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Retinal arteriole tortuosity changes over time in a veteran population with diabetes

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ABSTRACT

Purpose: Arteriole tortuosity is an important sign of retinal disease which is associated with diabetic retinopathy, but it is unclear how arteriole tortuosity changes over time in populations with diabetes. It has been suggested that retinal vasculature geometry changes precede diabetic retinopathy. Here, we evaluate whether arteriole tortuosity changes precede diabetic retinopathy by examining arteriole tortuosity and retinopathy at two points in time four years apart.

Methods: A population of 126 subjects had retinal photographs at baseline and approximately four years later (48 ± 9 months) in a telehealth screening program. The photographs from both eyes at baseline and follow up were graded for tortuosity (straight, wavy, or tortuous) and retinopathy using clinical ETDRS guidelines. Consensus grades (across graders) were used, but when consensus was not reached or the image quality was too poor to grade, the subject was removed from analysis. Other health markers, such as duration of diabetes, hemoglobin A1c (HbA1c), neuropathy status, and insulin usage, were also recorded. Differences in time points were assessed with paired t-tests.

Results: Of the 109 subjects (218 eyes) included in final analysis, 24 eyes had retinopathy at baseline and 26 eyes had retinopathy at follow up, which was almost all mild (93%). Tortuosity was largely unchanged at follow up (76%) and on average was straight or wavy. Nine eyes had decreased tortuosity (4.3%). The final 19.7% had arteriole tortuosity which increased a level from baseline. The subjects with increased tortuosity had a shorter duration of diabetes at baseline (5.8 years vs 7.4 years, $p<0.04$). There was no relationship between retinopathy development and arteriole tortuosity increasing or between HbA1c and change in tortuosity.

Conclusions: It appears that retinal arteriole tortuosity may increase most over early years of diabetes development and then stabilize. Therefore, it may be more valuable to monitor retinal arteriole tortuosity in early years of diagnosis in both clinical and telemedicine settings. More research is needed following changes in tortuosity over time in patients with diabetes.

Introduction

Diabetes mellitus (DM) is a world-wide public health crisis with cases increasing at an epidemic rate [1]. The number of individuals with DM worldwide is predicted to grow to 429 million by 2030 [2]. DM can affect multiple systems in the body and may lead to various micro- and macro-vasculature complications, such as diabetic retinopathy, nephropathy, and peripheral neuropathy [3,4]. Patients with one microvascular complication are likely to have a higher incidence of other micro- or macro-vascular complications [4]. The vascular tree of the retina offers opportunity for in-vivo inspection and examination of the impact of systemic diseases on the microvasculature [3], and previous studies have reported an association between diabetic retinopathy and an increased risk of peripheral neuropathy [5]. Our previous work suggests that retinal arteriole tortuosity can be graded accurately by clinicians using a three-step scale [6,7]. Additionally, we found that increased retinal arteriole tortuosity was associated with increased levels of diabetic retinopathy [7]. Furthermore, it is known that individuals with early retinal arteriolar abnormalities were found to be more likely to have peripheral neuropathy [8].

Since diabetic retinopathy is a leading cause of preventable blindness in working-aged individuals in the United States [9], identifying

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biomarkers that may predict, precede, or accompany early manifestations of diabetic retinopathy is an important strategy to prevent blindness. Furthermore, if these biomarkers can be graded straightforwardly by primary care physicians, endocrinologists, optometrists, ophthalmologists, and telemedicine specialists, then potentially earlier eye care may be offered for diabetes patients, which could make an impact on public health. One such biomarker may be retinal arteriole tortuosity [10–14]. Our group has evaluated clinical tortuosity in other studies; however, our previous work in this area was a cross-sectional study, so we were unable to evaluate changes in arteriole tortuosity over time. It has been suggested that such changes to the retinal vasculature geometry could occur earlier than diabetic retinopathy [14,15]. It is not known how the vascular tree changes over time in early diabetes. In this current study, we set out to evaluate whether retinal arteriole tortuosity changes over time by examining the retinas of subjects with and without systemic complications of diabetes (i.e., peripheral neuropathy) at two points in time about four years apart. Our hypothesis is that tortuosity changes over time, increasing as diabetes progresses and that tortuosity changes can be evaluated in either a clinical or telemedicine setting.

Methods

Subjects

Two hundred forty-six subjects with type 2 DM were initially included in a case control study evaluating retinal tortuosity changes in peripheral neuropathy [16]. All the subjects underwent Diabetic Retinopathy Surveillance Screening via the teleretinal imaging program within the Southern Arizona Veteran Affairs Health Care System (SAVAHCS). As this study was designed to retrospectively evaluate retinal images captured as part of the teleretinal imaging program, the inclusion criteria for this screening program limited the available study population to those 76 years of age or younger with no history of laser surgery for diabetic retinopathy and best-corrected visual acuity better than 20/200 in each eye. A certified teleretinal imager captured the retinal images without use of mydriatic drops using a TRC—NW6S non-mydriatic digital fundus camera (topconhealthcare.com) following the Veterans Health Administration Teleretinal Imaging Program protocol [17]. These images were 45° across with three fields per eye: macula centered, disc centered, and superior temporal vascular arcade centered. Additional exclusion criteria for this study included diagnosis of type 1 DM, diagnosis of glaucoma or glaucoma suspect, diagnosis of age-related macular degeneration, and history of retinal vascular occlusion. Qualified subjects were selected in consecutive order. About half of the subjects initially selected (n = 124) had peripheral neuropathy and half did not (n = 122). This was done to allow for evaluation of retinal differences in subjects with more advanced systemic disease. All procedures adhered to the tenets of the Declaration of Helsinki, and the project was approved by the SAVAHCS Institutional Review Board and Research and Development Committee.

Fundus evaluation and data collection

Investigators who were not familiar with the subject data independently reviewed the retinal photographs from both eyes of the 246 subjects and graded the level of arteriole tortuosity and diabetic retinopathy using a combination of the three available fields for each eye. The investigators were masked to the gradings of the other investigators and subject data while reviewing the photographs. Arteriole tortuosity grading was based upon the categories described by Taarnhoj et al. [18]. and classified as straight, wavy, or tortuous as in our other publications [7,16]. The level of diabetic retinopathy was categorized according to the current standard of care [19] into five possible groups: no retinopathy, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, or proliferative diabetic retinopathy. However, none of the subjects had proliferative diabetic retinopathy. For both arteriole tortuosity and retinopathy, data from the graders was compiled and a consensus grade was assigned for each eye. If no consensus was reached for either metric in either eye, the subject (both eyes) was excluded from statistical analysis. Previously, we found venous tortuosity was not additive to arteriole tortuosity [7], thus only the arterioles were graded in this study.

Subject demographic information, all systemic medications prescribed for any condition (acute or chronic), and health factors at the time of the retinal photograph were also collected. Candidate measures for association with increased tortuosity included increased level of retinopathy, presence of nephropathy, increased inflammatory markers (i.e., erythrocyte sedimentation rate and/or C-reactive protein), higher hemoglobin A1c (HbA1c), and higher cholesterol (i.e., total cholesterol, HDL and/or LDL). Additionally, important confounders, such as duration of diabetes, age and sex of the subject, and blood pressure (systolic and diastolic) were also collected.

Follow up data

One hundred twenty-six of the original 246 subjects had follow up retinal photographs obtained 36–60 months after the first photograph (mean = 48 ± 9 months) and are presented in this follow up study. The inclusion criteria for the teleretinal program had to be met for subjects to remain eligible for follow up. Additional reasons for attrition include follow up outside of the study timeframe, relocating/moving, and death (n = 32). In the subjects who had follow up retinal photographs available, the level of arteriole tortuosity and diabetic retinopathy was graded in each eye as described above. While grading the retinal photographs, the graders deemed the images from 15 subjects as unreadable due to poor image quality, and there were two subjects without a consensus grade. Therefore, 218 eyes from 109 subjects were included in final analysis of data over time. Of the 109 subjects with follow up who were included in the final analysis, 42 had peripheral neuropathy at baseline and 67 did not. The study design of subject selection is shown in Fig. 1. Additional health markers at the time of follow up, such as HbA1c, cholesterol levels, blood pressure, neuropathy status, and if the subject was taking insulin was also recorded.

Statistical analysis

Overall data was analyzed with backward multivariate regression. Timepoints were evaluated for differences with paired t-tests.

Results

Baseline data and follow up data characteristics

The 109 subjects who had follow up data available for analysis were first evaluated as a subgroup at baseline. They were evaluated for their overall characteristics as well as for differences from the original cross sectional baseline data from our previous work [16]. Table 1 highlights this data for the three groups: original study population at baseline, subgroup with follow up at baseline, and the follow up data. The subgroup with follow up had a shorter duration of diabetes and slightly lower HbA1c than the originally selected cross sectional data. The subgroup with follow up included seven women (6.4%). Over the course of the follow up timeframe, four subjects initially without peripheral neuropathy developed peripheral neuropathy. Overall, the study population with follow up had an average cholesterol of 169.4 ± 36.7 mg/dL and well controlled blood pressure at baseline.

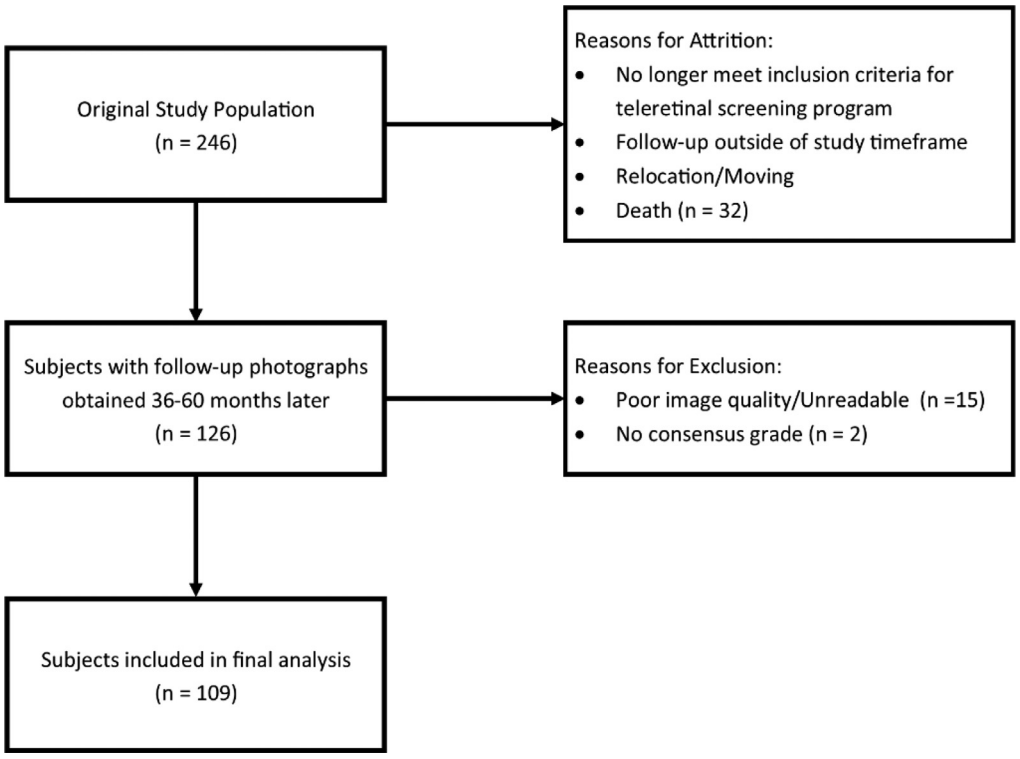

Fig. 1. Study design outlining subject selection.

One of the notable changes in evaluating the data over the follow up period was the number of subjects taking insulin. At the start of the study period, there were 26 subjects on insulin, but at follow up there were 40 subjects on insulin. There were 23 subjects who began insulin treatment and nine who discontinued insulin; the remainder were stable throughout the follow up window. There was no difference in HbA1c between the baseline and follow up, but this medication change shows a significant change of therapy for at least 32 subjects. The effect of change in insulin therapy as it relates to retinopathy and tortuosity was evaluated, but it was not significant in this sample (p = 0.77 and p = 0.88 for tortuosity and retinopathy, respectively).

Evaluation of retinopathy at baseline and follow up

In the original cross-sectional study population, 83 eyes from the 246 subjects had non-proliferative diabetic retinopathy. The 83 eyes came from 47 subjects with peripheral neuropathy and 20 subjects without peripheral neuropathy. Of these eyes with retinopathy, only 24 of the eyes (from 14 subjects) returned to the screening program for follow up. It is important to remember that eyes with retinopathy would not have met eligibility criteria for the teleretinal screening program, and those subjects would have been monitored for retinal changes with in-person comprehensive eye exams. In total, 26 eyes had retinopathy at follow up, which was almost all mild (93%) and the rest was moderate diabetic retinopathy. Only a few of the subjects progressed from no or mild retinopathy to moderate retinopathy in the follow up timeframe. Having retinopathy at follow up was associated with having peripheral neuropathy (p<0.0002).

Evaluation of arteriole tortuosity at baseline and follow up

Arteriole tortuosity, both at baseline and on follow up, was either straight or wavy on average. Arteriole tortuosity grades were largely

Table 1
Subject demographics for original study population at baseline, subgroup with follow data at baseline, subgroup at follow up. *Duration of diabetes was significantly different between the original and subgroup study populations.

	Baseline Original Study Population	Subgroup of Study Population with follow-up	Follow up (48 ± 9 months later)
Number of subjects	246	109	109
Age (years)	62.8 ± 7.9	58.9 ± 8.3	63.2 ± 8.3
Duration of Diabetes (years)*	11.3 ± 7.66	7.17 ± 5.5	11.3 ± 5.5
Hemoglobin A1c (%)	7.3 ± 1.4	7.1 ± 1.3	7.4 ± 1.3
Cholesterol (mg/dL)	168.3 ± 39.1	169.4 ± 36.7	160.9 ± 35.2
Systolic Blood Pressure (mmHg)	132.9	131.4	132.3
Diastolic Blood Pressure (mmHg)	76.1	76.0	75.1
Number of subjects taking insulin	80	26	40
Number of subjects with peripheral neuropathy	124	42	46
Number of eyes with diabetic retinopathy	83	24	26

unchanged over the follow up period (76% stayed the same). There were nine eyes with decreased arteriole tortuosity (4.3%). The final 19.7% had a higher degree of arteriole tortuosity over the follow up period.

When evaluating differences between those with and without increased tortuosity, it was noted that the subjects with increased arteriole tortuosity at follow up had a shorter duration of diabetes at baseline. The average was 5.8 years for those subjects who increased and 7.4 years for those who did not ($p < 0.04$). There was no relationship between retinopathy development and arteriole tortuosity increasing over time. There was no difference in age (average of 58.7 years for both groups). There was also no relationship between HbA1c and change in arteriole tortuosity (7.4% and 7.1% for same tortuosity and increased tortuosity, respectively). However, there was a relationship between having peripheral neuropathy and a higher degree of tortuosity ($p<0.001$). The sample size of subjects converting to peripheral neuropathy during the follow up window was not sufficient to evaluate them separately.

Discussion

Retinal arteriole tortuosity is an ideal biomarker for changes in diabetes because it can be incorporated into a clinical fundus examination or as part of a telemedicine/teleretinal program with ease. Telemedicine readers could add evaluation of tortuosity changes to their grading with very little additional effort. Notable changes may indicate further evaluation is needed. While there is software that can evaluate tortuosity well [20,21], the method described here is clinical and does not need additional software for evaluation. This could make it a valuable first step and an accessible biomarker to employ across eye exams and telehealth.

This study revealed two important findings regarding arteriole tortuosity in DM. First, it appears that arteriole tortuosity may increase most in the early years of diabetes pathogenesis as subjects with increased tortuosity over the study timeframe occurred in subjects with shorter durations of DM. Second, there is a relationship between the diagnosis of peripheral neuropathy and changes in the retina, both in retinopathy and arteriole tortuosity, over time. This study helps to establish a timeline of tortuosity changes occurring in the early years of diabetes development and then stabilizing prior to the development of additional complications such as neuropathy.

This follow up study shows that the increase of arteriole tortuosity tends toward subjects with shorter durations of diabetes. Thus, it may be more valuable for clinicians to monitor arteriole tortuosity in early years of diagnosis before retinopathy is present. It is also notable that the subjects with and without changes in arteriole tortuosity in the study had similar blood pressures which were generally well controlled. While it is known that blood pressure can cause tortuosity in retinal vessels [22], this is likely not the reason for changes in tortuosity in this dataset.

However, it remains unclear from this study why only a small proportion of subjects with DM have tortuosity changes over time. Our study did not find many changes in tortuosity with longer duration of diabetes, but other studies have found that the capillary microvasculature continues to remodel as diabetes progresses. The data presented here suggests the timeline of changes in the larger vessels may be different. Sasongko et al. [21]. evaluated tortuosity in a large cross-sectional group with diabetes and found that more tortuous vessels are associated with longer durations of diabetes. While it is difficult to compare a cross-sectional dataset with a follow up study, our findings are in line with this study; with longer durations, these vascular changes occurring in early DM would have already occurred and likely stabilized. Therefore, monitoring arteriole tortuosity may be a good target for future studies looking at diabetes development.

Previously we noted that arteriole tortuosity is not a good marker of advanced systemic changes; the data presented here are consistent with and add to our previous work. Other studies have found a relationship between ocular vascular metrics and systemic complications which support evaluating these changes in this study [3,8,14,15]. Rasmussen et al. found that neuropathy and nephropathy were associated with increased vessel branching in type 1 diabetes [3]. However, we do not know of any other studies specifically looking at neuropathy and arteriole tortuosity. In this study, we found that there was a relationship between the diagnosis of peripheral neuropathy and worsening in severity of diabetic retinopathy and a higher degree of tortuosity over time. Although arteriole tortuosity was not indicative of other systemic complications at any given point in time, knowing the systemic history of the patient may give valuable data about risk of pathological retinal changes. There was no relationship between these retinal changes and changes in insulin therapy or HbA1c.

This study has a few of limitations. The most important is that there is a selection bias with our study population by retrospectively reviewing data available from the teleretinal screening program. Since we only have access to the follow up data for subjects who remain in the teleretinal screening program, these subjects tend to be those who have healthier retinas and have a shorter duration of disease. Thus, our subgroup of subjects with follow up data may not be fully representative of a veteran population of patients with diabetes, with and without peripheral neuropathy, and may instead represent the healthier members of that population. This limitation of seeing only the healthier subjects does make our study more applicable to an average optometry practice which would tend to follow healthier patients in office and refer those patients with more advanced retinal disease. Additionally, we feel this information could be helpful for primary care providers who see healthier patients. The other limitation is that the smaller follow up sample size does not allow full evaluation of factors initially planned to be evaluated. For example, only four subjects converted to have peripheral neuropathy during our follow up timeframe, so this rate did not allow us to study the effect of this conversion on the eye in a meaningful way. Finally, there were 4% of subjects who had a decrease in tortuosity. As an improvement in tortuosity is biologically improbable, this likely represents intraobserver variability or error in the application of the tortuosity grading scale.

In conclusion, there are increases in arteriole tortuosity over time in about 20% of subjects who have controlled diabetes. This could be an important biomarker for changes in their diabetes disease progression. More follow up is needed to determine what makes this 20% different from the rest of the population. It appears that worsening of arteriole tortuosity tends to occur in the early years after diabetes diagnosis which may make it a more valuable biomarker early in the disease process. Moreover, additional study should be undertaken to better understand the relationship between the development of peripheral neuropathy and a higher degree of arteriole tortuosity over time. For doctors involved in telemedicine as well as clinicians, monitoring patients for arteriole tortuosity changes could be a valuable tool for evaluating overall retinal health and needs to be further explored.

Disclaimer

The contents of this work do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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