

Diabetic Foot and Its Clinical Characteristics among Uncontrolled Diabetic Patients in Ad-Dawadmi General Hospital, Riyadh Province, KSA

Khalid Saad AlSidr, Majed Ali Khaled Alotaibi, Sami Khaled Alotaibi, Faisal Abdullah Alhammadi, Menwer Abdullah Menwer Alotaibi, Mohammad Azhar Rashikh*

Department of Basic Medical Science, College of Medicine, Ad-dawadmi, Shaqra University, Kingdom of Saudi Arabia

*Corresponding author: Mohammad Azhar Rashikh

| Received: 15.05.2019 | Accepted: 25.05.2019 | Published: 30.05.2019

DOI:10.21276/sjbr.2019.4.5.10

Abstract

Diabetic foot and their complications are considered to be a serious cause of morbidity and mortality in diabetes. The aim of this study was to investigate the clinical characteristics in diabetic foot patients along with glycosylated hemoglobin levels and diabetes duration. We performed a retrospective study from June 2016 to March 2017 on a sample composed of 26 patients with type 2 diabetes mellitus and diabetic foot. Age of patients, duration of diabetes, HbA1c- level and diabetic foot complications data were collected from patient's medical reports and hospital records. Most of the diabetic foot patients (DFPs) were affected with more than one comorbid complications such as hypertension (76.35%), peripheral neuropathy (57.7%), hyperlipidemia (43.9%), peripheral vascular disease (23.1%), coronary artery disease (19.2%), diabetic nephropathy (19.2%) and diabetic retinopathy (15.4%). It was also seen that all the DFPs had uncontrolled glycosylated hemoglobin (HbA1c) levels (>7.5%) and 73.1% had diabetes >10 years old. Prevalence of hypertension, diabetic peripheral neuropathy and hyperlipidemia were found in higher percentage as compare to other complications in DFPs.

Keywords: diabetes mellitus, diabetic foot, mortality, diabetic foot complications, vascular complications, Saudi Arabia.

Copyright @ 2019: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

INTRODUCTION

Diabetes mellitus (DM) is one of the major public health problems of the twenty-first century. According to World Health Organization, DM will be the seventh-leading cause of death worldwide in 2030 [1]. The International Diabetes Federation Atlas has reported that about 17.7% of the Saudi Arabia adult population suffered from DM [2]. In the Middle East, Saudi Arabia is leading country with high diabetes prevalence [3]. DM has been associated with other health complications, such as hypertension, coronary artery disease (CAD), myocardial infarction, stroke, peripheral vascular disease (PVD), retinopathy, nephropathy, peripheral neuropathy and foot complications in long term [4-6]. Progression of vascular complications of diabetes depends on the severity and duration of hyperglycemia [7]. Therefore, the primary aim of clinicians in DM management is to maintain blood glucose levels around the normal range and thus impede the related complications [8].

Diabetic foot is one of the most distressing and final event of the chronic complications of DM, which

may be complicated to foot ulcers, gangrene & amputation. In Saudi Arabia, the annual prevalence of diabetic ulcer and imputation was 6% and 1.5% among the diabetic patients, respectively [9]. Recent studies have indicated multiple risk factors associated with development of diabetic foot ulcer [10-12]. Risk factors may be duration of diabetes, advanced age of patients, high glycosylated hemoglobin level, high Body Mass Index, microvascular and macrovascular complications and inappropriate foot self-care habits [11-15].

Patients with peripheral neuropathy and insufficient peripheral artery flow have a greater risk of developing ulcers than those only have PVD [16, 17]. PVD reduces blood supply to the feet by affecting distal blood vessels, may compromise both nutrition and oxygen. PVD is more prone at a younger age in people with diabetes [18]. Peripheral neuropathy reduces pain sensation and patients are unaware of injury to their feet. The fail of sensitivity causes permanent damage to the tissues and may lead to the development of ulcers [19, 20]. Foot ulceration is the commonest reason for hospitalization and accounting for an enormous amount

of economic burden to health care system [21]. Therefore, early recognition of high risk population is immensely important to take rigorous modification of risk factors accompanied with foot care.

The present study aimed to investigate the prevalence of clinical characteristics of diabetic foot in patients with type 2 diabetes mellitus in a general hospital, Al-dawadmi, Riyadh province.

PATIENTS AND METHODS

A retrospective study was performed from June 2016 to March 2017 on patients admitted to the Emergency Room of the General Hospital, Al-Dawadmi, Riyadh province. The sample consisted of 26 patients diagnosed with T2DM and diabetic foot.

Inclusion Criteria

- DFPs, aged between 20-80 years old
- A minimum 5 years type 2 diabetes diagnosis

Exclusion Criteria

- The patients who had cancer, parkinsonism, drug addiction, use of antipsychotic drugs and pregnancy.

Data Collection

Data was collected from the patient's medical records and hospital databases. The data collected include information on age, gender and clinical history data: known DM duration, glycosylated hemoglobin level (HbA_{1c}), comorbidities (hyperlipidaemia, hypertension), macrovascular complications (CAD,

PVD) and microvascular complications (diabetic peripheral neuropathy, retinopathy, nephropathy). The institutional review board (IRB) did not require the patients' consent to review their medical record because their information was abstracted by the treating physician. Every effort was made to protect the patient data confidentiality. The research ethics committee of the Faculty of Medicine at Shaqra University approved this study.

Statistical Analysis

Data were entered into Microsoft Excel software. Quantitative variables were represented as mean \pm standard deviation and categorical data as a percentage (%). Chi-square test was used to compare the differences between the groups. The difference was considered significant if two-tailed P-value was ≤ 0.05 . Statistical analysis was carried out using SPSS version 20.

RESULTS

The sample consisted of 26 patients admitted to the Emergency Room of the General Hospital, Al-Dawadmi, Riyadh Province. The patients were diagnosed with T2DM and diabetic foot.

Age of Diabetic Patients

Table-1 shows demographic characteristics of the patients. The average age of the male patients were 59.73 years and for the female 53.2 years. Most female patients were significantly younger than the male patients ($P = 0.01$). All the diabetic foot patients (DFPs) age was between 43 to 72 years.

Table-1: Demographics information of DFPs (Male=15, Female=11)

| Parameters | Male (Mean \pm SD) | Female (Mean \pm SD) |
|--|-------------------------|------------------------------|
| Age of DFPs (years) | 59.73 \pm 6.43* | 53.2 \pm 6.06 [#] |
| Glycosylated Hemoglobin (HbA _{1c}) % | 8.4 \pm 0.43* | 7.96 \pm 0.35 [#] |

Diabetic foot patients (DFPs); * $P < 0.05$; considered as significant compared with female; [#] $P < 0.05$; considered as significant compared with male; using independent sample t-test to calculate p-value and mean

Glycosylated hemoglobin (HbA_{1c}) level in DFPs

Table-1 shows HbA_{1c} level. We observed that male diabetic foot patients showed significantly higher percentage of HbA_{1c} (8.4%) as compared to female (7.96%) DFPs ($P = 0.01$).

Duration of diabetes in DFPs

Figure-1 shows duration of diabetes. We found that 26.9% of DFPs had diabetes ≤ 10 years old and 73.1% of DFPs had diabetes > 10 years old.

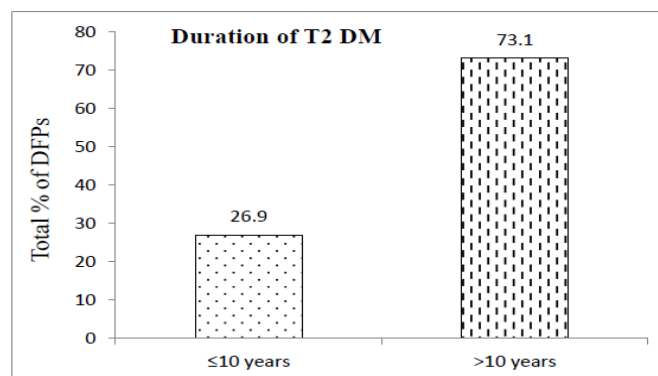


Fig-1: Duration of diabetes in diabetic foot patients (DFPs)

Macrovascular and other complications in DFPs

Figure-2 shows total percentage of macrovascular and other complications. The prevalence

of hypertension (76.35%), hyperlipidemia (43.9%), CAD (19.2%) and PVD (23.1%) were seen in DFPs.

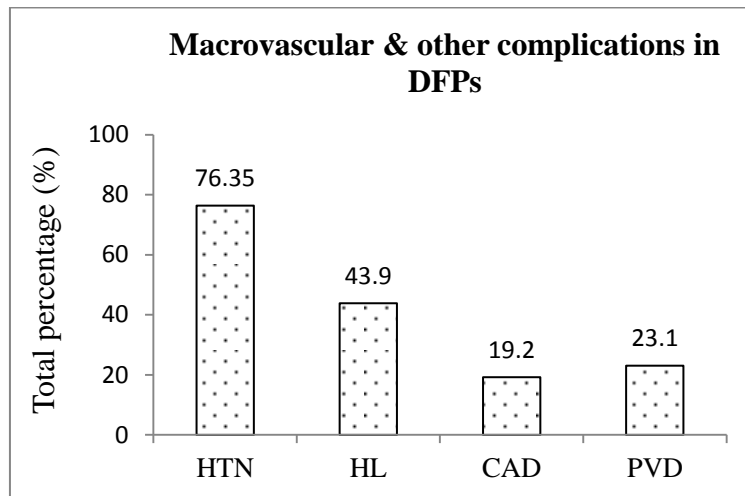


Fig-2: Total percentage of macrovascular and other complications in diabetic foot patients (DFPs)
Hypertension (HTN), Hyperlipidemia (HL), Coronary artery disease (CAD), Peripheral vascular disease (PVD)

Table-2 shows comparison of macrovascular and other complications between male & female DFPs.

The prevalence of hypertension and CAD were higher in male DFPs as compared to female DFPs (80% and 20% versus 72.7% & 18.2% respectively;

$p > 0.05$). In case of hyperlipidemia and PVD, female showed greater prevalence as compared to male DFPs (54.5% and 27.3% versus 33.3% and 20% respectively; $p > 0.05$), but their differences between male and female patients were non-significant.

Table-2: Macrovascular and other complications in male & female DFPs (Male=15, Female=11)

| Complications | Male n, (%) | Female n, (%) | P value |
|-----------------------------|-------------|---------------|---------|
| Hypertension | 12 (80) | 8 (72.7) | 0.664 |
| Hyperlipidemia | 5 (33.3) | 6 (54.5) | 0.279 |
| Coronary Artery Disease | 3 (20) | 2 (18.2) | 0.907 |
| Peripheral vascular disease | 3 (20) | 3 (27.3) | 0.664 |

Diabetic foot patients (DFPs); $P > 0.05$; considered as non-significant (differences b/w male & female); using chi-square t-test to calculate the percentage and p-value

Microvascular complications in DFPs

Figure-3 shows total percentage of microvascular complications in DFPs. The prevalence of diabetic peripheral neuropathy (DPN), diabetic

nephropathy and diabetic retinopathy in diabetic foot patients were seen 57.7%, 19.2% and 15.4% respectively.

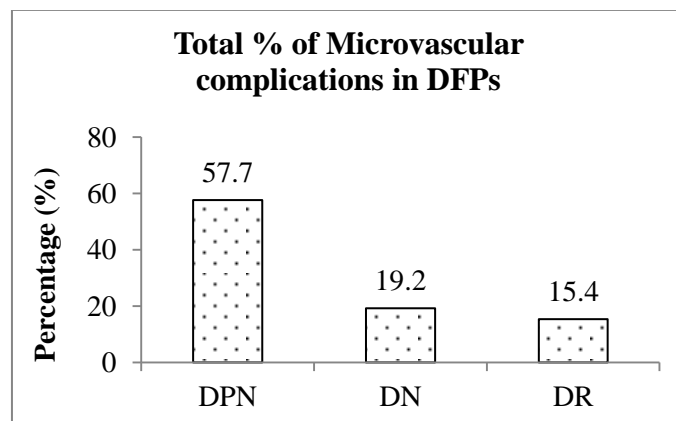


Fig-3: Total percentage of microvascular complications in diabetic foot patients (DFPs)

Diabetic peripheral neuropathy (DPN), Diabetic retinopathy (DR), Diabetic nephropathy (DN)

Table-3 shows comparison of microvascular complications between male & female DFPs. The

prevalence of DPN and diabetic retinopathy were higher in female as compared to male DFPs (63.6% and 18.2% versus 53.3% and 13.3%, $P>0.05$), but their differences between male and female patients were non-significant.

Table-3: Microvascular complications in Male & Female DFPs (Male=15, Female=11)

| Complications | Male n, (%) | Female n, (%) | P value |
|--------------------------------|----------------|------------------|---------|
| Diabetic peripheral neuropathy | 8 (53.3) | 7 (63.6) | 0.599 |
| Diabetic nephropathy | 3 (20) | 2 (18.2) | 0.907 |
| Diabetic retinopathy | 2 (13.3) | 2 (18.2) | 0.735 |

Diabetic foot patients (DFPs); $P>0.05$; considered as non-significant (differences between male & female)

DISCUSSION

To our knowledge, this is the first study to assess the prevalence of clinical characteristics on diabetic foot patients (DFPs) in Saudi Arabia. During data collection, we included only those patients who had diabetic foot associated with increased level of HbA1c. We found that the prevalence of DM-associated complications was higher among DFPs who had diabetes >10 years, which was consistent with previous studies [22, 23]. As the patients' age and their duration of T2DM increases, they were more susceptible to develop diabetic foot and other complications such as microvascular and macrovascular diseases [24]. In our study, the prevalence of diabetes was higher in the male as compared to female DFPs, similar results have been reported in other studies [25, 26].

Our results also indicated that one of the main characteristics of the diabetic foot ulcers was high glucose level in blood, since we found that the level of HbA1c was high in all 26 patients. A sedentary lifestyle and excess intake of carbohydrate might be one of the associated factors of uncontrolled HbA1c levels in the Saudi population. High levels of glucose in blood lead to structural changes in the skin, joint capsules and tendons. Principally, the skin loses the stretching capacity and can break easily, leading to the formation of an ulcer [27].

The observed prevalence of DPN was 57.7 % in DFPs, which was much higher than international reports [28]. But a similar high rate of DPN was reported in previous local studies [24, 29]. Risk of developing DPN is proportional to both the magnitude and duration of hyperglycemia. More than 80% of amputations occur after foot ulceration or injury, which can result from DPN [30]. Sorbitol and fructose accumulates in the blood because of hyperglycemia that causes reduced nerve conduction with neuropathy [31].

We also found that the prevalence of hypertension was 76.3% which is higher than previous reports [32, 33]. High level of glucose combined with hypertension can lead to diabetic nephropathy and retinopathy. In this study, 19.2% diabetic nephropathy

was reported which is consistent with previous international studies [34, 35]. Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes [36]. In the present study, 15.4% diabetic retinopathy was encountered which is lower than previous study [32, 37].

The observed prevalence of hyperlipidemia was 43.9% in DFPs. However, Female DFPs had higher rate of prevalence of hyperlipidemia as compared to male DFPs, which is consistent with previous local and international findings [9, 32, 38, 39]. Dyslipidemia contributes to the risk of macrovascular disease, nephropathy, and retinopathy [40].

The prevalence of CAD and PVD were found 19.2% and 23.1% respectively among DFPs which was less than previous studies [24, 37, 38]. There were no significant differences between genders. Macrovascular disease when associated with diabetes is most leading cause of mortality [41]. The overall cumulative effect of hypertension, DPN, PVD and CAD leads to ischemia in the lower extremity and an increased risk of diabetic foot [42-44].

CONCLUSIONS

We conclude that DFPs are having high prevalence of hypertension, neuropathy and hyperlipidemia in Saudi population and it is progressive. Most of the patient admitted at the hospital with higher percentage of HbA1c and advance stages of diabetic foot ulcers and their associated complication. Duration of diabetes, HbA1c, high blood pressure, PVD and DPN are main determinant risk factors for diabetic foot and its complications. Early diagnosis of diabetes and tight control of serum glucose, lipid and blood pressure may be helpful. Further prospective studies are suggested to validate these results.

Limitations of the study

First, All information regarding the patients was based on their hospital records. Second limitation of our study is the low number of patients with diabetic foot.

Conflict of interest

The authors report no conflicts of interest in this work.

REFERENCES

- Mathers, C. D., & Loncar, D. (2006) Projections of global mortality and burden of disease from 2002 to 2030, *PLoS Medicine*, 3(11), e442.
- International Diabetes Federation. (2017). IDF Diabetes Atlas. 6th ed. Brussels: IDF.
- Al-Daghri, N. M., Al-Attas, O. S., Alokail, M. S., Alkharfy, K. M., Yousef, M., Sabico, S. L., & Chrousos, G. P. (2011). Diabetes mellitus type 2 and other chronic non-communicable diseases in the central region, Saudi Arabia (Riyadh cohort 2): a decade of an epidemic. *BMC medicine*, 9(1), 76.
- Khawaja, N., Abu-Shennar, J., Saleh, M., Dahbour, S. S., Khader, Y. S., & Ajlouni, K. M. (2018). The prevalence and risk factors of peripheral neuropathy among patients with type 2 diabetes mellitus; the case of Jordan. *Diabetology & metabolic syndrome*, 10(1), 8.
- Chawla, A., Chawla, R., & Jaggi, S. (2016). Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian Journal of Endocrinology and Metabolism*, 20(4), 546–551.
- Amin, N., & Doupis, J. (2016). Diabetic foot disease: from the evaluation of the “foot at risk” to the novel diabetic ulcer treatment modalities. *World Journal of Diabetes*, 7(7), 153–164.
- Rebolledo, O. R., & Dato, S. A. (2005). Postprandial hyperglycemia and hyperlipidemia-generated glycoxidative stress: its contribution to the pathogenesis of diabetes complications. *European review for medical and pharmacological sciences*, 9(4), 191.
- Goldstein, B. J., Gomis, R., Lee, H. K., & Leiter, L. A. (2007). Type 2 diabetes: treat early, treat intensively. *International Journal of Clinical Practice Supplement*, 61(157), 16–21.
- Khan, A. R., Lateef, Z. N., Fatima, S., Al Yousuf, S. A., Afghan, S. Z., & Al Marghani, S. (2014). Prevalence of chronic complication among type 2 diabetics attending primary health care centers of Al Ahsa district of Saudi Arabia: a cross sectional survey. *Global Journal of Health Science*, 6(4), 245-253.
- Bortoletto, M. S. S., de Andrade, S. M., Matsuo, T., Haddad, M. D. C. L., González, A. D., & Silva, A. M. R. (2014). Risk factors for foot ulcers—a cross sectional survey from a primary care setting in Brazil. *Primary care diabetes*, 8(1), 71-76.
- Waijman, R., de Haart, M., Arts, M. L., Wever, D., Verlouw, A. J., Nollet, F., & Bus, S. A. (2014). Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. *Diabetes care*, 37(6), 1697-1705.
- [12] Monteiro-Soares, M., Boyko, E.J., Ribeiro, J., Ribeiro, I., & DinisRibeiro, M. (2012). Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metabolism Research and Reviews*, 28, 574-600.
- Shahbazian, H., Yazdanpanah, L., & Latifi, S. M. (2013). Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of International Working Group on Diabetic Foot (IWGDF). *Pakistan journal of medical sciences*, 29(3), 730-734.
- Iraj, B., Khorvash, F., Ebneshahidi, A., & Askari, G. (2013). Prevention of diabetic foot ulcer. *International journal of preventive medicine*, 4(3), 373-376.
- McEwen, L. N., Ylitalo, K. R., Herman, W. H., & Wrobel, J. S. (2013). Prevalence and risk factors for diabetes-related foot complications in Translating Research Into Action for Diabetes (TRIAD). *Journal of Diabetes and its Complications*, 27(6), 588-592.
- Neville, R. F., Kayss, A., Buescher, T., & Stempel, M. S. (2016). The diabetic foot. *Current Problems in Surgery*, 53, 408–437.
- Al-Rubeaan, K., Al Derwish, M., Ouizi, S., Youssef, A. M., Subhani, S. N., Ibrahim, H. M., & Alamri, B. N. (2015). Diabetic foot complications and their risk factors from a large retrospective cohort study. *PloS one*, 10(5), e0124446.
- Huysman, F., & Mathieu, C. (2009). Diabetes and Peripheral Vascular Disease. *Acta Chirurgica Belgica*, 109(5), 587-594.
- Hingorani, A., LaMuraglia, G. M., Henke, P., Meissner, M. H., Loretz, L., Zinszer, K. M., ... & Mills Sr, J. L. (2016). The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *Journal of vascular surgery*, 63(2), 3S-21S.
- Kasznicki, J. (2014). Advances in the diagnosis and management of diabetic distal symmetric polyneuropathy. *Archives of Medical Science*, 10(2), 345–354.
- Driver, V. R., Fabbi, M., Lavery, L. A., & Gibbons, G. (2010). The costs of diabetic foot: the economic case for the limb salvage team. *Journal of American Podiatric Medical Association*, 100(5), 335-41.
- Cortez, D. N., Reis, I. A., Souza, D. A., Macedo, M. M., & Torres, H. D. (2015). Complications and the time of diagnosis of diabetes mellitus in primary care. *Acta Paulista Enfermagem*, 28(3), 250–255.
- Momin, A. A., Bankar, M. P., & Bhoite, G. M. (2013). Glycosylated hemoglobin (HbA1C): association with dyslipidemia and predictor of cardiovascular diseases in type 2 diabetes mellitus patients. *International Journal of Health Sciences and Research*, 3(8), 40-46.
- Al-Wakeel, J. S., Hammad, D., Al Suwaida, A., Mitwalli, A. H., Memon, N. A., & Sulimani, F.

- (2009). Microvascular and macrovascular complications in diabetic nephropathy patients referred to nephrology clinic. *Saudi Journal of Kidney Diseases and Transplantation*, 20(1), 77-85.
25. Musa, I. R., Ahmed, M. O., Sabir, E. I., Alsheneber, I. F., Ibrahim, E. M., Mohamed, G. B., ... & Gasim, G. I. (2018). Factors associated with amputation among patients with diabetic foot ulcers in a Saudi population. *BMC research notes*, 11(1), 260.
 26. Wang, D. D., Bakhotmah, B. A., Hu, F. B., & Alzahrani, H. A. (2014). Prevalence and correlates of diabetic peripheral neuropathy in a Saudi Arabic population: a cross-sectional study. *PloS one*, 9(9), e106935.
 27. Christman, A. L., Selvin, E., Margolis, D. J., Lazarus, G. S., & Garza, L. A. (2011). Hemoglobin A1c predicts healing rate in diabetic wounds. *Journal of Investigative Dermatology*, 131(10), 2121-2127.
 28. Davies, M., Brophy, S., Williams, R., & Taylor, A. (2006). The prevalence, severity and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*, 29(7), 1518-1522.
 29. Akbar, D. H., Mira, S. A., Zawawi, T. H., Malibary, H. M. (2000). Sub clinical neuropathy: a common complications in Saudi diabetics. *Saudi Medical Journal*, 21(5), 433-437.
 30. Boulton, A. J., Vinik, A. I., Arezzo, J. C., Bril, V., Feldman, E. L., Freeman, R., Malik, R. A., Maser, R. E., Sosenko, J. M., & Ziegler, D. (2005). Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care*, 28(4), 956-62.
 31. Michael, J. F. (2008). Microvascular and macrovascular complications of diabetes. *Clinical diabetes*, (26), 77-82.
 32. Abdulghani, H. M., AlRajeh, A. S., AlSalman, B. H., AlTurki, L. S., AlNajashi, N. S., Irshad, M., ... & Ahmad, T. (2018). Prevalence of diabetic comorbidities and knowledge and practices of foot care among diabetic patients: a cross-sectional study. *Diabetes, metabolic syndrome and obesity: targets and therapy*, 11, 417-425.
 33. Famuyiwa, O. O., Sulimani, R. A., Laajam, M. A., Al-Jasser, S. J., & Mekki, M. O. (1992). Diabetes mellitus in Saudi Arabia: the clinical pattern and complications in 1,000 patients. *Annals of Saudi medicine*, 12(2), 140-151.
 34. Shatnawi, N. J., Al-Zoubi, N. A., Hawamdeh, H. M., Khader, Y. S., Garaibeh, K., Heis, H. A. (2018). Predictors of major lower limb amputation in type 2 diabetic patients referred for hospital care with diabetic foot syndrome. *Diabetes, Metabolic Syndrome and Obesity*, 22(11), 313-319.
 35. Gross, J. L., De Azevedo, M. J., Silveiro, S. P., Canani, L. H., Caramori, M. L., & Zelmanovitz, T. (2005). Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes care*, 28(1), 164-176.
 36. Fong, D. S., Aiello, L., Gardner, T. W., King, G. L., Blankenship, G., Cavallerano, J. D., ... & Klein, R. (2004). Retinopathy in diabetes. *Diabetes care*, 27(suppl 1), s84-s87.
 37. Noor, S., Ahmad, J., Parwez, I., & Ozair, M. (2016). Culture-based screening of aerobic microbiome in diabetic foot subjects and developing non-healing ulcers. *Frontiers in Microbiology*, 7, 1792.
 38. Scaini, S. F., Franzen, E., & Hirakata, V. N. (2018). Effects of nursing care on patients in an educational program for prevention of diabetic foot. *Revista Gaucha de Enfermagem*, 29, 39:e20170230
 39. Sosale, A., Kumar, K. P., Sadikot, S. M., Nigam, A., Bajaj, S., Zargar, A. H., & Singh, S. K. (2014). Chronic complications in newly diagnosed patients with type 2 diabetes mellitus in India. *Indian journal of endocrinology and metabolism*, 18(3), 355-360.
 40. Rhim, B., & Harkless, L. (2012). Prevention: can we stop problem before they arise? *Seminars in Vascular Surgery*, 25(2), 122-128.
 41. Picard, F., Adjedj, J., & Varenne, O. (2017). Diabetes Mellitus, a prothrombotic disease. *Annales de Cardiologie et d'Angéiologie (Paris)*, 66(6), 385-392.
 42. Clayton, W., & Elasy, T. A. (2009). A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients. *Clinical diabetes*, 27(2), 52-58.
 43. Ferguson, T. S., Tulloch-Reid, M. K., Younger, N. O. M., Wright-Pascoe, R. A., Boyne, M. S., McFarlane, S. R., ... & Wilks, R. J. (2013). Diabetic foot complications among patients attending a specialist diabetes clinic in Jamaica: prevalence and associated factors. *West Indian Medical Journal*, 62(3), 216-223.
 44. Boulton, A. J. (2008). The diabetic foot: grand overview, epidemiology and pathogenesis. *Diabetes/metabolism research and reviews*, 24(S1), S3-S6.