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Research Article

Long-Term Visual Outcomes in Diabetic Patients with Diabetic Foot Ulcers with and without Peripheral Vasculopathy and Diabetic Neuropathy

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Abstract

Introduction: Diabetes affects 11.6% of South Texans, leading to disabling conditions including diabetic foot ulcers (DFU) and diabetic retinopathy (DR). Peripheral vasculopathy (PV) and diabetic neuropathy (DN) have been reported as independent risk factors for developing DFU. However, the relationship between systemic parameters of DFU (PV and DN) and ocular outcomes of DR (visual acuity) remain unknown. Therefore, we investigated visual outcomes of diabetic patients with DFU alone compared to patients with additional PV or DN in relation to diabetic retinopathy (DR).

Methods: A retrospective review was done on patients visiting a tertiary center in San Antonio that were diagnosed with DFU and underwent ophthalmic and neurovascular examinations within the past 10 years; 144 diabetic eyes were included. The prevalence of DR with DFU with or without concomitant PV or DN was assessed using visual acuity (Log MAR) as the primary endpoint.

Results: The study group of 144 eyes (72 subjects) had an average age of 59.9 and was 54.2% male. At the final visit, proliferative diabetic retinopathy (PDR) was found in 73.4% of the DFU-only group, 75.0% of the DFU-with-PV group, and 73.4% of the DFU-with-DN group. New onset of PDR was noted in 43.3% of DFU-only, 63.3% of DFU-with-PV, and 54.1% of DFU-with-DN during the follow-up period ($p > 0.05$). Initial average visual acuity, represented by Log MAR, was 0.627 for the DFU-only, 0.491 for DFU-with-PV, and 0.514 for the DFU-with-DN. Final average visual acuity was 0.429 for DFU-only, 0.515 for DFU-with-PV, and 0.593 for DFU-with- DN. With an average follow-up period of 50.7 months, the DFU-only group demonstrated an average Log MAR change of -0.198 compared to +0.024 in the DFU-with-PV group and +0.078 in the DFU-with-DN group ($p = 0.036$). Furthermore, diabetic patients with DFU were more likely to require panretinal photocoagulation (PRP) during the follow-up period if they experienced concomitant PV (72.9%) compared to DFU alone (60.9%) or with concomitant DN (29.7%, $p = 0.0007$).

Conclusion: Most patients with DFU experienced a progression of DR to PDR. DFU patients with DN experienced significant declining visual acuity despite necessary treatment for DR. Those with PV were slightly more likely to develop PDR and were significantly more likely to receive PRP treatment. All patients with DFU should undergo timely retinal examinations and management to prevent premature blindness from DR-in particular those with PV and DN.

Keywords: *Diabetic Retinopathy; Peripheral Vasculopathy; Foot Ulcer; Neuropathy; Diabetes; Proliferative Diabetic Retinopathy*

Introduction

An estimated 8.3% of Americans (25.8 million people) have diabetes and if current trends continue, that proportion is estimated to rise to one in three American adults by 2050 [1]. About 2 - 3% of diabetics will develop a diabetic foot ulcer (DFU) each year. DFU develops in

association with chronic diabetic neuropathy (DN) and peripheral vasculopathy (PV) and affects 15 - 20% of diabetics in their lifetime, DFU is the most common cause of both non-traumatic foot amputation worldwide and hospitalization in patients with diabetes [2-5].

While DFUs often arise secondary to diabetic neuropathy or peripheral vasculopathy, this is not always the case. Yunus., *et al*. reported that although DFU patients were more likely to have associated neuropathy when compared to diabetics without ulcers, still less than half of DFU patients experience painful neuropathy [6]. Thus, for some patients, dual diagnoses of DFU and DN may represent a more severe manifestation of diabetes than either alone. Likewise, Rahman., *et al*. describe a population in Pakistan where vasculopathy was detected in only 19 of 30 patients during laboratory vascular assessments, suggesting that although often associated with one another, some DFUs exist independently of clinical vasculopathy [7].

Among the strongest independent risk factors for developing DFUs are peripheral neuropathy and peripheral vascular disease [8-10]. Previous studies have suggested that these same microvascular and neuropathic mechanisms contributing to DFU may also have a role in diabetic retinopathy (DR), one of the major causes of blindness worldwide [5,11,12]. Several studies have revealed an association between DR, neuropathy, and vasculopathy, but current research has been mixed regarding the relationship between DFU and DR. Hwang., *et al*. showed no significant association between DR and DFU severities but found increased prevalence of proliferative diabetic retinopathy (PDR) in patients with DFU compared to those without DFU [11]. Utilizing a different DFU grading system than Hwang., *et al*, Shahbazian., *et al*. found that retinopathy was significantly more prevalent in neuropathic diabetics with a history of DFU or related amputation [13].

The current landscape of associating DFU with DR leaves much to be elucidated, including consideration of the relationship between their shared underlying mechanisms. Despite the debilitating effects of DFUs and DR, little is known regarding the relationship between the underlying systemic concerns of DFUs (PV and DN) and ocular outcomes of DR (visual acuity). Therefore, we investigated visual outcomes of diabetic patients with DFU alone compared to patients with additional PV or DN in relation to diabetic retinopathy (DR).

Materials and Methods

A retrospective review of 144 eyes from 72 patients with DFU who visited the Department of Ophthalmology at the University of Texas Health San Antonio at least once between January 2012 and January 2022 was conducted. Only patients with type 2 diabetes mellitus diagnosed with a DFU were included. All patients presented to the ophthalmology clinic with a diagnosis of DFU and underwent at least two ophthalmic exams.

The change in severity of DR and in visual acuity (calculated as final visit LogMAR minutes initial visit LogMAR) was assessed for DFU patients who met the inclusion criteria. In addition, information regarding the concomitant presence of PV and DN was collected. Patients with DFU were then divided into three groups based on additional PV and/or DN presence: DFU-only vs. DFU-with-PV vs. DFU-with-DN. Information regarding macular edema (ME), vitreous hemorrhage (VH), tractional retinal detachments (TRD), history of vitrectomy, number of PRP treatments, intravitreal injections and demographic characteristics were additionally compared between groups.

Retinopathy assessment was determined through fundoscopy of the entire retina following mydriasis by a retina specialist. After a thorough fundoscopic exam, patients showing any features of DR underwent color fundus photography using an Optos ultra-wide field fundus camera (Optos, United Kingdom). A single fundus photograph centered on the fovea was taken for each eye and all photographs were reviewed by a retina specialist. The presence and severity of DR were graded into one of five stages based off guidelines from the Global Diabetic Retinopathy Project Group: no retinopathy; mild, moderate, or severe non-proliferative DR (NPDR); and proliferative DR (PDR).

PRP was performed in cases of PDR without concurrent visually significant macular edema, new-onset iris neovascularization (NVI), high-risk PDR (as defined by the Diabetic Retinopathy Study), or new fibrovascular membranes. The number of laser shots was limited to 800-1500 per session. Additional PRP sessions were performed in cases with progressive proliferative disease despite prior PRP treatments.

Approval for this study was obtained from the Institutional Review Board and the methods utilized comply with the Health Insurance Portability and Accountability Act (HIPAA).

Statistical analysis

Statistical analyses were performed using Graphpad Prism (Graphpad Software, San Diego, CA, USA). Multivariate analyses using ANOVA with a posthoc Tukey test was performed for visual acuity between the three groups: DFU only, DFU + PV, and DFU + DN. The relationship between ME, VH, TRD, PRP, vitrectomy history, injection, and demographic data among the three groups were evaluated by chi-square testing. Statistical significance was defined as $p < 0.05$.

Results

This study included 144 eyes from 72 patients. The mean age of the DFU patients was 59.9 ± 11.0 years (range, 36 - 85 years) and 39 subjects (54.2%) were male. Overall, 46.53% (67/144) of DFU patients had a PDR diagnosis at the initial visit. This rate increased to 73.61% (106/144) by the final visit. Among all DFU patients in this present study, PDR conversion from NPDR was observed in 50.65% (39/77).

The average length of follow up between initial and final visits was 50.0 ± 26.9 months (range, 2.5 - 110 months). At the initial visit, proliferative diabetic retinopathy (PDR) was found in 53.1% of the DFU-only group, 35.4% of the DFU-with-PV group, and 42.2% of the DFU-with-DN group. At the final visit, PDR was found in 73.4% of the DFU-only group, 75.0% of the DFU-with-PV group, and 73.4% of the DFU-with-DN group. New onset of PDR was noted in 43.3% (13/30) of the DFU-only group, 63.3% (19/31) of the DFU-with-PV group, and 54.1% (20/37) of the DFU-with-DN group during the follow-up period ($p > 0.05$, chi-square).

At the beginning of the study period, the average HgbA1c of the DFU-only group was 7.5%, the DFU-with-PV group 8.7%, and the DFU-with-DN group 8.9%. The final HgbA1c of each group was 8.0%, 7.6%, and 7.8% respectively. The DFU-only group experienced an average increase of +0.5% in A1c over the course of the study compared to a net decrease of -1.1% in the DFU-with PV group ($p = 0.011$, ANOVA) and -1.0% among DFUs-with-DN ($p = 0.013$, ANOVA).

Average blood pressure over the course of the study was also measured. Initial average blood pressures measured 145/79 for DFU-only, 145/78 for DFU-with-PV, and 147/82 for DFU-with DN. The final average blood pressure for each group was 143/75 for DFU-only, 141/71 for DFU-with-PV, and 133/71 for DFU-with-DN. The DFU-only group experienced an average decrease of 2.0 mmHg systolic and 3.5 mmHg diastolic throughout the study. The DFU-with-PV group experienced a decrease of 4.4 mmHg systolic and 6.8 mmHg diastolic, and DFU-with-DN a decrease of 14 mmHg systolic and 11 mmHg diastolic ($p > 0.05$, ANOVA).

Initial average visual acuity, represented by Log MAR, was 0.627 for the DFU-only group, 0.491 for the DFU-with-PV group, and 0.514 for the DFU-with-DN group. Final average visual acuity was 0.429 for the DFU-only group, 0.515 for the DFU-with-PV group, and 0.593 for the DFU-with-DN group. Over the course of the study, the DFU-only group demonstrated an average LogMAR change of -0.198 compared to +0.024 in the DFU-with-PV group and +0.078 in the DFU-with-DN group ($p = 0.036$).

Furthermore, diabetic patients with DFU and PDR were more likely to require PRP during the follow-up period if they experienced concomitant PV (72.9%) compared to DFU alone (60.9%) or with concomitant DN (29.7%, $p = 0.0007$). Among DFU-only patients, 60.94%

(39/64) required and received PRP during the length of this study compared to 72.92% (35/48) of the DFU-with-PV group and 29.69% (19/64) of the DFU-with-DN group ($p < 0.05$, chi-square). When comparing the DFU-with-PV group against the DFU-with-DN group, this significance further increased ($p < 0.0001$). The three groups were further analyzed based on the total number of PRP treatments each eye required. Multivariable analysis comparing the three groups demonstrated statistical significance ($p = 0.0299$). Comparing the DFU-only and DFU-with-PV groups alone by posthoc Tukey revealed further significance ($p = 0.0250$). No significant differences between the three groups were found for macular edema, tractional retinal detachments**,** anti-VEGF injections, or vitrectomy history.

Discussion

Our findings suggest that patients presenting to clinic with existing diagnoses of both DFU and DN ultimately suffer worse visual acuity outcomes compared to patients with only a DFU diagnosis or a diagnosis of DFU and PV. When comparing A1c levels among each group, initially, the DFU-with-DN group had the highest A1c average. Yunus., *et al*. when describing the separation of DFU and DN diagnoses, noted that poor glycemic control at the onset of diagnosis may exacerbate neuropathic pain, alerting providers to the presence of DN and correlating with the higher initial A1c seen in the DFU-with-DN group [6]. However, over the course of our study, the DFU-with-DN group was surpassed by the DFU-only group in terms of average A1c, suggesting a mechanism alternative to A1c fluctuations may be responsible for decreased visual acuity in neuropathy. One explanation for the A1c observation in our study is that DFU-with-DN and DFU-with-PV started with higher A1c levels and had multiple diabetic sequelae documented. Both factors would signal to primary care providers the necessity of stricter blood glucose control, leading to a significant lowering of their A1c compared to DFU-only patients who generally started with lower A1c values and a single diabetic sequelae (DFU) documented.

Prior studies have suggested neurodegeneration as a contributor to the progression of DR in addition to the well-established notion that microvascular disease underpins retinopathy. Rasheed., *et al*. studied 500 patients with type 2 diabetes and reported a significant association between DR and DN, finding significant thinning of the ganglion cell (GC) and inner plexiform layer (IPL) in patients with DN compared to diabetics without neuropathy. They also demonstrated that this neurodegeneration precedes the onset of clinical DR and affected patients' visual acuity [14]. Several other authors have proposed common pathophysiologic mechanisms behind peripheral neuropathy and retinopathy, including the secondary effects of glycation products, oxidative stress, inflammation, and accelerated atherosclerosis and plaque formation [15-22].

Given the fact that DN is often considered less acutely threatening than DFU alone in the primary care setting, our study suggests it is worthwhile for patients with concomitant DN to receive more prompt screening and referral if necessary for possible retinopathy. In addition, DFU patients with DN may benefit from closer follow-up in ophthalmology clinics. Studies in animal models have suggested that somatostatin, a known neuroprotective molecule produced by the retina, may have utility as a topical application for the treatment of DR [23-26]. Other proposed targets for neuroprotection include pigment epithelium derived factor, which has known anti-inflammatory and neurotrophic properties via nitric oxide (NO) and receptor for advanced glycation end products (RAGE) expression and glucagon-like protein 1 (GLP1) [27-32].

For these DFU patients with DN, the development of additional neuroprotective treatment modalities would provide significant potential in preserving visual acuity in the long-term. In our study group of DFU-with-PV, we observed a higher incidence of PDR (63.3% or 19/31) compared to DFU-only patients (43.3% or 13/30) and DFU-with-DN patients (54.1% or 20/37). However, this measure itself was not statistically significant. Patients in the DFU-with-PV group had a higher proportion of vitreous hemorrhage (50.0% or 24/48) compared to DFU-only (42.2% or 27/64) and DFU-with-DN (45.3% or 29/64) and required significantly greater numbers of PRP treatments over the course of their care ($p < 0.05$) [18]. As areas of the retina become increasingly ischemic, neovascularization develops with vitreous hemorrhage, prompting further laser treatment [33].

Our retrospective study's limitations include the DFU-only group members not always presenting to their primary care provider with a chief complaint or symptoms of vasculopathy, neuropathy, or associated pain, which would mitigate additional diagnoses of PV or DN. Further, diabetic foot ulcer patients may not have received proper evaluation of concurrent DN or PV with monofilament or ankle-brachial index testing at the time of DFU diagnosis.

Conclusion

In conclusion, DFU patients upon diagnosis deserve a timely eye exam for DR and vice versa, especially if they have additional PV and/or DN as these are associated with worsening long-term visual outcomes. Though our data shows worsening vision despite appropriate treatment, detecting these diabetic sequelae earlier would be beneficial in rendering these treatments more effective in these patients' futures.

The majority of those with DFU who presented to an ophthalmology clinic, regardless of additional PV and/or DN, experienced a worsening of their DR to PDR. Despite appropriate medical, laser, and surgical treatments, DFU-with-DN patients experienced significantly worse vision over time. Those with concomitant PV were slightly more likely to develop PDR and vitreous hemorrhages and were significantly more likely to require PRP treatment. All patients with DFU should undergo timely retinal examinations and management to prevent premature blindness from DR. In addition, patients with multiple systemic manifestations of DFU, especially PV and DN, should receive higher stratification for such screenings. A better understanding of the relationship between DR and the systemic manifestations of diabetes will help in creating a coordinated approach to managing these life-altering conditions.

Conflict of Interest

No financial interest or any conflict of interest exists among the authors of this article.

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