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FACTORS RELATED TO THE GRADE OF DIABETIC FOOT ULCERS AMONG DIABETIC PATIENTS ADMITTED TO AUBMC

by
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AN ABSTRACT OF THE THESIS OF

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Title: Factors Related to the Grade of Diabetic Foot Ulcers among Diabetic Patients Admitted to AUBMC

Background
Diabetic foot ulcers are a significant complication of Diabetes Mellitus (DM) and often result in lower-extremity amputations. Today, diabetic foot complications are contributing to both mortality and morbidity among the diabetic population resulting in considerable physical, physiological and financial burden for the patients and their communities. It has been estimated that the Middle East and North Africa (MENA) region, in addition to the Gulf Cooperation Council (GCC), will have the second highest increase in percentage of people with DM by 2030, as compared to other parts of the world. More specifically, DM affects almost 13% of the Lebanese population over 25 years of age and therefore, it has become a significant source of morbidity and mortality risk among diabetic patients in Lebanon.

Objective: This study aims at investigating the association between social, economic and health-related factors associated with diabetic foot ulcer severity.

Methodology: A secondary analysis of a cross-sectional study of 278 diabetic patients admitted with diabetic foot ulcer at the American University of Beirut Medical Center (AUBMC). The investigated predictors included socio demographic variables (age, weight, gender, etc.), patients health history (type of Diabetes, smoking status, hypertension, chronic kidney disease, etc.), and lab values (HbA1c, HDL, BUN, SGOT, etc.). Association between different covariates and the outcome of DFU severity was studied in an ordinal approach using cumulative logit models with proportional odds property. Statistical analysis was performed using SPSS version 24 and STATA version 13.

Results
The mean age of patients was 66 years. Male represented 70% of the study population. Majority of patients (73%) were non-smokers at the time of the study. Out of the 278 patients, 98% had Type II Diabetes, 63% had DM for more than 10 years, 20% had past DFU on a different site than the current one, 81% were hypertensive, 66% were dyslipidemic, 30% had chronic kidney disease, 43% had CAD, 24% had CHF and 6% had COPD. Bivariate analysis showed that Nationality, residence, financial status, past foot ulcer of the same site, past amputation, duration of diabetes mellitus were significantly associated with the severity of Diabetic foot ulcer. Multivariable ordered

regression showed that area of residence, nationality, duration of diabetes mellitus, and chronic kidney disease were significantly associated with severity and grade of DFU.

Conclusion: With type 2 diabetes mellitus being by far the most common type of diabetes and risk factors associated with the grade of DFU not being well identified internationally and not in Lebanon, this study offers insights into the risk factors associated with the severity of DFU. In this regard, our results confirm the higher prevalence of men with a history of DFU than women in accordance with previous studies. Severity of DFU had direct correlation with the residence area, history of past amputation, duration of Diabetes Mellitus and chronic kidney disease. . Study findings can set the foundation for future national, regional and international studies that can be conducted on a larger scale.

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CHAPTER I

INTRODUCTION

The American Diabetes Association defines diabetes as "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both." The prolonged hyperglycemia in diabetic patients is correlated with long term consequences that could lead to severe and long-term health complications and organ malfunctioning (Diagnosis and Classification of Diabetes Mellitus, 2014).

Among the long-term complications of diabetes is peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joint. Today, diabetic foot complications are contributing to both mortality and morbidity among the diabetic population resulting in considerable physical, physiological and financial burden for the patients and their communities (Al-Rubeaan, et al., 2015).

Foot ulcers are a significant complication of Diabetes Mellitus (DM) and often result in lower-extremity amputations (Frykberg, 2002). These are cutaneous erosions characterized by "a loss of epithelium that extends into or through the dermis to deeper tissues. Ulcers result from various etiologic factors and are characterized by an inability to self-repair in a timely and orderly manner" (Reiber, Lipsky, & Gibbons, 1998).

Diabetes mellitus is a widely prevalent health issue that results in substantial health and economic outcomes. In fact, diabetes mellitus is prevailing today as one of the most common chronic diseases in all countries (Shaw, Sicree, & Zimmet, 2010). Its numbers have been increasing significantly in the past few years. The worldwide prevalence of diabetes was estimated to be 6.4% among adults (18+) in 2010 only to reach 8.4% in 2017 (Yazdanpanah, et al., 2018), a rate that is forecast to increase further in 2030, notably in low- and middle-income countries (Shaw, Sicree, & Zimmet, 2010) (Guariguata, et al., 2014). Repeated trauma to lower extremities in a diabetic patient in unison with peripheral arterial disease and decreased wound healing leads to the formation of foot ulcers. The reported prevalence of DFUs is estimated to be 4-10%, and lifetime incidence has been estimated to be as high as 25% among Diabetics (Singh, Armstrong, & Lipsky, 2005), (Reiber, Lipsky, & Gibbons, 1998). DFU infections can be difficult to treat and may extend into soft tissues to cause cellulitis or abscess formation, or into bone to cause osteomyelitis. Within the Diabetic population, 85% of lower-limb amputations are preceded by DFU.

Furthermore, statistical studies show that there will be an increase of 69% and 20% in numbers of adults with diabetes both in developing and developed countries, respectively (Sweileh, Zyoud, Al-Jabi, & Sawalha, 2014). It has also been estimated that the Middle East and North Africa (MENA) region, in addition to the GCC, will have the second highest increase in percentage of people with DM by 2030, as compared to other parts of the world (Sweileh, Zyoud, Al-Jabi, & Sawalha, 2014). Currently, DM affects almost 13% of the Lebanese population over 25 years of age and therefore, it has become a significant source of morbidity and mortality risk among diabetic patients in Lebanon (Lebanon: WHO Statistical Profile , 2015). Nonetheless, the risk factors and covariates that associate with the grade of DFU are yet to be identified in the country and worldwide.

Among the multitude of diabetes complications addressed in Literature, DFUs and amputations are the most prevalent (Cho, et al., 2018). There has also been an association between insulin treatment and the development of DFU in one study (Monteiro- Soares, Boyko, Ribeiro, Ribeiro, & Dinis- Ribeiro, 2012), whereas a cross-sectional study showed that distal neuropathy is an important risk factor in the development of DFUs (Parisi, et al., 2016). Other studies showed that foot deformities such as hammer toe, hallux valgus, bunion, and prominent metatarsal head were significant risk factors for the development of DFUs (Al-Rubeaan, et al., 2015).

This study assesses the association between severity of DFU and covariates that include socio-demographic characteristics (age, gender, BMI, health and medical history (smoking status, diabetes duration, CKD, Dyslipidemia, CAD) and laboratory studies comprising HbA1c, lipid profiles, Blood Urea Nitrogen (BUN) and Creatinine.

A. Aim

The objective of this study is to investigate the association between socio-demographic and health-related factors associated with diabetic foot ulcer severity in a study population of patients with DFU presenting to the American University of Beirut Medical Center (AUBMC). This would help better understand the current and future status of the severity of DFU, a diabetes related complication in the MENA region and Lebanon in particular. The study findings would serve to assist health practitioners and policy makers outline preventive methods for better prognosis of diabetic foot ulcer patients.

B. Research question

What are the different factors related to the severity of diabetic foot ulcer disease amongst patients with DFU presenting to AUBMC?

C. Significance

This study will be one of the first to target Lebanese population with diabetic foot complications and will explore potential risk factors affecting the grade of Diabetic Foot Ulcer disease. Moreover, it will serve as pilot study for cooperation between different medical centers and Ministry of Health to establish national guidelines for effective prevention and management of these complications.

Diabetes is an epidemic problem not only in Lebanon but more so in the Arab region. According to a study published in 2011 in The Journal of Diabetic Foot Complications, Arab countries were amongst the top ten in prevalence of diabetes worldwide, and the complications resulting from diabetes are rising dramatically due to several factors common to the region (Ahmed, Elsharief, & Alsharief, 2011). Therefore, the findings of this study may result in preventive measures and management guidelines that can benefit Lebanon and the entire Arab region.

CHAPTER II

LITERATURE REVIEW

A. The Epidemiology and Burden of Diabetic Foot Disease

1. At the Global Level

Diabetes is cited as one of the most common metabolic disorders in the world, and diabetes mellitus one of the most common chronic diseases in both developed and developing countries (Jenkins, Klein, & Januszewski, 2014), one of the leading causes of limb loss, currently affecting 382 million people worldwide (Obeid, et al., 2018) (Merheb, Gharios, Younes, Cheikh, & Chaaban, 2017). While more than 60% of the diabetic patients are reported to live in Asia (Adab, et al., 2019), the frequency of the disease is found to be increasing continuously in parallel with shifting lifestyles leading to “reduced physical activity, and increased obesity” (J.E. Shaw, 2010). Type 2 diabetes mellitus (T2DM) accounts for 87-95% of all diabetes cases globally (Adimoolam, Muthukrishnan, & B.Albu, 2017). Studies show that the prevalence of diabetes is expanding as fast as its complications; diabetic foot being amongst the most challenging complications to address, both in developed as well as developing countries (Yazdanpanah, et al., 2018). The World Health Organization (WHO) expects diabetes mellitus to be the seventh leading cause of death by 2030 (Obeid, et al., 2018).

Furthermore, research estimates that 24.4% of the total health care expenditure amongst diabetes is related to foot complications. A study conducted in Iran reveals that 10.7% of the total costs of diabetes complications in the country are associated with diabetic foot, accounting to USD 107.1 Billion (Yazdanpanah, et al., 2018), whereas the costs of treating the latter are estimated at USD 11 Billion and USD 456 Million in the United States and the United Kingdom, respectively (Al-Rubeaan, et al., 2015). More specifically in the United States, the diabetic foot and its sequelae account for billions of dollars in medical expenditure (Frykberg, 2002).

Of the total number of diabetics, 20-25% are subject to developing foot ulcer (Yazdanpanah, et al., 2018). Moreover, “85 percent of all diabetes-related lower-extremity amputations are preceded by foot ulcers” (Frykberg, 2002) (Obeid, et al., 2018). Diabetes in general is the leading source of over half of non-traumatic lower limb amputations (Yazdanpanah, et al., 2018). In fact, it is suggested that foot illnesses such as ulceration, infection, and gangrene are the primary reasons of hospitalization in patients with diabetes mellitus (Frykberg, 2002). For instance, in the United States, 15-20% of the patients of diabetes mellitus are hospitalized due to a foot complication, while many require an amputation as a consequence of severe infection, neuropathy or peripheral ischemia (Frykberg, 2002).

With a rate of one lower limb amputation every 30 seconds in the world (Yazdanpanah, et al., 2018), adding to “both mortality and morbidity” among diabetics, this reality inflicts significant physical, physiological, and financial affliction both for patients and their communities (Al-Rubeaan, et al., 2015). Moreover, it results in DFU becoming a major global health problem and among the main challenges for health care systems around the world. For instance, along with Pacific island nations led by Tokeloau, Saudi Arabia, Kuwait and Qatar head the list of the highest prevalence country rates, well above the global prevalence of 8.3% (Guariguata, et al., 2014).

It is thus suggested that, given that the growth of foot ulcers and amputations are avertable, where simple interventions can decrease amputation by 70%, it is important to shed the light on the importance of prevention of this problem, for it alleviates direct and indirect cost burdens on society (Yazdanpanah, et al., 2018). Moreover, the identification of risk factors and their role/ function within the context of DFU allows health providers to enhance their prevention systems, thus improving patients' quality of life, and reducing the economic burden for both the patient, and the healthcare system (Al-Rubeaan, et al., 2015).

2. At the Regional Level – Middle East & North Africa

While an increase of 69% and 20% in number of adults with diabetes in developing and developed countries, respectively, is forecast between 2010 and 2030, the second highest increase in percentage of DM patients is forecast for the Middle East and North Africa (MENA) region in 2030, as compared to other parts of the world (Sweileh, Zyoud, Al-Jabi, & Sawalha, 2014).

As a matter of fact, the MENA is reported to have the highest prevalence of diabetes (Merheb, Gharios, Younes, Cheikh, & Chaaban, 2017), and diabetes mellitus is reported as a significant cause of mortality and morbidity in the region, where the highest global comparative prevalence of diabetes occurs, ranging from 8% to 24%, and where the number of diabetic adults is estimated to reach 67.9 million, approximately (Costanian, Bennett, Hwalla, Assaad, & Sibai, 2014). Moreover, according to International Diabetes Federation (IDF), "six out of the world's top ten countries for highest prevalence of diabetes are in the Middle East and North Africa Region"

(Sweileh, Zyoud, Al-Jabi, & Sawalha, 2014); and the MENA region has witnessed an upsurge in cardiovascular risk factors, further contributing to the diabetes epidemic (Costanian, Bennett, Hwalla, Assaad, & Sibai, 2014).

While international health care organizations consider self-management to be “a core component” of diabetes care, a review conducted in the MENA region has revealed that amongst diabetic patients, more than 50% do not meet the recommended care targets, resulting in the occurrence of diabetes complications (Costanian, Bennett, Hwalla, Assaad, & Sibai, 2014).

For instance, the prevalence of diabetic foot complications in Saudi population has reached the international means, and DFU are reported to contribute to more than 50% of the total diabetic foot cases (Al-Rubeaan, et al., 2015), while over 10% of adult deaths in the Middle East are diabetes-related (Sweileh, Zyoud, Al-Jabi, & Sawalha, 2014). Also, some studies have shown that diabetes related complications are common in the Arab world with a higher prevalence in eastern Arab countries (Obeid, et al., 2018) such as Saudi Arabia (23.9%), UAE (19.0%), and Egypt (16.8%), as well as other neighboring countries such as Syria (15.6%) and Jordan (17.1%). In this regard, a study conducted on patients in the Middle East reported a major short come as to diabetes education, where around 40% of participants had not received any, calling for an intensive focus on diabetes education and teaching, notably for patients with T1DM (Gagliardino, et al., 2019). Hence, the control of diabetes-related death and disorders in the MENA region calls for a better understanding of the progress of the respective countries’ diabetes scientific research, so as to be able to effectively develop a response plan and gather the necessary support, both public and political.

3. At the National Level – Lebanon

According to the International Diabetes Federation (IDF), Lebanon is among the world's top ten countries for highest prevalence of diabetes (Sweileh, Zyoud, Al-Jabi, & Sawalha, 2014), where 20.2% of the Lebanese population suffers from diabetes, causing approximately 4,525 mortalities per year (Merheb, Gharios, Younes, Cheikh, & Chaaban, 2017), with diabetic foot ulcers being one of the utmost severe infections in Lebanon (Obeid, et al., 2018).

As a matter of fact, the rapid urbanization that the country is going through, coupled with the population growth, economic transition, and high rates of physical inactivity, obesity, and metabolic syndrome, have contributed to it being at the front of the epidemiological transition, where diabetes is one of the leading causes of morbidity and mortality (Costanian, Bennett, Hwalla, Assaad, & Sibai, 2014).

The prevalence of diabetes mellitus in Lebanon was reported to be 8.5% in 2014, comparable to the 2013 world estimate of 8.3%, as well as to those of the United States and Canada, reported at 10.9% and 8.0%, respectively (Costanian, Bennett, Hwalla, Assaad, & Sibai, 2014). While the high rates are directly associated with obesity and family history of diabetes and physical inactivity, they are still lower than those of other countries in the region. Today, diabetes mellitus is estimated at approximately 15.8% among Lebanese adults, a percentage that is still close to those of industrialized countries, but lower than those of neighboring countries such as Bahrain (25.5%), United Arab emirates (23.3%) and Kingdom of Saudi Arabia (23.7%) (Karaoui, Deeb, Nasser, & Hallit, 2018).

Epidemiological data about etiology and susceptibility profiles of bacteria that cause DFU remain scarce in Lebanon. Depending on the health care practitioner, both American and European guidelines are available for treatment of DFU (Obeid, et al., 2018). Nevertheless, a study conducted on Lebanese diabetes patients tackled the most common organisms isolated from DFU infections and their susceptibility to specific drugs and treatment regimens. The results obtained call for a screening of local DFU susceptibilities in the neighboring countries rather than the automatic resort to American and European guidelines which do not certainly apply in this context, given that the epidemiology of DFU varies among countries, hence the importance of local guidelines for treating foot infections in Lebanon. On a different note, research findings report a limited or poor knowledge and practice about DM, which also calls to the development of health awareness and counseling programs at the Lebanese community level (Karaoui, Deeb, Nasser, & Hallit, 2018).

B. The Determinants and Risk Factors of Diabetic Foot Disease

Although DFU is recognized as a multifactorial disorder, its pathophysiology is still ambiguous, whereas it has been established that both genetic and environmental factors may be implicated in the development of DFU (Palatini, 2018). It therefore reveals difficult to achieve an accurate global prevalence of risk factors and complications associated with DFU, for there exists no standards agreed upon internationally as to how to diagnose and assess diabetes complications. It has been however reported that the majority of patients with T2DM suffer from at least one complication at the time of diagnosis (Adimoolam, Muthukrishnan, & B.Albu, 2017).

Those complications at large are believed to be the culmination of long-term exposure to elevated-blood glucose, coupled with associated risk factors such as elevated blood pressure, as well as other components of the metabolic syndrome (Adimoolam, Muthukrishnan, & B.Albu, 2017). This part will mainly explore the risk factors included in our study, as well as highlight other important components.

1. Socio-Demographics

According to the International Diabetes Federation (IDF) statistics, more people with diabetes live in urban than in rural areas (269.7 million and 145.1 million, respectively). This pattern is even applicable in low- and middle-income countries (Guariguata, et al., 2014); where over 80% of deaths among diabetic patients occur (Obeid, et al., 2018).

Moreover, the risk of developing DFU and amputation among diabetic patients is shown to increase with age (Al-Rubeaan, et al., 2015). Countries with large adult populations were reported to have high numbers of diabetics: eight of the ten most populated countries in the world take place in the top ten countries with the highest number of adults with diabetes. For instance, China and India mark the highest numbers of people with diabetes with over 98.4 million and 65.1 million adults affected, respectively. Moreover, while studies including both developed and developing countries have reported a poor diabetes-related knowledge among DM patients, research show a negative correlation between age and both the level of understanding of diabetes mellitus and the practice score (Karaoui, Deeb, Nasser, & Hallit, 2018).

On the other hand, the prevalence of male patients developing DFU has been noted in several studies (68.57% versus 31.43% in women) and attributed to different factors, such as diabetes severity at the time of diagnosis (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013), level of exposure to trauma (Al-Rubeaan, et al., 2015) and outdoor activity (Yazdanpanah, et al., 2018).

Also, DFU is reported to be an expensive problem, where the socio-economic burden of diabetic patients on the health care system is significant (Reiber, Lipsky, & Gibbons, 1998); this is notably due to high treatment costs and lost productivity (Karaoui, Deeb, Nasser, & Hallit, 2018), with the "major driver" of diabetes costs being the treatment of its complications and where estimates suggest that healthcare costs among diabetic patients are twice those in people without diabetes (Cho, et al., 2018). Furthermore, studies suggest that there exists a significant fluctuation in the pattern of diabetes depending on countries' economic statuses. While more than 80% of diabetic patients live in low- and middle-income countries (Merheb, Gharios, Younes, Cheikh, & Chaaban, 2017), the majority of diabetic patients are of working age in developing countries, whereas they are over 60 years in developed countries (J.E. Shaw, 2010). Al-Rubeaan also notes that DFU cases were considerably older than the non-affected diabetic patients and had considerably lower BMI (Al-Rubeaan, et al., 2015).

Additionally, cases of Diabetes are forecasted to increase by 54% by 2030, due to factors such as urbanization, and population growth (J.E. Shaw, 2010). Married cases accounted for 91.45% of the total number of cases, and smoking was significantly higher among DFU cases (Al-Rubeaan, et al., 2015).

On a national level and with regards to health expenditure, the World Health Organization reports that of the total health expenditure, 36.4% of the health financing in Lebanon is out-of-pocket expenditure (EMRO, 2016); whereas El-Jardali et al. (2014) report out-of-pocket expenditure in Lebanon to have reached 56.5%, a percentage that is “considered catastrophic by WHO”.

Other factors include the educational level and job activity (Yazdanpanah, et al., 2018). A study conducted in Lebanon suggests that the risk of diabetes increases with a low educational level, as well as with marriage and divorce, a fact that is explained by parenting stress and the stresses of separation and bereavement in the development of diabetes (Costanian, Bennett, Hwalla, Assaad, & Sibai, 2014). A correlation has also been reported between diabetes-related knowledge and medication adherence in DM patients. Several studies conducted on patients with diabetes mellitus reported limited knowledge of the medication, its mode of action as well as side effects, especially in patients on multidrug regimens (Karaoui, Deeb, Nasser, & Hallit, 2018). Examples from the United Kingdom and Germany revealed that teaching and awareness programs lead to reduction in the number of severe hypoglycemic episodes and improvement of quality of life in addition to a reduction in costs and emotional outcomes (Gagliardino, et al., 2019).

The increase in prevalence of diabetes mellitus is also attributed to shifts in lifestyle risk behaviors due to urbanization, which is frequently associated with inactive and unhealthy lifestyles (Karaoui, Deeb, Nasser, & Hallit, 2018).

2. Health Factors

a. History

The risk of developing DFU and amputation among diabetic patients is thought to increase by two to four folds with the duration of diabetes. The latter was shown to be significantly higher in DFU and amputation cases compared with the non-affected diabetic patients (Al-Rubeaan, et al., 2015).

As per Yazdanpanah et al.'s study, previous history of diabetic foot ulcer or amputation was the main risk factor recorded, provided that diabetic patients with a history of foot ulcer may be prone to developing different micro- and macrovascular dysfunctions, as well as peripheral neuropathy (Yazdanpanah, et al., 2018). In fact, microvascular and macrovascular changes in patients with diabetes contribute to nerve damage of different degrees, coupled with the occurrence of impaired circulation in the lower limbs which could lead to the development of ulcerations, pathological fractures and bone damage and, at a later stage, infections and amputations (Adimoolam, Muthukrishnan, & B.Albu, 2017).

b. Chronic Diabetes Complications

Chronic diabetes complications, namely retinopathy and nephropathy were reported as more prevalent in diabetic foot patients than in non-affected diabetics (Al-Rubeaan, et al., 2015), (Yazdanpanah, et al., 2018) and were considerably associated with both foot ulcers and amputations (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013). The incidence frequency of chronic complications was reported as considerably higher among diabetic foot cases, notably neuropathy, touching 61.98% of foot ulcer cases. Studies have outlined that more than half of amputation, ulcer and gangrene incidents occurred in hypertensive patients, and those with significantly lower BMI (Al-Rubeaan, et al., 2015).

These complications are irreversible once they occur (Karaoui, Deeb, Nasser, & Hallit, 2018). As a matter of fact, Reiber reports that the majority, if not all diabetic patients who develop classic foot ulcers suffer from peripheral neuropathy, in degrees that reveal to be clinically significant (Reiber, Lipsky, & Gibbons, 1998).

It is also worthy of noting that high retinopathy rates were observed in patients with increased diabetes durations, poor glycemic control, inadequate blood pressure control and poor liquid control. Following up, retinopathy is reported to be possibly present at the time of diagnosis, and to progress fast to an advanced phase before vision is affected. As a matter of fact, it is possible to develop retinopathy as early as seven years before diabetes is diagnosed in patients with T2M (Adimoolam, Muthukrishnan, & B.Albu, 2017), a fact that calls for regular screenings and early diagnosis and intervention techniques so as to prevent or reverse loss of vision.

Distal neuropathy was also reported as a “well-known” risk factor; in the event of which, studies recommend the use of 10 g monofilament (Yazdanpanah, et al., 2018)**.**

c. Glycemic Control

Moreover, several studies reported a connection between DFU and insulin: diabetics on insulin therapy were found to be more susceptible to developing foot ulcer than patients on an oral treatment or subject to a lifestyle modification alone (Yazdanpanah, et al., 2018). Following up on glycemic control, it has been reported that a poor glycemic control is correlated with severe long term complications, which could greatly affect quality of life and increase the costs of the disease (Gagliardino, et al., 2019). On the other hand, a strict glycemic control could lead to the prevention of nerve damage (Adimoolam, Muthukrishnan, & B.Albu, 2017). Moreover, in order to lessen the risk of occurrence and progression of chronic complications, intensive insulin therapy coupled with dose adjustments based on self-monitoring blood glucose measurement has been advised, despite its difficulty in terms of the complexity and demands of diabetes self-management (Gagliardino, et al., 2019).

d. Lipid Profile

A well-known risk factor for cardiovascular disease, diabetes mellitus triggers dyslipidemia in its patients (Minhua, Yuelan, & Shihong, 2016). Dyslipidemia, inflammation, and oxidative stress are the major risk factors of atherosclerosis and cardiovascular diseases (Adab, et al., 2019). Studies' findings suggest the existence of abnormal lipoprotein metabolism in diabetes, even in patients who are in relatively good glycemic control and whose plasma lipid and lipoprotein levels are normal (Klein, 2013).

Resistance to insulin, as well as impaired insulin function can be a cause of dyslipidemia in diabetic patients (Adab, et al., 2019), characterized high serum triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), as well as total cholesterol (TC), and reduced serum high-density lipoprotein cholesterol (HDL-C) concentration (Minhua, Yuelan, & Shihong, 2016), (Adab, et al., 2019).

Research also addresses the role of plant-based compounds in reducing insulin resistance, oxidative stress and diabetes-related chronic inflammation. For instance, Adab et al. (include year for referencing purposes) address the properties of turmeric's (Curcuma longa) main compound, curcumin, and its manifold pharmacological actions, for it inhibits the development of oxygen free radicals and has antioxidant properties, which makes it a potential "effective" compound in reducing diabetes complications (Adab, et al., 2019). Research findings were that turmeric produced a substantial decrease in serum triglycerides and LDL-c in hyperlipidemic patients of type 2 diabetes, while also preventing the increase in serum total cholesterol. It has also been noted that it is probable that turmeric leads to an elevation in cholesterol catabolism leading to an improvement in dyslipidemia, where various studies have shown the role of curcumin in the prevention of fatty acid synthase enzyme activity and the increase in fatty acids β-oxidation, as such, reducing fat storage and regulating lipid metabolism (Adab, et al., 2019).

In the aim of improving the quantitative and qualitative changes in lipoproteins contributing to the microvascular and macrovascular complications in diabetes, as well as developing clinical outcomes, it is therefore of primary importance to understand the cellular metabolism of lipoproteins, with that of the modified lipoproteins that occur in diabetes mellitus (Klein, 2013).

e. <u>Amputations</u>

Studies confirm a relatively high prevalence of amputations in patients of type 2 diabetes, twice in men as much as in women. Among the "major predictors" of amputations were peripheral neuropathy, peripheral arterial disease, diabetic neuropathy, and impaired vision and blindness (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013).

In fact, Brunn et al. (include year) note that major amputations are reflective of a treatment failure, whereas "a sustained minor amputation" is reflective of a successful one, where, however, the risk of re-amputation is existent due to the "developing complex pathology in the diabetic foot" (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013). They also confirm that microalbuminuria, retinopathy and impaired vision are significant predictors with regard to amputations (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013).

f. <u>Other Factors</u>

Other factors such as foot deformity, were reported as a risk factor applicable only in a univariate analysis (Yazdanpanah, et al., 2018). The presence of Charcot joint was also reported as the most prevalent and significant risk factor "when all types of diabetic foot conditions were included", for it considerably increases the risk of DFU and amputation (Al-Rubeaan, et al., 2015).

Those also include cardiovascular diseases (CVD), reported to be at the origin of the majority of death and disability cases among patients with diabetes, with a two to four fold increased risk of CVD in T2DM versus non- diabetics (Adimoolam, Muthukrishnan, & B.Albu, 2017). The CVD accompanying diabetes includes angina, myocardial infarction, cerebrovascular disease and stroke, peripheral arterial disease, and congestive heart failure. Diabetes is also one of the primary causes of chronic kidney disease, which is triggered by hyperglycemia-related microvascular perturbations in the kidney, leaving place to a gradual decrease in renal function, resulting in renal failure. Among the primary risk factors of chronic kidney disease are smoking, hypertension and dyslipidemia. In fact, diabetes mellitus is an established risk factor for numerous causes of death such as renal disease, ischemic heart disease, strokes, infectious diseases and several cancers. Evidence also suggests that DFU carries a greater risk of premature death (Brownrigg, et al., 2014). Those factors will be further addressed and analyzed in our study.

CHAPTER III

METHODOLOGY

A. Study Design

A secondary analysis of a cross-sectional study of 278 diabetic patients admitted with diabetic foot ulcer at the American University of Beirut Medical Center (AUBMC).

B. Data Sources

Data used were adopted from a study entitled **"Diabetic foot complications in a tertiary care center in Lebanon: retrospective study identifying burden and gaps in management"**. The aim of the study was to:

- Understand health-related, social and economic factors leading to development of foot ulcers in Lebanon
- Assess burden of foot ulcers on health-care system and patients
- Identify the gaps in implementing appropriate management
- Outline preventive methods to decrease incidence and burden

Population included diabetic patients with DFUs admitted to the AUBMC between January 2008 and June 2017. Sample of 278 patients is considered with a total of 384 admissions.

<u>Inclusion criteria:</u>

- Patients admitted with DFUs at the American University of Beirut Medical Center (AUBMC) between January 2008 and June 2017.

Exclusion criteria:

- Younger than 18 years of age
- No history or biochemical evidence of diabetes
- Evidence of non-diabetic neurological disorders such as paraplegia
- Patients whose electronic medical records were not available

Medical records from AUBMC of the 278 patients admitted with DFUs were used to retrieve information on demographics, diabetes history, laboratory studies, glycemic control status and ulcer severity.

C. Outcome and covariates

The primary outcome of this study is the grade of the Diabetic Foot Ulcer. The Wagner Grading scheme was used as a classification system to define DFU severity. The scale ranges from 0 to 5 as follows: (Frykberg, 2002)

Table1: Wagner Ulcer Classification System

GRADE	**LESION**
0	No open lesions +/- deformity or cellulitis
1	Superficial ulcer partial/full thickness
2	Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
3	Deep ulcer with abscess, osteomyelitis, or joint sepsis
4	Gangrene localized to portion of forefoot or heel
5	Extensive gangrenous involvement of the entire foot

As shown in Figure 1, the distribution of patients among the six ordinal categories of the Wagner Diabetic Foot Ulcer Grade varied widely. Only four patients had grad 0, 29 had grade 1, 70 had grade 2, 53 had grade 3, 100 had grade 4 and 22 had grade 5. Accordingly, the primary outcome was re-categorized in this study into three levels as such: I (Grades 0 and 1), II (Grades 2 and 3) and III (grades 4 and 5).

Investigated covariates, their types, units of measurement, and cutoffs or categories were summarized in the following table:

Table 2: Description of the covariates of the DFU patients

Variable	Type	Description
Socio-demographic		
Age	Continuous	In years
Weight	Continuous	In Kg
BMI	Continuous	Weight in Kg/ (height in m)^2
Gender	Binary	1= male, 2= female
Nationality	Binary	1= Lebanese, 2=non-Lebanese
Residence	Categorical	1= Beirut, 2=outside Beirut, 3= outside Lebanon
Hospital payment	Binary	1= self payer, 2= insurance
Health History		
Type of DM	Binary	0= type I, 1= type II
Duration of DM	Binary	0= <10 years, 1= > 10 years
DM treatment	Binary	0= oral medication, 1= Insulin
Past diabetic foot ulcer	Categorical	0= none, 1=same site, 2= different site
Current smokers	Binary	0 = never smoked 1= ever smoked
Hypertension	Binary	0 = no, 1= yes
Dyslipidemia	Binary	0 = no, 1= yes
Chronic Kidney Disease	Binary	0 = no, 1= yes
Coronary Artery Disease	Binary	0 = no, 1= yes
Atrial Fibrillation	Binary	0 = no, 1= yes
Congestive Heart Failure	Binary	0 = no, 1= yes
Chronic Obstructive Pulmonary Disease	Binary	0 = no, 1= yes
Lab tests		
HbA_1c	Binary	0 = ≤ 7%, 1= >7%

Total cholesterol	Binary	0 = ≤ 200 mg/dl, 1= > 200 mg/dl
HDL	Binary	0 = Male: >45 mg/dL, Female: >55 mg/dL 1: Male: < 45 mg/dL Female: < 55 mg/dL
LDL	Binary	0 = ≤ 130 mg/dl, 1= > 130 mg/d
Triglycerides	Binary	0 = ≤ 200 mg/dl, 1= > 200 mg/dl
BUN define	Binary	0 = ≤ 25 mg/dl, 1= > 25 mg/dl
Creatinine	Binary	0: Male: ≤1.2 mg/dL Female: ≤1.0 mg/dL 1: Male: > 1.2 mg/dL Female: >1.0 mg/dL

D. Ethical consideration

The original study was IRB approved (SUR.JH.04) from the American University of Beirut prior to the initiation of the study. As for this secondary analysis, the dataset used was de-identified by Dr. Rola Jaafar, the research coordinator of the study. A research assistant student under the supervision of Dr. Rola initially collected the data from the patients' electronic medical charts of AUB and entered them to SPSS with no patients' names. Data entered to SPSS was then provided to us completely de-identified. Confidentiality of the data was maintained by assuring limited access. Only the investigators of the study were allowed to access the de-identified data set in order to perform the statistical analysis.

E. Statistical analysis

Data cleaning was conducted through numerical and graphical display of the data to identify any potential data entry errors, out of range values or outliers using frequency analyses, histograms and range of data. Data cleaning was conducted on SPSS version24.

1. Descriptive Analysis

Descriptive statistics, numerical and graphical, were carried out for all the variables (dependent and independent ones) whereby continuous data was summarized through mean ± SD and categorical data was presented using frequency (N) and valid percent.

2. Bivariate Analysis

Bivariate analysis was used to examine association between the dependent variable (DFU grade) and each of the covariates (independent variables) using STATA version 13. The outcome was ordinal (grades 0, 1, 2, 3, 4, &5) and categorized in an ordered manner as such: grade I (grades 0&1) grade II (grades 2&3) and grade III (grades 4&5).Therefore, cumulative logit model for ordinal response was performed using STATA version 13 to examine the association between each covariate (age, sex, duration of diabetes mellitus, type of DM, ulcer grade, ulcer duration, hypertension, etc.) and DFU grade.

The proportionality of odds was checked and maintained in all models. Unadjusted ORs along with their 95% confidence intervals and p-values were reported. Given that the outcome is ordered in three categories this implies that we have two cutoff points and the proportionality of odds assumption means that the obtained odds ratios could represent any of those two cutoff points. The OR could represent the odds of having a DFU grade that falls into the two higher categories (grades II and III) versus the lowest category grade I or the odds of having a DFU grade within the highest category (grade III) versus the two lower categories (grades I and II). Significance level of $\alpha = 0.05$ was assured. Variables of p-value less than or equal to 0.2 at this level (Bivariate) were eligible to be included in the final multivariable cumulative logit ordered model.

3. Multivariable analysis

Proportional odds model (ordered logit model) was performed to model the DFU grade outcome. Covariates of p-values of 0.2 and less at the bivariate level, with level of significance $\alpha = 0.05$, were included at the multivariate analysis level. Test of proportionality was conducted for the final model to ensure that this assumption is met in the ordinal analysis. Adjusted ORs along with their 95% confidence intervals and p-values were reported.

Variables that were thought to overlap and explain the same part of the outcome and cause violation of the proportionality of odds assumption, such as residence and nationality or chronic kidney disease and creatinine values were assessed carefully when included together in the same model, and in most cases they disrupted the model and were therefore considered separately in different models.

CHAPTER IV

RESULTS

A. Descriptive and Frequency Analysis

Frequency analysis was conducted and the percentages of the whole sample – in addition to the valid percentages accounting for missing values – were reported in the analysis.

1. Socio-Demographic Characteristics (Table 3)

The mean age of the study participants was 65.7 (±12.3) years (ranging between 29 and 94). Individual weights ranged between 40 and 150 Kg with a mean of 80.9 (±17.7). Male cases significantly outweighed women cases (70% versus 30%, respectively). The majority of patients held the Lebanese nationality (66%). Almost 39% of patients resided in Beirut, 30% resided outside Beirut, while 32% of the total number of participants resided outside Lebanon.

On the financial aspect, 50% of the patients were self-payers while the other 50% covered their hospital bill through National Social Security Fund (NSSF), AUB Health Insurance Plan (HIP) or other private insurance scheme (Table 3).

There were no missing values in socio-demographic variables except for the weight variable 85 values were missing accounted for 30% of values. However, weight did not show any significance at the bivariate analysis and was included in our multivariable analysis.

2. Patients History (Table 4)

Almost all patients had type II diabetes (98%) and 63% of the patients had diabetes for more than 10 years, Almost half of the DFU patients (48%) were on oral medication whereas the other half (52%) were on Insulin.

As shown in Table 4, 52% of the subjects had no past diabetic foot ulcer, 28% had past ulceration on the same site and 20% had past ulceration on a different site. While the majority of the patients were non-smokers (73%), most of them (81%) suffered from hypertension and 66% were dyslipidemic.

More than third of the patients had Coronary Artery Disease (53%) whereas one fourth had Congestive Heart Failure (24%). Very few patients had Chronic Obstructive Pulmonary Disease (6%) and 83 patients had Chronic Kidney Disease accounting for 30% of the sample.

There were almost no missing values in patient history variables. Missing values ranged between 0 to 2 values accounting for 0.7% of the sample.

3. Patients Clinical Chemistry Tests Results (Table 5)

At the time of admission, most patients had relatively a good glycemic control of $HbA_1c \leq 7$ %, accounting for 71% of the 213 patients tested. Although most of the patients were dyslipidemic, the majority showed normal lipid profile results. Out of those who were tested, 88% had normal Total Cholesterol, 86% had normal LDL values and 77% had normal Triglycerides values. However, only 6% had normal HDL levels. Fifty eight patients got tested for their liver profile, 71% of which had normal Alkaline phosphatase, 63% had normal Gamma-glutamyl transferase levels, 85% had normal SGOT values and 93% had normal SGPT levels in their blood. Moreover, the majority of patients (approximately 260 subjects) were tested for their renal function, which results revealed that almost half of them had abnormal BUN and Creatinine levels of percentages 49% and 52%, respectively.

Missing values ranged up to 141 missing values out of 278 accounting for 50% of missing values. This was the case since clinical chemistry tests ordered usually differs for each patient depending on their medical history and current medical status. None of these variables were significantly associated with our outcome at the bivariate level. Moreover, there was no statistical significant difference between the characteristics of those who had triglycerides values available and those who did not.

B. Bivariate Analysis

This dependent variable (outcome) falls into 3 categories:

i. I (Grades 0 and 1)

ii. II (Grades 2 and 3)

iii. III (grades 4 and 5)

As this outcome is ordinal, a bivariate ordered logistic regression analysis was conducted for the primary outcome of the study with the different independent variables to detect any significant associations. The assumption of proportional odds was satisfied (with a p-value > 0.05). The Unadjusted ORs along with their 95% confidence intervals and p-values were reported.

1. Socio-demographic covariates (Table 6)

Mean age, mean weight, and gender of patients were not different across the three different Wagner Ulcer grades with unadjusted ORs of almost 1 for all three variables and p-values of more than 0.05. On the other hand, the nationality of patients showed a statistically significant association with the severity of foot ulcer with p-value = 0.006 and OR = 1.97 (CI: 1.22, 3.19). The odds of having higher grades of Wagner Ulcer Classification System versus lower ones for those who are non-Lebanese is 1.97 times that of those who are Lebanese. Hence, without adjusting for other covariates, patients who are not Lebanese showed positive correlation (positive trend) with DFU grade when compared to those that are Lebanese.

As for the residence area, only those living outside Lebanon were significantly associated with the grade of diabetic foot ulcer when compared to those living in Beirut with a p-value < 0.0001 and OR = 2.69 (CI: 1.54, 4.67). The odds of having higher grades of Wagner Ulcer Classification System versus lower ones for those who live outside Lebanon is 2.69 times that of those who live in Beirut. Therefore, living in Beirut showed negative trend with DFU grade when compared to living outside Lebanon. Moreover, Hospital Payment was significantly associated with diabetic foot ulcer grade (p-value = 0.013, OR = 0.56, CI: 0.36, 0.89). The odds of having higher grades of Wagner Ulcer Classification System versus lower ones for those who are self-payers is 1.78 times that of those who rely on insurance.

2. Patients History Covariates (Table 7)

Both The history of past foot ulcer (same site) and past amputation showed significant association with the severity of diabetic foot ulcer with p-values of 0.008 (CI: 1.2, 3.52) and 0.005 (CI: 1.26, 3.58), respectively. The odds of having higher grades of Wagner Ulcer Classification System versus lower ones for those who had past foot ulcer on the same site as the current one is 2.06 times that of those had no past diabetic foot ulcer. Whereas, the odds of having higher grades of Wagner Ulcer Classification System versus lower ones for those who had past amputation is 2.13 times that of those had no past amputation. In addition, as Duration of diabetes increases from less than or equal to 10 years to more than 10 years, the odds of having higher grades of Wagner Ulcer Classification System versus lower ones increases multiplicatively by 2.08 with a p-value of 0.04 (CI: 1.03, 4.04). Hypertension and Chronic Kidney Disease showed no statistical significance at the bivariate level, however they had p – values of <0.2 and they were included at the multivariable regression level.

3. Clinical Chemistry Tests Covariates (Table 8)

None of the clinical chemistry tests results showed any statistical significance with the grade of diabetic foot ulcer; however, Triglycerides had a p-value < 0.2 and was included in the multivariable regression model.

C. Multivariable Regression using Cumulative Logit Models with Proportional Odds Property (Table 9)

Most the covariates that had a p-value equal or less than 0.2 at a bivariate level in addition to age and gender (universal confounders) were included in the multivariable analysis. An ordinal regression, in specific the multivariable regression using cumulative logit models with proportional odds property was employed using STATA. The assumption of proportional odds was satisfied (with a p-value > 0.05).

Variables that had a p-value less than 0.2 and were included in the multivariable analysis were: Nationality, residence, hospital payment, past foot ulcer, past amputation, duration of diabetes mellitus, hypertension, chronic kidney disease, triglycerides levels and Creatinine. Although age and gender were not statistically significant at the bivariate level, they were included at the multivariable analysis level since they are considered universal confounders. Variables that showed no statistical association with the wagner grade at bivariate level and other variables that had p-values of greater than 0.2 were not included in any final model. Those variables were: Diabetes Mellitus treatment, smoking status, Dyslipidemia, Coronary Artery Disease, Atrial Fibrillation, Congestive Heart Failure, Chronic Obstructive Pulmonary Disease and all lab test values except for Triglyceride and creatinine. When triglyceride was included as a binary variable, it disrupted the assumption of proportional odds (with a p-value < 0.05). Hence, it was included as a continuous variable to be able to satisfy the assumption of proportional odds.

Two final models were proposed for the primary outcome (Wagner grade) at the Multivariable analysis stage. Each model included a different combination of covariates explained in more details in the coming section.

Model 1: Age, gender, nationality, residence, hospital payment, past amputation, duration of diabetes mellitus, hypertension, chronic kidney disease, triglycerides levels and Creatinine (Table 9).

This model included all covariates having p-values less than 0.2 in addition to age and gender with the exception of history of past foot ulcer since it disrupted the assumption of proportionality when included.

Two variables showed significance in this model. The residence area was significantly associated with the grade of diabetic foot ulcer after adjusting for all the other variables with p-values of 0.02 (CI: 1.23, 10.45) for patients residing out of Beirut when compared to those residing in Beirut. Those residing out of Beirut had 3.6 times higher odds of having higher DFU grades versus lower ones when compared with DFU patients living in Beirut. Moreover, history of amputation showed a positive trend with Wagner grade (p-value = 0.01, CI: 1.36, 9.45). Those who had previous amputation have 3.6 times higher odds of having higher DFU grades versus lower ones when compared with DFU patients with no previous amputation.

Model 2: Age, gender, residence, hospital payment, past foot ulcer, past amputation, duration of diabetes mellitus, hypertension, chronic kidney disease and triglycerides levels (Table 10).

In the second model, nationality and residence were thought not to be included together because they are very similar variables. Almost all patients residing in Lebanon are Lebanese and most of those living outside Lebanon have a non-Lebanese nationality. Therefore, to prevent including variables that are overlapping and could be explaining the same parts in the outcome, it was decided to include either one of them in this model. For this same reason,, chronic kidney disease and creatinine level were not included together in this model.

In this model only three variables remained significantly associated with our primary outcome. The three statistically significant variables were: Residence, duration of diabetes mellitus and chronic kidney disease (CKD). First, the residence area was significantly associated with the grade of diabetic foot ulcer after adjusting for all the other variables with p-values of 0.017 (CI: 1.26, 10.85) and 0.006 (1.69, 21.15) for patients residing out of Beirut and out of Lebanon respectively when compared to those residing in Beirut. Those residing out of Beirut had 3.7 times higher odds of having higher DFU grades versus lower ones when compared with DFU patients living in Beirut. As for those residing outside Lebanon, they had 5.98 times higher odds of having higher DFU grades versus lower ones when compared with DFU patients living in Beirut. Moreover, duration of diabetes mellitus showed statistical significance with the grade of diabetic foot ulcer adjusting for all other variables (p-value = 0.043, CI: 1.04, 8.03). The odds of having higher grades of Wagner Ulcer Classification System versus lower ones for those who had diabetes for more than ten years is 2.88 times that of those had diabetes for 10 year or less. Chronic kidney disease was significantly associated with our primary outcome (p-value = 0.019, CI: 1.22, 9.52). DFU patients with Chronic Kidney Disease had 3.42 times higher odds of having higher DFU grades versus lower ones when compared with DFU patients that do not have Chronic Kidney Disease. Therefore, adjusting for all other covariates, having CKD showed a positive trend with DFU grade when compared to not having the disease.

CHAPTER V

DISCUSSION

Risk factors and covariates associated with severity of DFU having not been well identified neither worldwide nor in Lebanon, our current study offers findings as to the association between socio-demographic and health factors on the one hand, and severity of DFU on the other. Based on the literature, many risk factors are attributed to the etiology of foot ulcers, the majority of which are attributed to the "critical triad of peripheral sensory neuropathy, trauma, and deformity" (Frykberg, 2002), whereas infection is rarely an implication but rather a consequence once the wound is present.

Our study, conducted on patients diagnosed with DFU and receiving treatment at the American University of Beirut Medical Center (AUBMC), provided insights on of the risk factors affecting the severity of foot ulcers. The odds of having higher grades of Diabetic foot ulceration was higher in the case of previous lower extremity amputation (OR, 3.58), chronic kidney disease (OR, 3.42), higher duration of Diabetes Mellitus of more than ten years (OR, 2.88) and living outside of Beirut (OR, 3.7) or outside Lebanon (OR, 5.98) versus living in Beirut.

Duration of Diabetes Mellitus

The odds of having higher grades of Wagner Ulcer Classification System versus lower ones for those who had diabetes for more than ten years is almost three times that of those had diabetes for ten years or less. Studies from the literature confirm this result, where longer duration of Diabetes Mellitus (more than ten years) was shown to be a risk factor of DFU. This also holds true for several studies in the literature that showed increased risk of diabetic ulcer disease development for patients having more than ten years duration of diabetes (Al-Rubeaan, et al., 2015) (Crawford, et al., 2015) (Kaminski, et al., 2015). The association between Duration of Diabetes and severity of DFU is not surprising. One of the indicators of the severity of diabetes is actually is duration. The longer the duration the more severe is the disease. Actually, diabetes is often associated with the development of peripheral artery disease and diabetes peripheral neuropathy (Mørkrid, Ali, & Hussain, 2010) (Al-Delaimy, et al., 2004). Given that both are well defined in the literature as strong risk factors of foot complications (Hu, et al., 2014), this could explain the relationship between the duration of Diabetes and the grade of DFU.

Chronic Kidney disease

Several studies have established a correlation between severe renal disease and ulcers in patients with diabetes (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013) and our study is in line with those findings. Chronic kidney disease was significantly associated with our primary outcome. DFU patients with Chronic Kidney Disease had more than three times higher odds of having higher DFU grades versus lower ones when compared with DFU patients that do not have Chronic Kidney Disease. However, blood urea nitrogen (BUN) and creatinine values of our study population patients did not show any significant association with the severity of DFU

These results confirm that patients with longer duration of diabetes and severe kidney disease are at particularly higher risk for having higher grades of DFU. Patients with higher level of DFU are at higher risk of lower extremity amputation (Pemayun, Naibaho, Novitasari, Amin, & Minuljo, 2015). Consequently, Future research should preferentially include this population.

Past Amputation

The odds of having higher grades of DFU versus lower ones was more than three times higher in DFU patients with previous lower extremity amputation when compared to those with no history of lower extremity amputation (LEA). This finding is actually consistent with several other studies that showed an association between the history of LEA and the development of DFU (Kaminski, et al., 2015). As per Yazdanpanah et al.'s study, previous history of diabetic foot ulcer or amputation was one of the main risk factors recorded, provided that diabetic patients with a history of foot ulcer may be prone to developing different micro- and macrovascular dysfunctions, as well as peripheral neuropathy (Yazdanpanah, et al., 2018). In fact, microvascular and macrovascular changes in patients with diabetes contribute to nerve damage of different degrees, coupled with the occurrence of impaired circulation in the lower limbs which could lead to the development of ulcerations, pathological fractures and bone damage and, at a later stage, infections and amputations (Adimoolam, Muthukrishnan, & B.Albu, 2017). However, past diabetic foot ulcer was not shown to be statistically associated to the grade of DFU as opposed to the studies mentioned in this section in addition to several others that showed an association between this factor and the development of DFU (Kaminski, et al., 2015) (Crawford, et al., 2015).

Residence Area

DFU patients residing out of Beirut had almost four times higher odds of having higher DFU grades versus lower ones when compared with DFU patients living in

Beirut. This could be interpreted in terms of financial limitations which may deter patients from seeking timely treatment. Usually, those living in a capital such as Beirut or in more urbanized areas in general, have better socioeconomic status in terms of financial capacity (higher income) and higher education level. Also, they tend to be more health conscious and have better access to health care services and medical facilities (Fujita, Sato, Nagashima, Takahashi, & Hata, 2016) (Yamada, Chen, Naddeo, & Harris, 2015).

As for those residing outside Lebanon, they had around six times higher odds of having higher DFU grades versus lower ones when compared with DFU patients living in Beirut. A possible explanation to this finding is that patients coming from outside Lebanon to seek medical care have already failed to be treated locally at their home countries. The majority of our sample population coming from outside Lebanon was Iraqis. The health care system in Iraq is incapable of delivering medical services that should be provided to the Iraqi population neither sustainably nor equitably. With political instability and lack of security, the health system in Iraq is not able to even cover the major health problems suffered by their citizens. (WHO, 2019)

Moreover, crossing borders to find suitable medical services usually happens when the patient is already in an advanced level of the disease. All this could explain why patients coming from outside Lebanon and from Iraq in particular have higher grades of DFU

Gender

Although gender was not associated with the grade of DFU, however our findings confirm that compared with women, history of diabetic foot ulcer is more prevalent among men (69.8% versus 30.2% in women), in accordance with previous studies (Molvær, et al., 2014) (Crawford, et al., 2015) (Rossaneis, Haddad, Mantovani, Marcon, & Pissinati, 2017). In fact, the prevalence of male patients developing DFU has been noted in several research reports and attributed to different factors. Yazdanpanah et al. (2018) attribute it to men's more frequent outdoor activity and foot exposure to different risks and plantar pressure than those of women. Al-Rubeaan (2015) attributes it to the fact that males have limited joint mobility and higher foot pressure, higher mean height and peripheral insensate neuropathy, and within certain cultures, are more susceptible to developing trauma and do not accord importance to the quality of their footwear (Al-Rubeaan, et al., 2015). On the other hand, Brunn et al. (2013) suggest that women are more active in precautionary foot care, as compared to the passive attitude adopted by men; they also attribute it to the fact that the severity of diabetes at the time of diagnosis is worse in men than in women (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013). Nonetheless, male association with DFU is often reported in univariate analysis and considered insignificant in multivariate analysis (Yazdanpanah, et al., 2018).

Glycemic control measured by HbA1c upon admission,

Significant association has been made in literature between diabetic foot conditions and the degree of glycemic control, where poor glycemic control was correlated to a two-fold increase in the risk of foot lesions among diabetic patients (Al-Rubeaan, et al., 2015). However, this is not held true in our study where the primary outcome is the grade of DFU and not its development. There was no significant association between Hba1c value upon admission and the severity of DFU.

Dyslipedemia

Neither Dyslipidemia nor Hypertension showed significant association with our outcome (DFU grade). Dyslipidemia and Hypertension were prevalent among our study population (66.2% and 81.3 % of patients respectively). Studies conducted on the Lebanese population confirm that hypertension is the most prevalent co-existing condition, whereas hyperlipidemia followed by heart disease is the most common macrovascular complication (Costanian, Bennett, Hwalla, Assaad, & Sibai, 2014). However, the majority of our study population had normal Total Cholesterol Level, LDL and Triglycerides levels, whereas only few had normal HDL levels. The relatively good lipid profile results could be attributed to the fact that patients were already on cholesterol medication. Al-Rubeaan et al. reports similar findings with regards to lipid profiles, and attribute it to the fact that the majority of cases were controlled with lipid lowering agents during the time of analysis (Al-Rubeaan, et al., 2015).

Age

Although age was not associated with the grade of foot ulceration in our study, it was found to be associated to DFU development in some other studies (Molvær, et al., 2014). Another study failed to show age as risk factor for diabetic foot ulceration (Rossaneis, Haddad, Mantovani, Marcon, & Pissinati, 2017). In any case, it is common that with aging, people have less self-care especially with the improved life expectancy of Diabetic patients (Monteiro- Soares, Boyko, Ribeiro, Ribeiro, & Dinis- Ribeiro, 2012) (Shahbazian, Yazdanpanah, & Latifi, 2013) (Morey-Vargas & Smith, 2015) (Bansal, Dhaliwal, & Weinstock, 2015). This fact is explained by the prevalence, with ageing, in the development of macroangiopathies which lead to the compromise of the cerebral, coronary and lower limb arteries, in addition to microangiopathies that affect the retina, renal glomerulus and peripheral nerves. As a result of these complications, practice of self-care of the feet is reduced due to the difficulty in inspection of lower limbs for injuries by the elderly and by individuals with visual impairment and/ or physical sequelae, as well as difficulty in taking care of skin hydration and hygiene (Shahbazian, Yazdanpanah, & Latifi, 2013).

Diabetes Mellitus treatment (insulin, oral medication)

No association was found between insulin treatment and the grade of DFU in our study; however, the association between insulin treatment and the development of DFU was shown in several studies across the literature (Monteiro- Soares, Boyko, Ribeiro, Ribeiro, & Dinis- Ribeiro, 2012) (Molvær, et al., 2014) (Rossaneis, Haddad, Mantovani, Marcon, & Pissinati, 2017). Same case applies for smoking status. Smoking was significantly higher among DFU cases in some studies (Al-Rubeaan, et al., 2015) but it was not a significant factor for the grade of DFU.

Coronary Artery Disease

Studies corroborate the high prevalence of cardiovascular diseases in patients with foot problems (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013), as well as the fact that CAD exhibits the highest percentages among vasculopathic patients for foot ulcer, amputation and gangrene (Al-Rubeaan, et al., 2015). This finding could be interpreted in terms of the high prevalence of CAD among diabetic populations, in addition to its high prevalence among diabetes foot cases (Al-Rubeaan, et al., 2015). Other studies confirm the independent association between CAD and Diabetic foot ulceration (Kaminski, et al., 2015). As for other cardiovascular diseases (such as Atrial Fibrillation and Congestive Heart Failure) and Chronic Obstructive Pulmonary Disease, they didn't show any association with the severity of DFU in our study.

Lipid profile

A meta-analysis exploring the effects of lipids and lipoproteins on diabetic foot showed that decreased HDL-cholesterol was significantly associated with DFU, but no statistical significance was found between DFU and Triglycerides, LDL-cholesterol or total Cholesterol levels (Pei, et al., 2014). Although they found an association between HDL level and the development of DFU, our results are consistent with the rest of their findings where patients' lipid profile had no significant association with the grade of DFU.

Limitations

This study is a secondary analysis of data adopted from the study entitled "diabetic foot complications in a tertiary care center in Lebanon: retrospective study identifying burden and gaps in management." The cross-sectional analysis was conducted on a population of 278 patients admitted with DFU at AUBMC and involves a select sample of patients diagnosed with diabetes and receiving treatment accordingly. Several limitations of this study should be considered.

It is worthy of noting that it is difficult to account for undiagnosed DFU, which could be due to a multitude of factors, such as ignorance, lack of financial capacities or nonchalance. As a matter of fact, Former studies have relatively underestimated the prevalence of foot ulcers and amputations due to method limitations such as uncertain registration of the diabetes diagnosis, patient selection according to healthcare sector, high dropout rate, short follow-up period or cross-sectional study design (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013). This limitation is of particular concern especially if the characteristics of those who sought care differ from those who did not.

Study took place only in one hospital and the patients visiting this medical center are not necessarily representative of other patients that seek treatment in other medical center in Lebanon. This raises the issue of generalizabilty or external validity to patients who were not represented in the study and potential selection bias.

Given that the focus in this study was on the grade of DFU as the primary outcome of the study, it was difficult to accurately compare with reports from international studies due to disparities in research methodologies, criteria observed and outcomes studied.

Moreover, while the Wagner ulcer classification system – adopted in this study – is based on several parameters such as the depth of penetration, the presence of osteomyelitis or gangrene, and the extent of tissue necrosis, it fails to address ischemia and infection, two critically important parameters (Frykberg, 2002).

Strengths

This study is the first of its kind to target the Lebanese population experiencing foot complications while exploring potential risk factors affecting the grade of Diabetic Foot Ulcer disease. Moreover, it is the first study to look at the grade of Diabetic Foot Ulcer disease as an ordinal outcome both regionally and internationally. Given the source of data collected being the patients' electronic medical records this attenuate recall bias.

CHAPTER VI

CONCLUSION AND RECOMMENDATION

Significant covariates at the multivariable analysis: The residence area, history of amputation, duration range of diabetes mellitus and chronic kidney disease. Our findings indicate that particular consideration must be accorded with special emphasis for rural residence and managing Diabetes and Chronic Kidney disease would prevent a diabetic foot ulcer from worsening or developing higher grades according to the.

Diabetic foot disease is a lifelong condition that requires thorough monitoring and follow-up. Early prevention and punctual referrals are of fundamental and critical importance, as is early referral to specialized centers when the prevention fails (Bruun, Siersma, Guassora, Holstein, & Olivarius, 2013). Early recognition and diagnosis can help in fact prevent hospitalization as well as complications of diabetes (Adimoolam, Muthukrishnan, & B.Albu, 2017). Prevention of an initial or subsequent foot lesion is crucial to avoiding amputation.

Given the multi-faceted nature of risk factors associated with DFU, the ultimate approach is to provide a multidisciplinary approach to foot care, which has confirmed significant progress in outcomes (Merheb, Gharios, Younes, Cheikh, & Chaaban, 2017). Furthermore, early diagnosis of risk and prevention of T2DM is fundamental to further limit the incidence of complications.

It is worthy of noting that rest and the relief of pressure from the affected foot are measures of crucial importance in the treatment process, as reported across literature (Merheb et al. 2017) add that attention must also be drawn upon the quality of footwear, which should be pressure-relieving. (Merheb, Gharios, Younes, Cheikh, & Chaaban, 2017).

Treatment also calls for highly specialized knowledge and collaboration between different health areas and specialties, where the primary concern must be the achievement of a wound closure in DFU. T2DM must be approached through the support of physicians, diabetes educators, and patients themselves (Adimoolam, Muthukrishnan, & B.Albu, 2017). Furthermore, accurate estimates of the current and future burden of diabetic foot disease especially in Lebanon and the region are necessary for allocating community and health resources, as well as for creating strategies to counteract these rising trends.

Finally, Large- nation-wide studies are in need in order to benefit the diabetic patients with DFU and inform health policies. Multidisciplinary management with an emphasis on preventative care results in less diabetic foot complications especially that severity of DFU could be attenuated with early diagnosis and proper prognosis and follow up.

FIGURES AND TABLES

A. Descriptive and frequency analysis

Figure 1: The distribution of patients among the categories of the Wagner Diabetic Foot Ulcer Grade

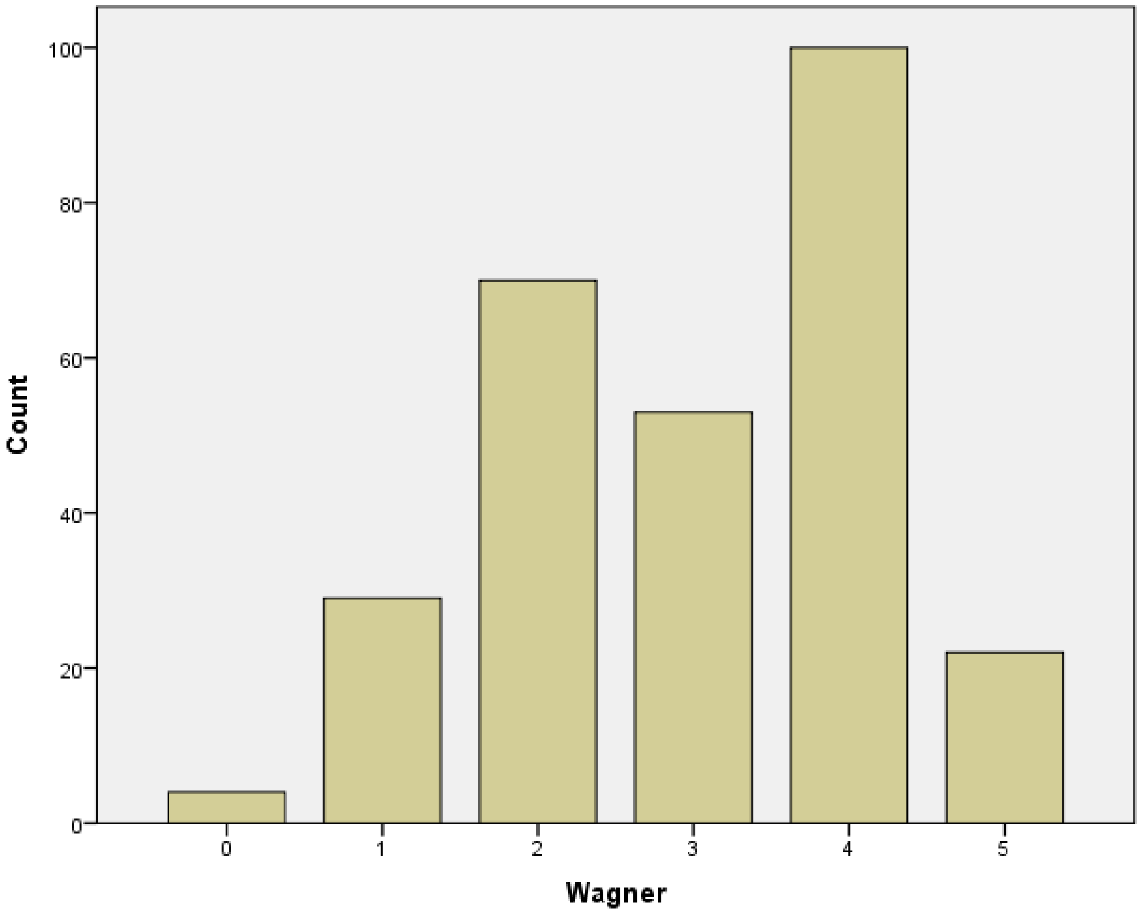

Table 3: Socio Demographic Characteristics of Patients

	Mean	SD	Minimum	Maximum
Age (Years)	65.7	12.3	29	94
Weight (Kg)	80.9	17.7	40	150

BMI (Kg/m^2)	29.2	6.3	16.4	64.9

	N	**Percentage (%)**	**Valid Percentage (%)**
Gender			
Male	194	69.8	69.8
Female	84	30.2	30.2
Nationality			
Lebanese	183	65.8	65.8
Non-Lebanese	95	34.2	34.2
Residence			
Beirut	108	38.8	38.8
Out of Beirut	83	29.9	29.9
Out of Lebanon	87	31.3	31.3
Hospital Payment			
Self Payer	138	49.6	49.6
Insurance	140	50.4	50.4

Table 4: Patients History

	N	Valid Percentage (%)
Type of Diabetes Mellitus		
Type I	6	2.2
Type II	272	97.8
Duration of Diabetes Mellitus		
≤ 10 years	39	14
>10 years	174	62.6
Diabetes Mellitus Treatment		
Oral Medication	131	47.5
Insulin	145	52.5
Past Diabetic Foot Ulcer		
None	144	51.8
Same site	79	28.4
Different site	55	19.8
Current Smokers		
Yes	75	27.2
No	201	72.8
Hypertension		
Yes	226	81.3
No	52	18.7
Dyslipidemia		
Yes	184	66.2
No	94	33.8
Chronic Kidney Disease		
Yes	83	29.8
No	195	70.1
Coronary Artery Disease (CAD)		
Yes	119	42.8
No	159	57.2
Atrial Fibrillation		
Yes	35	12.6
No	243	87.4
Congestive Heart Failure		
Yes	67	24.1
No	221	75.9
Chronic Obstructive Pulmonary Disease (COPD)		
Yes	16	5.8
No	262	94.2

Table 5: Patients Clinical Chemistry Tests Results upon Admission

	N	**Valid Percentage (%)**
Diabetes Profile		
HbA1c		
≤ 7 %	151	70.9
> 7 %	62	29.1
Cholesterol Profile		
Total Cholesterol		
≤ 200 mg/dL	122	87.8
> 200 mg/dL	17	12.2
‘ High-Density Lipoprotein (HDL)		
Normal	8	5.8
Abnormal	130	94.2
Low-Density Lipoprotein (LDL)		
≤ 130 mg/dL	121	85.8
>130 mg/dL	20	14.2
Triglycerides		
≤ 200 mg/dL	105	76.6
>200 mg/dL	32	32.4
Renal Function		
Blood Urea Nitrogen (BUN)		
≤ 25 mg/dL	128	49.2
>25 mg/dL	132	50.8
‘Creatinine		
Normal	136	51.9
Abnormal	126	48.1

(’): HDL: Normal: Male: > 45 mg/dL Female: > 55 mg/dL / Abnormal: Male: < 45 mg/dL Female: < 55 mg/dL
(‘): SGPT: Normal: Male: ≤65 IU/L Female: ≤ 50 IU/L / Abnormal: Male: >65 IU/L Female: >50 IU/L
(‘)*: Creatinine:* Normal: Male: ≤1.2 mg/dL Female: ≤1.0 mg/dL / Abnormal: Male: > 1.2 mg/dL Female: >1.0 mg/dL

B. Bivariate analysis

Table 6: Univariate Ordered Logistic Regression Analysis of Diabetic foot ulcer grade compared to the demographic characteristics of patients

	Wagner Ulcer Grade					
Covariates	**I (Grade 0&1)**	**II (Grades 2&3)**	**III (Grades 4 & 5)**	**Unadjusted OR**	**CI for unadjusted OR (95%)**	**P-value**
Age mean ±s	66.6 ± 1.8	66.0 ± 1.2	65.4 ± 12.3	0.99	(0.98,1.01)	0.621
Total	33	123	122	-	-	-
Weight mean ±s	83.7 ± 3.0	80.0 ± 1.5	81.3 ±21.5	1.00	(0.98, 1.01)	0.972
Total	17	92	84	-	-	-
Gender						
Male	21(63.6%)	87(70.7%)	86(70.5%)	-	-	-
Female	12(36.4%)	36(29.3)	36(29.5%)	0.89	(0.54, 1.45)	0.635
Total	33	123	122			
Nationality						
Lebanese	26(78.8%)	87(70.7%)	70(57.4%)	-	-	-
Non-Lebanese	7(21.1%)	36(29.3)	52(42.6%)	**1.97**	**(1.22, 3.19)**	**0.006***
Total	33	123	122	-	-	-
Residence						
Beirut	15(45.5%)	59(48.0%)	34(27.9%)	-	-	-
Out of Beirut	12(36.4%)	33(26.8%)	38(31.1%)	1.55	(0.89,2.68)	0.119
Out of Lebanon	6(18.2%)	31(25.3%)	50(41%)	**2.69**	**(1.54,4.67)**	**<0.0001***
Total	33	123	122	-	-	-
Hospital Payment						
Self Payer	15(45.4%)	51(41.5%)	72(59%)	-	-	-
Insurance	18(54.5%)	72(58.5%)	50(41.0%)	**0.56**	**(0.36, 0.89)**	**0.013***
Total	33	123	122	-	-	-

(*): P-value < 0.05

Table 7: Univariate Ordered Logistic Regression Analysis of Diabetic foot ulcer grade compared to the history of Patients

	Wagner Ulcer Grade					
Covariates	**I (Grades 0&1)**	**II (Grades 2&3)**	**III (grades 4 & 5)**	**Unadjusted OR**	**CI for unadjusted OR (95%)**	**P-value**
Past foot Ulcer						
No	24(72.7%)	65(52.8%)	55(45.1%)	-	-	-
Same site	6(18.2%)	30(24.4%)	43(35.2%)	2.06	**(1.20, 3.52)**	**0.008***
Different site	3(9.1%)	28(22.8%)	24(19.7%)	1.50	(0.83, 2.69)	**0.176**
Total	33	123	122	-	-	-
Past amputation						
No	29(87.9%)	95(77.2%)	80(65.6%)	-	-	-
Yes	4(12.1%)	28(22.8%)	42(34.4%)	**2.13**	**(1.26, 3.58)**	**0.005***
Total	33	123	122			-
Duration of Diabetes Mellitus						
≤ 10 years	8(42.1%)	17(17.5%)	14(14.4%)	-	-	
>10 years	11(57.9%)	80(82.5%)	83(85.6%)	**2.06**	**(1.03, 4.04)**	**0.04***
Total	19	97	97			
Diabetes Mellitus Treatment						
Oral Medication	18(54.5%)	59(48.8%)	54(44.3%)	-	-	-
Insulin	15(45.5%)	62(51.2%)	68(55.7%)	1.28	(0.82, 2.01)	0.277
Total	33	121	122		-	-
Current Smokers						
No	24(72.7%)	84(68.9%)	93(76.9%)	-	-	-
Yes	9(27.3%)	38(31.1%)	28(23.1%)	0.75	(0.46, 1.24)	0.270
Total	33	122	121	-	-	-
Hypertension						
No	7(21.2%)	28(22.8%)	17(13.9%)	-	-	-
Yes	26(78.8%)	95(77.2%)	105(86.1%)	1.59	(0.90, 2.81)	**0.106**
Total	33	123	122	-	-	-
Dyslipidemia						
No	9(27.3%)	47(38.2%)	38(31.1%)	-	-	-
Yes	24(72.7%0	76(61.8%)	84(68.9%)	1.10	(0.69, 1.76)	0.692
Total	33	123	122	-	-	-
Chronic Kidney Disease						
No	26(78.8%)	88(71.5%)	81(66.4%)	-	-	-
Yes	7(21.2%)	35(28.5%)	41(33.6%)	1.42	(0.87, 2.32)	**0.161**
Total	33	123	122	-	-	
Coronary Artery Disease (CAD)						

No	19(57.6%)	73(59.3%0	67(54.9%)	-	-	-
Yes	14(42.4%)	50(40.7%)	55(45.1%0	1.14	(0.73, 1.80)	0.561
Total	33	123	122	-	-	-
No	30(90.9%)	108(87.8%)	105(86.1%)	-	-	-
Yes	3(9.1%)	15(12.2%)	17(13.9%)	1.28	(0.65, 2.52)	0.474
Total	33	123	122	-	-	-
No	25(75.8%)	94(76.4%)	92(75.4%)	-	-	-
Yes	8(24.2%)	29(23.6%)	30(24.6%)	1.04	(0.61, 1.75)	0.894
Total	33	123	122			
Chronic Obstructive Pulmonary Disease (COPD)						
No	33(100%)	115(93.5%)	114(93.4%)	-	-	-
Yes	0(0%)	8(6.5%)	8(6.6%)	1.55	(0.60, 3.99)	0.365
Total	33	123	122	-	-	-

(*): P-value < 0.05

Table 8: Univariate Ordered Logistic Regression Analysis of Diabetic foot ulcer grade compared to the Patients Clinical Chemistry Tests Results

(’): HDL: Normal: Male: > 45 mg/dL Female: > 55 mg/dL / Abnormal: Male: < 45 mg/dL Female: < 55 mg/dL

	Wagner Ulcer Grade					
Covariates	**I (Grade 0&1)**	**II (Grades 2&3)**	**III (grades 4 & 5)**	**Unadjusted OR**	**CI for unadjusted OR (95%)**	**P-value**
Diabetes Profile						
HbA1c						
≤ 7 %	8(27.6%)	27(26.0%)	27(23.7%)	-	-	-
> 7 %	21(72.4%)	77(74.0%)	87(76.3%)	1.15	(0.67, 1.99)	0.612
Total	29	104	114	-	-	-
Cholesterol Profile						
Total Cholesterol						
≤ 200	14(93.3%)	49(81.7%)	59(92.2%)	-	-	-
>200	1(6.7%)	11(18.3%)	5(7.8%)	0.63	(0.25, 1.59)	0.327
Total	15	60	64	-	-	-
‘ High-Density Lipoprotein (HDL)						
Normal	15(100%)	53(89.8%)	62(96.9%)	-	-	-
Abnormal	0(0.0%)	6(10.2%)	2(3.1%)	0.65	(0.18, 2.26)	0.496
Total	15	59	64	-	-	-
Low-Density Lipoprotein (LDL)						
≤130 mg/dL	14(93.3%)	50(82.0%)	57(87.7%)	-	-	-
>130 mg/dL	1(6.7%)	11(18.0%)	8(12.3%)	0.91	(0.38, 2.18)	0.829
Total	15	61	65	-	-	-
Triglycerides						
≤ 200 mg/dL	9(60.0%)	45(76.3%)	51(81.0%)	-	-	-
>200 mg/dL	6(40.0%)	14(23.7%)	12(19.0%)	0.56	(0.26, 1.21)	**0.142**
Total	15	59	63	-	-	-
Renal Function						
Blood Urea Nitrogen (BUN)						
≤ 25 mg/dL	17(58.6%)	55(49.5%)	56(46.7%)	-	-	-
>25 mg/dL	12(41.4%)	56(50.5%)	64(53.3%)	1.27	(0.79, 2.02)	0.32
Total	29	111	120	-	-	-
‘Creatinine						
Normal	20(66.7%)	58(51.8%)	58(48.3%)	-	-	-
Abnormal	10(33.3%)	54(48.2%)	62(51.7%)	1.41	(0.89, 2.25)	**0.144**
Total	30	112	120	-	-	-

(‘)*: Creatinine:* Normal: Male: ≤1.2 mg/dL Female: ≤1.0 mg/dL / Abnormal: Male: > 1.2 mg/dL Female: >1.0 mg/dL
(*): P-value < 0.05

B. Multiple Regression

Table 9: Ordered Logistic Regression – Model 1

Covariates	**Adjusted OR**	**CI for adjusted OR (95%)**	**P-value**
Age (Years)	0.97	(0.93, 1.01)	0.15
Gender			
Male (ref)	-	-	-
Female	1.36	(0.60, 3.27)	0.494
Origin			
Lebanese	-	-	-
Non-Lebanese	0.60	(0.07, 5.17)	0.642
Residence			
Beirut (ref)	-	-	-
Out of Beirut	**3.59**	**(1.23, 10.54)**	**0.020***
Out of Lebanon	8.00	(0.97, 66.01)	0.053
Hospital Payment			
Self Payer (ref)	-	-	-
Insurance	0.78	(0.25, 2.51)	0.687
Past amputation			
No (ref)	-	-	-
Yes	**3.58**	**(1.36, 9.45)**	**0.010***
Duration of Diabetes Mellitus			
≤ 10 years (ref)	-	-	-
>10 years	2.62	(0.91, 7.57)	0.073
Hypertension			
No (ref)	-	-	-
Yes	1.26	(0.50, 3.15)	0.622
Chronic Kidney Disease			
No (ref)	-	-	-
Yes	2.41	(0.72, 8.08)	0.154
Triglycerides	1.00	(0.99, 1.00)	0.072

‘Creatinine			
Normal	-	-	-
Abnormal	1.59	(0.59, 4.35)	0.360

(*): P-value < 0.05

(‘)*: Creatinine:* Normal: Male: ≤1.2 mg/dL Female: ≤1.0 mg/dL / Abnormal: Male: > 1.2 mg/dL Female: >1.0 mg/dL

Table 10: Ordered Logistic Regression – Model 2

Covariates	Adjusted OR	CI for adjusted OR (95%)	P-value
Age (Years)	0.97	(0.93, 1.01)	0.17
Gender			
Male (ref)	-	-	-
Female	1.47	(0.60, 3.56)	0.394
Residence			
Beirut (ref)	-	-	-
Out of Beirut	**3.70**	**(1.26, 10.85)**	**0.017***
Out of Lebanon	**5.98**	**(1.69, 21.15)**	**0.006***
Hospital Payment			
Self Payer (ref)	-	-	-
Insurance	0.86	(0.30, 2.53)	0.792
Past foot Ulcer			
No (ref)	-	-	-
Same site	1.57	(0.54, 4.60)	0.406
Different site	2.08	(0.71, 6.11)	0.182
Past amputation			
No (ref)	-	-	-
Yes	2.37	(0.82, 6.86)	0.112
Duration of Diabetes Mellitus			
≤ 10 years (ref)	-	-	-
>10 years	**2.88**	**(1.04, 8.03)**	**0.043***
Hypertension			
No (ref)	-	-	-
Yes	1.24	(0.49, 3.16)	0.647
Chronic Kidney Disease			
No (ref)	-	-	-
Yes	**3.42**	**(1.22, 9.52)**	**0.019***
Triglycerides	1.00	(0.99, 1.00)	0.102

(*): P-value < 0.05

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