.

b. Grouping Variable: Intervention

Phrasing Test Result: *Debridement level is significantly the most frequently encountered intervention (26=43.3%), followed by minor amputation (21=35%), major amputation 9=15.5%, and least was conservative treatment alone (4=6.7%) [H(df=3) = 51.5, p<0.001].*

Multiple Logistic Regression Analysis: *Cost <35000 and >35000*

Case Processing Summary

Unweighted Cases [a]		N	Percent
Selected Cases	Included in Analysis	60	100.0
	Missing Cases	0	.0
	Total	60	100.0
Unselected Cases		0	.0
Total		60	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
1.00	0
2.00	1

Categorical Variables Codings

		Frequency	Parameter coding (1)
Sex Nominal	f	17	1.000
	m	43	.000

Block 0: Beginning Block

Classification Table[a,b]

			Predicted		
			Cost Category		Percentage Correct
	Observed		1.00	2.00	
Step 0	Cost Category	1.00	41	0	100.0
		2.00	19	0	.0
	Overall Percentage				68.3

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	-.769	.278	7.680	1	.006	.463

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	Sex(1)	.144	1	.704
		Age	8.510	1	.004
	Overall Statistics		8.552	2	.014

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	12.511	2	.002
	Block	12.511	2	.002
	Model	12.511	2	.002

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	62.408[a]	.188	.264

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	6.505	8	.591

Contingency Table for Hosmer and Lemeshow Test

		Cost Category = 1.00		Cost Category = 2.00		
		Observed	Expected	Observed	Expected	Total
Step 1	1	6	5.880	0	.120	6
	2	5	5.491	1	.509	6
	3	5	4.334	0	.666	5
	4	4	3.220	0	.780	4
	5	3	4.691	3	1.309	6
	6	3	2.779	1	1.221	4
	7	5	4.648	2	2.352	7
	8	6	5.284	4	4.716	10
	9	1	2.045	4	2.955	5
	10	3	2.627	4	4.373	7

Classification Table[a]

			Predicted		
			Cost Category		Percentage
	Observed		1.00	2.00	Correct
Step 1	Cost Category	1.00	37	4	90.2
		2.00	11	8	42.1
	Overall Percentage				75.0

a. The cut value is .500

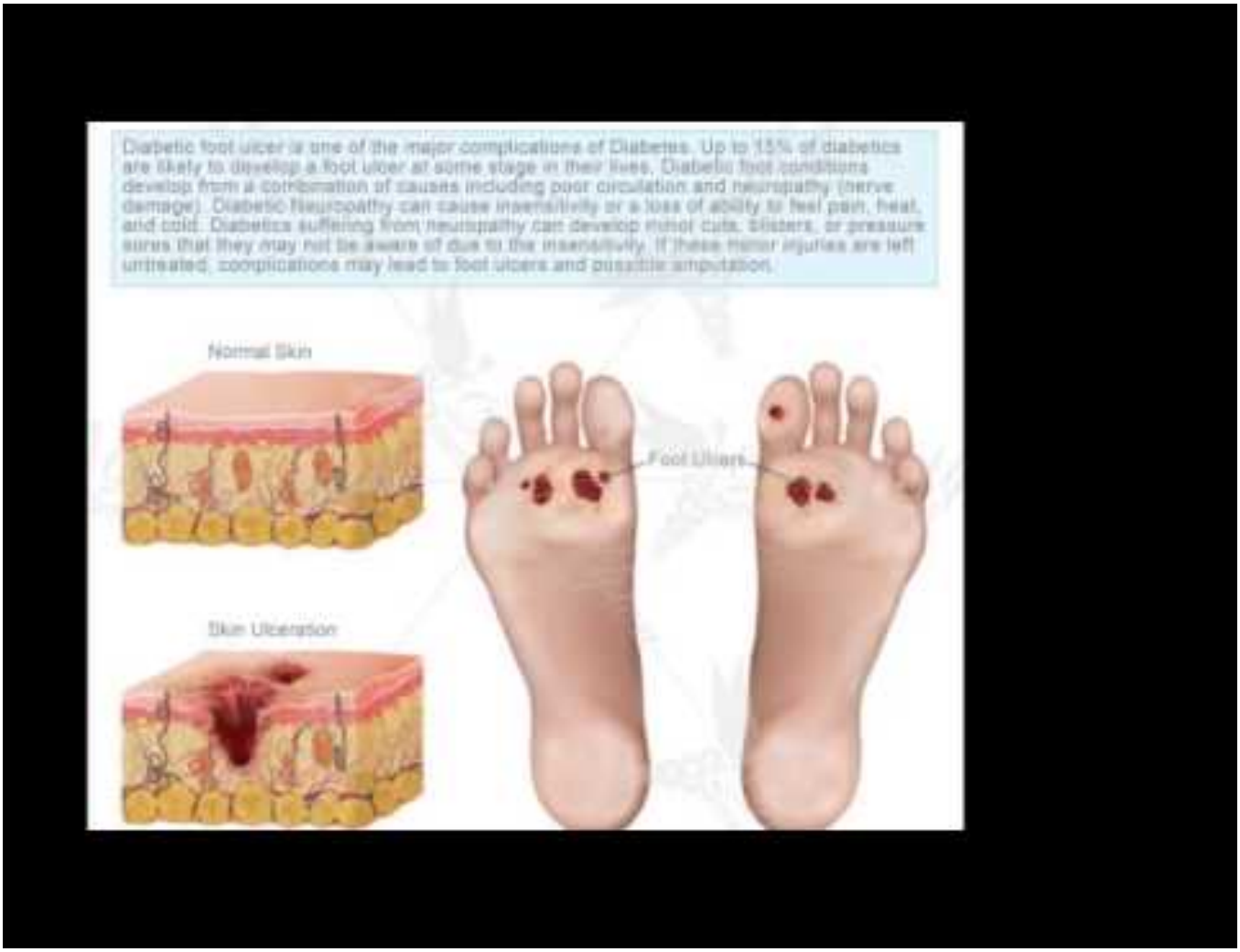
Variables in the Equation

								95.0% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	Sex(1)	-.141	.667	.045	1	.832	.868	.235	3.209
	Age	.596	.210	8.003	1	.005	1.814	1.201	2.740
	Constant	-35.221	12.262	8.250	1	.004	.000		

a. Variable(s) entered on step 1: Sex, Age.

Appendix E

Diabetic Foot Ulcer



Cited: ICD-9 Code Diabetic Foot Care
http://www.smilediabetic.com/icd-9-code-diabetic-foot-care

Appendix F

Thesis Timeline

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Starting	February		March		April		May		June		July		August			September			Oct.
	1	15	1	22	1	15	1	15	1	15	1	15	1	16	30	1	11	22	1
Preparation for master thesis																			THESIS END
Writing the proposal of master thesis																			
Application for master thesis																			
Data collection																			
Initial analysis																			
Literature review I																			
Methodology																			
Final analysis																			
Literature review II																			
Discussion																			
Conclusion																			
Introduction																			
Abstract																			
Revision and corrections																			
Final revision																			
Printing																			
Submission of Master thesis																			