Correlation Between Extracutaneous Microvascular Complications and Diabetic Foot Ulcers in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetes is a metabolic disease that is taking an epidemic proportion around the world. The occurrence of microvascular complications and diabetic foot ulcer is associated with an increased mortality and morbidity incidence, which is the most serious complication of this disease, which significantly reduce the quality of patient life. Objective. The aim of the study was to determine the correlation of extracutaneous microvascular complications with diabetic foot ulcer in patients with type 2 diabetes. Method. The study was prospective, and included 160 patients with type 2 diabetes. It was conducted at the University Clinical Center of the Republic of Srpska in the period from January 2016 until December 2019. The respondents were adults, of both sexes, suffering from type 2 diabetes, in whom complications of this disease are present. Glycemic control was established based on a target HbA1c value of 7%. Results. Of the 160 patients in the study, 53.8% were men and 46.2% were women. The average age of the patients was 70.11±10.05 years. Extracutaneous microvascular complications were present in 85 patients (53.1%); of which 30.2% had well-regulated glycemia (HbA1c≤7.0%), while 61.5% (p<0.001) had unregulated glycemia (HbA1c≥7.0%). Polyneuropathy was present in 23.3% of patients with HbA1c≤7.0%, while 41.0% of patients had HbA1c<7.0% (p=0.043). Nephropathy with HbA1c≤7.0% was present in 36.8% of cases compared to patients with HbA1c<7.0% in whom the prevalence was 36.8% (p=0.004). Out of total, 25.6% had retinopathy with HbA1c<7.0% (p=0.021). At the same time, 5.6% of patients had a diabetic foot ulcer with polyneuropathy (p=0.010), 4.4% had neuropathy (p=0.058) and 5.6% had retinopathy (p=0.014). Conclusion: The high incidence of extracutaneous microvascular complications and diabetic foot ulcer in patients with type 2 diabetes requires a multidisciplinary approach of medical professionals that includes prevention of risk factors and good regulation of glycemia.

Key words: Diabetes mellitus, microvascular complications, diabetic ulcer foot.

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of glycemia may be associated with the pathogenesis of vascular damage (oxidative stress, endothelial damage, inflammation) leading to the development of micro and macrovascular complications (8). On the other hand, studies show that strict glycemic control as a standard in clinical approach can improve long-term outcomes, or postpone the development of microvascular complications, and thus improve the quality of life of patients (9-10).

2. OBJECTIVE

The aim of our study was to determine the correlation of extracutaneous microvascular complications with diabetic foot ulcer in patients with type 2 diabetes mellitus.

3. PATIENTS AND METHODS

The study was prospective, and included 160 patients with type 2 diabetes mellitus. It was conducted at the University Clinical Center of Republic of Srpska (UCC RS) in Banjaluka, in the period from January 2016 to December 2019 at the Skin and Venereal Diseases Clinic of the UCC RS. This study was approved by the Ethics Committee of the UCC RS.

The respondents were adults, of both sexes, suffering from type 2 diabetes mellitus. They were referred for hospital treatment or were treated as outpatients referred by a family doctor and other internal medicine and surgical branches of medicine. All patients underwent glycemic control based on HbA1c (%). In accordance with the American Diabetes Association (ADA) recommendations for target values of HbA1c 7%, good glycemic control, respondents were divided into two groups.

Group I consisted of respondents with good glycemic control, HbA1c <7.0%, while Group II consisted of respondents with unregulated glycemic values, HbA1c >7.1%. Body mass index (BMI) and anamnestic data related to the time (years) of diabetes and the therapy they use (insulin-dependent / independent therapy) were determined. In the clinical study, this study used relevant laboratory analyzes of blood and urine, and in addition to examinations by endocrinologists, it also used consultative examinations by other specialists in order to confirm the diagnosis of microvascular complications.

Statistical analyses were carried using IBM Statistics SPSS 22 software package. The data were described by mean values and standards deviations (SD) for continuous variables and incidence, and percentage for categorical variables. The differences between subgroup mean values were analyzed by the t-test and the one-way analysis of variance (ANOVA) depending on the number of groups. The chi-squared test was used to determine whether there was a significant difference between incidences of categorical variables. The p-values lower than 0.05 were considered as significant.

4. RESULTS

In a study of 160 adult patients diagnosed with type 2 diabetes mellitus, with various microvascular complications and diabetic foot ulcer, there were 86 men and 74 women (53.8% and 46.2%) whose average age was 70.11±10.05 years. According to HbA1c values, respon-
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Patients were divided into two groups, group I with well-regulated glycemic values (HbA1c <7.0%) and group II with unregulated glycemic values (HbA1c >7.1%).

In Group I, 43 respondents (26.9%) had well-regulated glycemic control. The average age in this group was 71.6±8.87 years. In group II, 117 respondents (73.1%) had unregulated glycemic control. The average age of the respondents in this group was 69.56±10.43 years.

There were 15 (34.9%) obese patients (BMI> 25 kg/m²) in group I, while there were 76 (65.9%) obese respondents in group II, which is a statistically significant difference (p=0.001) (Table 1). The correlation of obesity with microvascular complications was not statistically significant except in retinopathy where 41.8% of respondents with this complication had a BMI> 25 kg m².

There were 93 patients on insulin therapy (58.1%), 41.9% of respondents had good glycemic control, while 64.1% of respondents had unregulated glycemic control, which is a significant statistical difference (p=0.018). The majority of respondents with unregulated glycemic control values (27.4%) had been diagnosed with diabetes mellitus more than 20 years ago compared to well-controlled glycemia (7.0%), which is a statistically significant difference (p=0.006) (Table 1).

Examining the presence of extracutaneous microvascular complications in patients with type 2 diabetes mellitus in our study, out of a total of 160 respondents, 85 respondents (53.1%) had microvascular complications. Of these, in group I 30.2% of respondents had well-regulated glycemia (HbA1c<7.0), while in group II, 61.5% of respondents had unregulated glycemic values (HbA1c>7.1%) which is a statistically significant difference (p=0.001). Polyneuropathy was present in a total of 58 respondents (36.3%); in group I, in well-regulated glycemia in 23.3% of patients and in group II in 41.0% of patients, which is of statistically significant difference (p=0.043). Out of total, 49 respondents or 30.6% had nephropathy. In group I there were 14.0% of respondents, and in group II 36.8% of respondents with HbA1c>7.1% and nephropathy, which is a statistically significant difference (p=0.004). Retinopathy was present in 60 respondents or 37.5%, in group I there were 25.6% of patients, and in group II 41.9%, which was not statistically significant difference (p=0.067). A total of 13 respondents (8.1%) had diabetic foot ulcer in our study; in group I there was no occurrence of this complication (0.0%) while in group II all 13 patients were in the group with unregulated glycemic values or 11.1%, which is a statistical significance (p=0.021) (Table 2).

In our study, the total number of respondents with diabetic foot ulcer was 13. The simultaneous appearance of this complication and polyneuropathy was present in 9 cases or 5.6% (p=0.010), which is statistically significant. The simultaneous appearance of diabetic foot ulcer and neuropathy was present in 7 cases or 4.4% (p=0.058), which is not statistically significant. Of the 13 respondents with diabetic foot ulcer, 9 (5.6%) had retinopathy at the same time, which is statistically significant difference (p=0.014) (Table 3).

### Table 2. Prevalence of extracutaneous complications and diabetic foot ulcer in patients with type 2 Diabetes mellitus

| Extracutaneous microvascular complications | Diabetic foot ulcer |
|-------------------------------------------|---------------------|
| Polyneuropathy                             | Total |
| Yes                                       | 9     | 49 | 58 | 5.6% | 30.6% | 36.3% |
| % of Total                                |       |    |    |      |       |       |
| No                                        | 4     | 98 | 102| 2.5% | 61.3% | 63.7% |
| % of Total                                |       |    |    |      |       |       |
| Nephropathy                               | Total |
| Yes                                       | 7     | 51 | 58 | 5.6% | 31.9% | 37.5% |
| % of Total                                |       |    |    |      |       |       |
| No                                        | 4     | 96 | 100| 2.5% | 60.0% | 62.5% |
| % of Total                                |       |    |    |      |       |       |
| Retinopathy                               | Total |
| Yes                                       | 9     | 51 | 60 | 5.6% | 31.9% | 37.5% |
| % of Total                                |       |    |    |      |       |       |
| No                                        | 4     | 96 | 100| 2.5% | 60.0% | 62.5% |
| % of Total                                |       |    |    |      |       |       |
| Total                                     | Count | 13 | 147| 160 | 8.1% | 91.9% | 100.0% |

### Table 3. Correlation of diabetic foot ulcer with extracutaneous microvascular complications

Extracutaneous microvascular complications

| Variables | All patients N=160 | Group I (HbA1c <7.0%) N=43 | Group II (HbA1c ≥7.1) N=117 |
|-----------|-------------------|----------------------------|-----------------------------|
| Extracutaneous microvascular complications (N, %) | | | |
| Yes | 85 | 53.1% | 13 | 30.2% | 72 | 61.5% |
| No | 75 | 46.9% | 30 | 69.8% | 45 | 38.5% |
| p value | 0.001 | | | | | |
| Polyneuropathy | | | | | | 0.043 |
| Yes | 58 | 36.3% | 10 | 23.3% | 48 | 41.0% |
| No | 102 | 63.7% | 33 | 76.7% | 69 | 59.0% |
| Nephropathy | | | | | | 0.004 |
| Yes | 49 | 30.6% | 6 | 14.0% | 43 | 36.8% |
| No | 111 | 69.4% | 37 | 86.0% | 74 | 63.2% |
| Retinopathy | | | | | | 0.067 |
| Yes | 60 | 37.5% | 11 | 25.6% | 49 | 41.9% |
| No | 100 | 62.5% | 32 | 74.4% | 68 | 58.1% |
| Diabetic foot ulcer | | | | | | 0.021 |
| Yes | 13 | 8.1% | 0 | 0% | 13 | 11.1% |
| No | 147 | 91.9% | 43 | 100% | 104 | 88.9% |

Table 2. Prevalence of extracutaneous complications and diabetic foot ulcer in patients with type 2 Diabetes mellitus

Table 3. Correlation of diabetic foot ulcer with extracutaneous microvascular complications
5. DISCUSSION

Type 2 diabetes mellitus is a metabolic disease of chronic character and a large part of the burden of this disease is caused by its complications, which are divided into two groups: macrovascular (heart disease, stroke) and microvascular complications (polyneuropathy, nephropathy, retinopathy) (11). Microvascular complications are the leading cause of blindness, renal failure, and lower limb amputation in patients of all ages, including children and adolescents (12–13). Our study showed that extracutaneous microvascular complications were statistically significantly more common in elderly respondents with poorer glycemic control (HbA1c>7.1%) and were positively correlated with the duration of diabetes, which is consistent with the results of other scientific studies (9, 13-14).

Diabetic polyneuropathy, associated with neuropathic pain, diabetic foot ulcers, and autonomic dysfunction, is associated, like diabetic nephropathy, with a significant risk of mortality and reduced quality of life. In our study, the prevalence of polyneuropathy was 61.5%.

In diabetics, 30-40% of patients with HbA1c>7.1% and hypertension will develop diabetic nephropathy or chronic renal failure, which is a significant public health problem and lead to high treatment costs (15-16). Studies show that an important risk factor that contributes to the development of chronic microvascular complications, including this, is oxidative stress, which can adversely affect the action of acidic growth factor in fibroblasts, which has a protective effect against it, as well as strong angiogenic activity (17). In our study, the prevalence of nephropathy was in 36.8%.

Diabetic retinopathy, as a common complication of diabetes, remains the leading cause of blindness among the working-age population. For decades, diabetic retinopathy was considered only a microvascular complication, but the microvascular structure of the retina is closely related and guided by neurons and glia, which are affected even before clinically visible vascular lesions and visual field problems in patients (18). Therefore, early detection of diabetic retinopathy is crucial in the prevention of irreversible visual impairment. In our study, the prevalence of retinopathy was 41.9% in the group with poor glycemic regulation, or HbA1c>7.1%.

The average age of the respondents in our study, in total sample, was 70.11±10.05 years and in most respondents the glycemic control was poor, HbA1c>7.1%. These results are consistent with other scientific studies showing that the incidence of microvascular complications is significant in the elderly with poorer glycemic control (19-20).

In our study, 56.9% of the total number of respondents were obese (BMI> 25 kg/m²). There were statistically significantly more obese respondents with unregulated HbA1c values>7.1% compared to obese respondents with HbA1c<7.0% (34.9%) and only in the case of retinopathy it was shown that of the total number of respondents with BMI>25 kg/m², 41.8% of them have this microvascular complication, which is in line with the results of other scientific studies showing that obesity and poor glycemic control are significant risk factors for microvascular complications including diabetic foot ulcer (21-23).

In our study, 58.1% of the respondents were on insulin therapy. The majority of respondents (64.1%) had statistically significantly unregulated glycemic values of HbA1c>7.1% compared to respondents with HbA1c<7.0% and this is positively correlated with the duration of diabetes and age of the respondents, which is in accordance with the results of other scientific studies showing that in addition to the duration of diabetes, the development of chronic complications in unregulated glycemia of insulin-dependent patients leads to significant impairment of physical and mental health of patients and death (24-26).

In diabetics, macrovascular and microvascular complications greatly contribute to an increased risk of developing diabetic foot ulcers and consequent lower limb amputations (27). Zafar et al. find in their study that the prevalence of diabetic foot ulcer is relatively high in diabetics with diabetes longer than ten years, which is confirmed by other scientific studies (28-30). In our study, diabetic foot ulcer was statistically significantly more prevalent in respondents with unregulated glycemic values (in 11.1% of respondents). Other studies also confirm that risk factors for the development of diabetic foot ulcers include poor glycemic regulation and peripheral neuropathy, smoking, previous history of ulcers, foot deformities, diabetic nephropathy (especially in hemodialysis patients) and previous amnesia amputations (31). The results of the study show that the success rate of treatment and healing of ulcers / wounds is higher in patients with better regulated HbA1c values (32).

The results of our study show that the simultaneous appearance of diabetic ulcer on the foot and some of the microvascular complications is statistically significant. Namely, the results show that respondents with diabetic foot ulcer also have polyneuropathy in a statistically significant percentage (p = 0.010). Abdissa et al state that the connection between these two complications is conditioned by diabetic polyneuropathy, which causes loss of protective feeling of pain, loss of pressure perception and damage to microcirculation (33). Scientific studies also show that peripheral occlusive disease is a risk factor for the development of these complications in 15% of cases, as well as neuropathic and dystrophic tissue that is particularly susceptible to infections and injuries, especially in the elderly (34–35). The comorbid association of diabetic ulcer and nephropathy in our study was not statistically significant (p = 0.058) as confirmed by other studies that also found no association of diabetic foot ulcer with diabetic renal dysfunction, including other risk factors such as hypertension, serum creatinine, microalbumin, proteins in urine, HbA1c (36).

On the other hand, Rastogi et al. point out that prevalent nephropathy and incidental amputation after the development of diabetic foot ulcer are an indicator of increased mortality in patients and not glycemic control or previous coronary artery disease (37). The results of our study show that diabetic retinopathy is statistical-
ly significantly associated with diabetic foot ulcer and strongly predicts the occurrence of ulcers in the same patient (p=0.014). Recent scientific studies have identified certain genetic factors (single nucleotide variants) that are involved in the pathology of the development of diabetic retinopathy, although their precise mechanisms remain unclear (38). The results of other scientific studies show that the incidence of proliferative diabetic retinopathy is 3.9 times higher in patients with chronic diabetic foot ulcer in older males (14, 39).

6. CONCLUSION

There is an increased risk of extracutaneous microvascular complications, especially polyneuropathy and retinopathy, which may cause increased mortality in patients with type 2 diabetes mellitus who have had unregulated HbA1c glycemic values for many years and who have a diabetic foot ulcer. Adequate preventive examinations and better metabolic control of diabetes can lead to a reduction in the development of these complications and an improvement in the quality of patient’s life.

REFERENCES

1. Faselis C, Katsimardou A, Konstantinos I et al. Microvascular complications of Type 2 Diabetes Mellitus. Current Vascular Pharmacol. 2020; 18(2): 117-124.
2. IDF Diabetes Atlas. 8th ed. International Diabetes Federation; 2017.
3. Gian AA, Fadini P. Microvascular complications in diabetes: A growing concern for cardiologists. Int Journ Cardiovasc Med. 2019; 29: 29-35.
4. Arambewela MH, Somasundaram NP, Jayasekara HBPR et al. Prevalence of Chronic Complication, Their Risk Factors, and the Cardiovascular Risk Factors among Patients with Type 2 Diabetes Attending the Diabetic Clinic at a Tertiary Care Hospital in Sri Lanka. Journal of Diabetes Research 2018. Available from URL http://doi.org/10.1155/2018/4504287.
5. Lim JZM, Ng NSL, Thomas C. Prevention and treatment of diabetic foot ulcers. Journal of the Royal Society of Medicine 2017; 110(3): 104-109.
6. Adem AM, Andargie AA, AB Teshale et al. Incidence of diabetic foot ulcer and its Predictors Among Diabetes Mellitus Patients at Felege Hiwot Referral Hospital, Bahir Dar, North Ethiopia: A Retrospective Follow-Up Study. Diabetes Metab Syndr Obes. 2020; 13: 3703-3711.
7. Bowling F, Rashid S, Boulton A. Preventing and treating foot complications associated with diabetes mellitus. Nat Rev Endocrinol. 2015; 11: 606-616.
8. Škrha J, Soupla J, Škrha J Jr et al. Glucose variability, HbA1c and microvascular complications. Reviews in Endocrine and Metabolic disorders 2016; 17: 103-110.
9. Gibson CH, Goebel-Fabbri A. Microvascular Complications Associated With Improvements in Glycemic Control in Diabetes. Curr Diabetes Report 2017; 17: 48.
10. Trikkalinou A, Papazafiroupolou AK, Melidonis A. Type 2 diabetes and quality of life. Word J Diabetes 2017; 8(4): 120-129.
11. Cheema S, Mainsonneuve P, Zirie M et al. Risk Factors for Microvascular Complications of Diabetes in a High-Risk Middle East Population. Journal of Diabetes Reserch 2018. Available from URL http://doi.org/10.1155/2018/8964027.
12. Msanda D, Reis K, Kayange N. et al. Diabetic Microvascular Complications Among Children and Adolescents in North-western Tanzania: A Cross-Sectional Study. Ann Glob Health 2020; 86(1): 43.
13. Fawwad A, Mustafa N, Zafar AB. et al. Incidence of microvascular complications of type 2 diabetes: A 12 year longitudinal study from Karachi-Pakistan. Pak J Med Sci. 2018; 34(5): 1058-1063.
14. Selman A, Katzman P, Andreason et al. Complications Presence of chronic diabetic foot ulcers is associated with more frequent and more advanced retinopathy. Dia Bet Med. 2018; 35: 1364-1379.
15. Bönkhof GJ, Herder C, Strom A et al. Emerging Biomarkers, Tools, and Treatments for Diabetic Polyneuropathy. Endocrine Reviews. 2019; 40(1): 153-192.
16. Umanath K, Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018. Am J of Kidney Diseases. 2018; 71(6): 884-895.
17. Pena AM, Chen S, Feng B et al. Prevention of Diabetic Nephropathy by Modified Acidic Fibroblast Growth Factor. Nephron. 2017; 137: 221-236.
18. Rübsam A, Parihk S, Fort PR. Role of Inflammation in Diabetic Retinopathy. Int J Mol Sci. 2018; 19(4): 942.
19. Nanayakkara N, Ranasingha S, Gadowksi A. et al. Age, age at diagnosis and diabetes duration are all associated with vascular complications in type 2 diabetes. Journal of Diabetes and its Complications. 2018; 32(3): 279-290.
20. Herrington WG, Alegre-Diaz J, Wadw R. et al. Effect of diabetes duration and glycaemic control on 14-year cause-specific mortality in Mexican adults; a blood – based prospective cohort study. The Lancete Diabetes and Endocrinology 2018; 6(6): 455-463.
21. Bijelic R, Balaban J, Milicevic S et al. The Association of Obesity and Microvascular Complications with Glicemic Control in Patients with Type 2 Diabetes Mellitus. Med Arch. 2020; 74(1): 8-15.
22. Katsiki N, Panagiotis A, Kalliopi K. et al. Obesity, Metabolic Syndrome and the Risk of Microvascular Complications in Patients with Diabetes mellitus. Curr Pharmaceut Design 2019; 25(18): 2051-2059.
23. Abro M, Zafar AB, Fawwad A. et al. Prevalence of diabetic microvascular complications at a tertiary care unite of Karachi, Pakistan. Int Journal of Diabetes in Developing Countries. 2019; 39: 325-330.
24. Martino G, Catalano A, Bellone F et al. As time Goes by: Anxiety Negatively affects the Perceived Quality of Life in Patients With Type 2 Diabetes of Long Duration. Front Psychol. 2019. Available from URL http://doi.org/10.3389/fpsyg.2019.01779.
25. Kim Hj, an Sy, Han Sj. et al. The association of diabetes duration and glycemic control with depression in elderly men with type 2 diabetes mellitus. J Res Med Sci. 2019; 24: 17.
26. Ghouse J, Jonas L, Iasken MS. et al. Effect of diabetes duration on the relationship between glycaemic control and risk
of death in older adults with type 2 diabetes. Diabetes Obes Matab. 2020; 22: 231-242.
27. Orsanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. Journal of the American College of Cardiology. 2009; 53(5): 35-42.
28. Zafar S, Rahim K, KhanIU et al. Prevalence and Association of Diabetic Retinopathy with Diabetic Foot Ulcer: A Cross-Sectional Observational Study. Frontiers in Ophtalmology and Ocular Imaging. Alireza Ziaei IntechOpen. Available from URL http://doi: 10.5772/intechopen.82667
29. Almobarak A, Awadalla H, Osman M. et al. Prevalence of diabetic foot ulceration and associated risk factors: An old and still major public health problem in Khartoum, Sudan. Annals of Translational Medicine. 2017; 5(17): 340.
30. Hwang DJ, Lee KM, Park MS. et al. Association between diabetic foot ulcer and diabetic retinopathy. PloS One 2017; 12(4): e0175270.
31. American Diabetes Association. Microvascular complication and foot care. Sec.10. In Standars of Medical Care in Diabetes 2017. Diabetic Care. 2017; 40(1): 88-98.
32. Xiang J, Wang S, He Y. et al. Reasonable Glycemic Control Would Help Wound Healing During the Treatment of Diabetic Foot Ulcers. Diabetes Ther. 2019; 10: 95-105.
33. Abdissa D, Adugna T, Gerema U. et al. Prevalence of Diabetic Foot ulcer and Associated Factors among Adult Diabetic Patients on Follow-Up Clinic at Jimma Medical Center, Southwest Ethiopia, 2019: An Institutional-Based Cross-Sectional Study. Journal of Diabetes Research 2020; Article ID 4106383 Available from URL http://doi.org/10.1155/2020/4106383
34. Yazdanpanah L, Shahbazian H, Nazari I et al. Incidence and Risk Factors of Diabetic Foot Ulcer: A Population-Based Diabetic Foot Cohort ( ADFC study)- Two Year Follow-Up Study. Internal Journal of Endocrinology 2018; ID 767631659. Available from URL http://doi.org/10.1155/2018/7631659
35. Volmer-Thole M, LobmannR. Neuropathy and Diabetic Foot Syndrome. Int J Mol Sci. 2016; 17(6): 917.
36. Mahmood K, Aziz A. Risk Factors Developing Diabetic Foot Ulcer with Nephropathy, Diabetic Kidney Disease and Renal Failure Statistical Analysis of 10,680 Patients’ Cohort. Med Rxiv. 2020. Available from URL http://doi.org/10.1101/2020.06.11.20128488
37. Rastogi A, Goyal G, Kesavan R. et al. Long term outcomes after incident diabetic foot ulcer: Multicenter large cohort prospective study (EDI-FOCUS investigators) epidemiology of diabetic foot complications study: Epidemiology of diabetes foot complications study. Diabetes Research and Clinical Practice. 2020; 162: 108-113.
38. Mrozikiewicz- Rakowskal B, Lukawska M, Nehring P et al. Genetic predictors associated with diabetic retinopathy in patients with diabetic foot. Pol arch Intern Med. 2018; 128(1): 926-933.
39. Hoag A, Sohn JH, Foster A. Association between diabetic retinopathy and diabetic foot ulcer in South Texas. Investigative Ophthalmology&Visual Science. 2020; 61: 4838.