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Neural dysfunction and retinopathy in persons with type 1 diabetes

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Abstract

Objective: To determine associations of microvascular and neuropathic complications of diabetes cross-sectionally and longitudinally in persons with long-term type 1 diabetes (T1D).

Research Design and Methods: Persons receiving care for T1D in South Central Wisconsin were identified in 1979-1980 and examined approximately every five years. Associations between neuropathic and microvascular complications were examined at most prior visits, when information on several neuropathic complications was collected. Temporal relationships were examined by modeling incidence between examinations across the visits.

Results: Adjusting for duration of diabetes, glycated hemoglobin, and systolic blood pressure, the following were cross-sectionally associated with prevalent PDR (proliferative diabetic retinopathy): the presence of WESDR SN (sensory neuropathy reported at the WESDR examination) (odds ratio (OR)=2.76, confidence interval (CI)=1.71, 4.48) and the heartrate variability measures RMSD (square root of the mean of squared differences of successive RR intervals) (OR=0.24, CI=0.16, 0.37) and SDNN (standard deviation of successive RR intervals) (OR=0.26, CI=0.17, 0.39). Findings were similar for prevalent ME (macular edema) as assessed from spectral-domain optical coherence tomography (SD-OCT). The presence of PDR (OR=2.13, CI=1.63, 2.78) and ME (OR=2.36, CI=1.66, 3.34) were both significantly associated with incident WESDR SN. WESDR SN was associated with incident PDR (OR=1.53, CI=1.09, 2.15) but not incident ME (OR=1.31, CI=0.92, 1.87).

Conclusions: Sensory neuropathy and heartrate variability were significantly associated with prevalent PDR and ME in people with long-term T1D. PDR and ME were significantly associated with incident sensory neuropathy, and sensory neuropathy was significantly associated with

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incident PDR. Studies using earliest detectable markers of microvascular and neurologic abnormalities are needed to determine which of the two systems 'fails' first. Such information might suggest a temporal sequence of diabetes complications.

Introduction

Complications of diabetes are often attributed to the common ground of impaired microvascular function and/or structure.¹ Such sequelae include retinopathy,² nephropathy,³ and pathology in other microvascular beds such as those in the dermis.⁴ In addition, macrovascular sequelae may comprise additional outcomes associated with the microvascular pathology.⁵

Cognitive dysfunction has also been found to be associated with microvascular changes in persons with type 2 diabetes⁶ as well as adults with T1D.^{7–9}

However, there are data which suggest that neural changes such as apoptosis of many different retinal cells in different levels of the retina [e.g., ganglion, amacrine, and microglial cells] with different functional sequelae are manifestations of diabetes that may precede the development or detection of microvascular disease in humans.¹⁰ Furthermore, induced diabetes in a mouse model was associated with progressive thinning of the inner retina SD-OCT testing.^{10, 11} In addition, there may be functional neural changes such as altered contrast sensitivity,¹² abnormal color vision,¹³ and altered perimetry.¹⁴ Neural changes in the cornea, an avascular tissue,¹⁵ may precede proliferative diabetic retinopathy,¹⁶ though it is not known whether retinopathy precedes corneal neural changes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) provides an opportunity to observe long term complications of diabetes in persons with T1D and associations of microvascular and neuropathic complications through the duration of this condition. These potential associations are examined here.

Materials and Methods

Population

A systematic survey of eleven counties in South Central Wisconsin (Health Services Area 1) was done in 1978–79 to identify all persons receiving care for type 1 and type 2 diabetes.¹⁷ Participants at the first examination, 1980–1982, (n=996) were invited to follow-up examinations at approximately five-year intervals: 1984–1986 (n = 903) exam 2; 1990–1992 (n = 816) exam 3; 1994–1996 (n = 667) exam 4; 2000–2001 (n = 567) exam 5; 2005–2007 (n = 520) exam 6; and 2012–2014 (n = 414) exam 7. Most analyses are limited to cross-sectional data from those who participated at exam 7 because some neuropathic and microvascular complication measures were available for that examination only. Incidence analyses include data from exams 1, 2, 3, 4, 6, and 7, excluding exam 5 as PDR and ME because information concerning those outcomes were documented with a different photographic technique at that examination. Tenets of the Declaration of Helsinki were followed, the institutional review board approval was granted, and informed consent was obtained from each subject.

Interview, examination, laboratory and grading data

A standardized interview was conducted at each examination. We include here only those characteristics that are pertinent to this paper. This included questions concerning the participant's age, whether they had developed diabetes before the age of 30 and were initially and subsequently treated with insulin, and whether they had loss of sensation in their hands or feet or could tell the hotness or coldness of the things they touched. RMSD and SDNN, both of which are measures of heart rate variability and are related to autonomic dysfunction, were taken from standard 12 lead electrocardiograms measured according to the Minnesota code as applied by Epicare (E. Solomon). The latter characteristics were only available at the 5th and 7th examinations.

Postural hypotension, also related to autonomic function, was calculated by measuring blood pressure with the participant sitting and then repeating the measurement with the patient standing. At the most recent examination cognitive domains of mental efficiency and executive function were assessed, with Trail Making Test Parts A and B; Stroop Word and Interference Test; Grooved Pegboard; digit Symbol Substitution Test; and Verbal Fluency using the letters F, A, and S. Nonverbal Memory was assessed with the Rey Complex Figure Test and recall with Digit Symbol Substitution Test number-symbol pairs.¹⁸ Blood pressure, pulse, and standard electrocardiogram were taken according to protocol.¹⁹ Glycated hemoglobin (A1C) was measured in anti-coagulated whole blood on the Tosoh HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc. San Francisco, AC 94080).

Retinopathy lesions and macular edema were assessed from standardized stereoscopic fundus photographs using specific protocols.²⁰ In additional analyses, macular edema was identified from SD-OCT.

Definitions

Diabetes duration was defined by the period from date of diagnosis until the date of the examination contributing data to the specific analysis. A drop in systolic blood pressure from sitting to standing position of 20 mmHg or greater was considered postural hypotension. A positive response to either loss of sensation in hands or feet or hotness or coldness of things touched at any visit was considered evidence of sensory neuropathy, referred henceforth as Wisconsin Epidemiologic Study of Diabetic Retinopathy Sensory Neuropathy (WESDR SN). Cognitive dysfunction was defined based on the results of factor analysis with varimax rotation. Three domains were considered: executive function domain, nonverbal memory domain, and verbal memory domain. PDR was defined by the classification of either eye as level 60 or higher on the modified ETDRS severity scale.²⁰ ME from photographs was considered present if there was elevation of the retina with additional visual cues such as organized exudate, localized areas of the color orange, and deviation of the path of retinal blood vessels. ME from SD-OCT was defined by reflective space with well-defined margins in the retina or by the presence of at least one retinal cyst visible in at least 2 consecutive B-scans and larger than 15 microns vertically. Such cysts usually elevate or disrupt the retinal layers. If such changes occur in the presence of epiretinal membranes or vitreo-macular traction they were not considered ME. Table 1 lists the measures that were available at each examination.

Statistical analyses

SAS software (SAS Institute Inc., Cary, NC, Version 9.4) was used to perform all analyses. The relationships between neuropathic and microvascular complications were first examined cross-sectionally at exam 7, as this was the only examination during which all measures of interest were collected. Microvascular complications (PDR, ME as assessed from photographs, and ME as assessed from SD-OCT) were modeled using neuropathic complications (WESDR SN, RMSD, SDNN, postural hypotension, executive function, nonverbal memory, and verbal memory) separately as predictors. Logistic regression was used for all models, adjusting for diabetes duration, glycated hemoglobin, and systolic blood pressure. RMSD and SDNN were log-transformed for better model fit. Neuropathic complications were also explored as outcomes using microvascular complications as predictors, but results were similar and are not presented. We also examined the relationships between WESDR SN and the prevalence of PDR and ME as assessed from photographs at each of the earlier examinations (excluding exam 5).

Incidence relationships were modeled in order to explore the temporal sequence of neuropathic and microvascular complications. Incidence of PDR and ME were first modeled using the neuropathic complication WESDR SN as a predictor. Subsequently, incidence of WESDR SN was modeled using the microvascular complications PDR and ME separately as predictors. Due to unavailable detailed fundus photographs at exam 5, all models exclude incidence between exams 4 and 5 as well as exams 5 and 6. Logistic regression was used for all models, implementing generalized estimating equations to account for multiple examinations. Models were adjusted for diabetes duration, glycated hemoglobin, and systolic blood pressure.

Results

Outcomes with available data at each examination are given in Table 1.

Prevalence at exam 7

Table 2 shows the cross-sectional association of neuropathic complications with microvascular complications. To clarify the direction of relationships, the presence of sensory abnormalities, postural hypotension and cognitive dysfunction as well as less heart rate variability are complications of diabetes possibly mediated by vagal dysfunction. While adjusting for duration of diabetes, glycated hemoglobin, and systolic blood pressure, the presence of WESDR SN (OR=2.76, CI=1.71, 4.48) as well as having lower heart rate variability (OR=0.24, CI=0.16, 0.37 for RMSD and OR=0.26, CI=0.17, 0.39 for SDNN – per 5 unit change in each) were associated with increased odds of having prevalent PDR. Similarly, the presence of WESDR SN (OR= 3.23, CI=1.82, 5.72) and having lower heart rate variability (OR=0.41, CI=0.26, 0.67 for RMSD and OR=0.38, CI=0.24, 0.62 for SDNN – per 5 log unit change in each) were also associated with increased odds of having prevalent ME as assessed from photographs. The relationships between neuropathic complications and prevalent ME as assessed from SD-OCT were similar in direction and magnitude, but the associations were not as strong. Neither postural hypotension nor the

three cognitive dysfunction measures were significantly associated with any of the ocular complications.

Prevalence in exams 1, 2, 3, 4, 6

There was information on WESDR SN and both PDR and ME as assessed from photographs at exams 1–4 and 6. Prevalence analyses of these data indicated that the presence of WESDR SN was significantly associated with higher odds of having PDR as well as higher odds of having ME (Supplementary table). The ORs for the PDR models were similar across each examination, but the ORs for the ME models were greater at successively more recent examinations.

Incidence

Table 3 shows the associations of WESDR SN with incident PDR and ME as assessed from photographs. The presence of WESDR SN was modestly significantly associated with incident PDR (OR=1.53, CI=1.09, 2.15) but was not significantly associated with incident ME assessed from photographs (OR=1.31, CI=0.92, 1.87).

Table 4 shows the incidence associations of PDR and ME as assessed from photographs with WESDR SN. The presence of PDR (OR=2.13, CI=1.63, 2.78) and of ME (OR=2.36, CI=1.66, 3.34) were both significantly associated with incident WESDR SN.

Discussion

Findings from this study indicate that in long-term follow-up of persons with T1D there were significant cross-sectional associations of measures of neural abnormalities with PDR and ME. The associations between neural abnormalities and ME as assessed from photographs were greater at successively more recent examinations. The most recent prevalence information is important in that we were able to increase the number of measures of neural abnormalities assessed and confirm findings from other studies that many aspects of neural function and structure appear to be affected by diabetes (Table 2). These findings are corroborated by findings of others,^{21–25} including measures of autonomic dysfunction. This particular association appears to be stronger than the associations between the retinal outcomes and other measures of neural dysfunction. Autonomic dysfunction, as previously noted, is associated with diabetes,²⁶ and the autonomic nervous system regulates the degree of constriction or dilation of the blood vessels in body. It is possible that specifically autonomic neuropathy precedes or hastens the development of diabetic retinopathy. Further study is needed of the possibility that autonomic dysregulation may precede vascular dysfunction leading to morphologic abnormalities such as retinopathy and that resultant aberrations in the microvasculature have functional sequelae.

Aside from confirming our previous findings as well as those of others concerning the comorbidity of microvascular and neural abnormalities associated with diabetes, the WESDR provides the unique opportunity to examine long-term incidence associations as well as prevalence associations both current and at many times in the past. The incidence analyses indicate that PDR and ME precede WESDR SN with statistically significant ORs of 2.13 and 2.36 respectively, while WESDR SN precedes PDR with a more modestly

significant OR of 1.53 and does not have a significant association with ME incidence. It's possible that the strength and significance of the relationships between our microvascular measures and incidence of WESDR SN suggest to some readers that cases of microvascular abnormalities are causally related to the development of neural abnormalities. However, the microvascular and neural abnormalities are measured on different scales and both PDR and ME occur relatively late in the course of disease in most patients. Further, we measure the microvascular abnormalities from morphology as imaged in photographs but the measures of many of the neural findings that we found informative are from self-reported symptoms. Physiologic measures of pathologic pathways affecting both systems might permit a better understanding of the temporal associations of the neural and microvascular sequelae of diabetic complications.

Some investigators may have anticipated that ME as assessed from SD-OCT provides a more sensitive method to identify macular edema compared to photographs and therefore may have expected different associations to comorbidities, in this case to neural covariates. In our cross-sectional analyses, these relationships were similar and the specific frequency of co-occurrence of macular edema as assessed from photographs and specific neural characteristics were similar to those found for ME as assessed from SD-OCT with these neural characteristics (Table 2). It is possible that in observational investigations both modes of imaging provide equivalent information.

Limitations of this study derive largely from its nature as a long-term study of a group of persons defined by disease and age. Namely, selective survival and selective participation influenced by disease severity and treatment as well as senescence have likely affected prevalence estimates at each examination phases as well as incidence. In addition, the methods of evaluation of microvascular and neural abnormalities were limited by resources and by the state of technology at different examination phases. In the future, studies need to be undertaken to remedy deficiencies in this study design to further understand the development of microvascular and neural abnormalities, with an eye to determining whether preventive intervention early in the course of abnormalities in one of these systems will prevent or delay abnormalities in the other.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Summary of Measures Available at Each Examination

Examination	Vascular and Neurological Complications of Interest									
	Vascular Complications			Sensory Neuropathy	Autonomic Neuropathy			Cognitive Dysfunction		
	PDR	ME (Fundus)	ME (OCT)	WESDR SN	RMSD	SDNN	Postural Hypotension	Executive Function Domain	Nonverbal Memory Domain	Verbal Memory Domain
1	✓	✓		✓						
2	✓	✓		✓						
3	✓	✓		✓						
4	✓	✓		✓						
5				✓	✓	✓				
6	✓	✓		✓						
7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2:
The Cross-sectional Association of Neurological Complications with Microvascular Complications

Predictor	PDR [†]			ME (Photographs) ^{††}			ME (OCT) ^{†††}		
	N (% PDR)	OR (95% CI)	P	N (% ME)	OR (95% CI)	P	N (% ME)	OR (95% CI)	P
WESDR SN [*]									
Absent	203 (39.4%)	Ref.	<.001	174 (20.7%)	Ref.	<.001	172 (23.3%)	Ref.	<.001
Present	118 (66.1%)	2.76 (1.71, 4.48)	.	88 (46.6%)	3.23 (1.82, 5.72)	.	84 (47.6%)	2.86 (1.63, 5.02)	.
RMSD (per 5 log units) ^{**}	302 (49.0%)	0.24 (0.16, 0.37)	<.001	244 (28.7%)	0.41 (0.26, 0.67)	<.001	241 (31.1%)	0.58 (0.38, 0.89)	0.011
SDNN (per 5 log units) ^{***}	302 (49.0%)	0.26 (0.17, 0.39)	<.001	244 (28.7%)	0.38 (0.24, 0.62)	<.001	241 (31.1%)	0.56 (0.37, 0.86)	0.006
Postural hypotension									
Absent	262 (45.4%)	Ref.	0.117	222 (27.5%)	Ref.	0.481	219 (30.6%)	Ref.	0.993
Present	42 (61.9%)	1.73 (0.87, 3.46)	.	28 (35.7%)	1.38 (0.57, 3.37)	.	31 (32.3%)	1.00 (0.42, 2.34)	.
Executive function domain (per 1 unit)	204 (43.6%)	0.84 (0.56, 1.25)	0.386	169 (19.5%)	0.84 (0.48, 1.46)	0.532	171 (25.7%)	1.12 (0.68, 1.85)	0.655
Verbal memory domain (per 1 unit)	225 (44.9%)	1.15 (0.88, 1.49)	0.304	185 (24.9%)	1.11 (0.78, 1.58)	0.556	186 (30.1%)	1.37 (0.98, 1.91)	0.066
Nonverbal memory domain (per 1 unit)	212 (45.3%)	1.31 (0.90, 1.92)	0.157	175 (24.0%)	0.75 (0.46, 1.22)	0.246	176 (29.5%)	0.94 (0.60, 1.48)	0.801

^{*} Wisconsin Epidemiologic Study of Diabetic Retinopathy Sensory Neuropathy

^{**} Mean of Squared Differences of Successive RR Intervals from Standard Electrocardiogram

^{***} Standard Deviation of Successive RR Interval from Standard Electrocardiogram

[†] Proliferative Diabetic Retinopathy

^{††} Macular Edema from Fundus Photography

^{†††} Macular Edema from Optical Coherence Tomography

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Table 3:

Association of WESDR SN with PDR and ME Incidence

Predictor	PDR [†] Incidence		ME ^{††} (Photographs) Incidence		
	N (% SN)	OR (95% CI)	P	N (% SN)	OR (95% CI)
WESDR SN [*]					
Absent	1469 (12.7%)	Ref.	0.020	1514 (10.2%)	Ref.
Present	323 (20.4%)	1.53 (1.09, 2.15)	.	361 (14.7%)	1.31 (0.92, 1.87)

^{*} Wisconsin Epidemiologic Study of Diabetic Retinopathy Sensory Neuropathy
[†] Proliferative Diabetic Retinopathy
^{††} Macular Edema from Fundus Photography

Table 4:

Association of PDR and ME with WESDR SN Incidence

Predictor	WESDR SN* Incidence		
	N (% Disease)	OR (95% CI)	P
PDR [†]			.
Absent	1741 (12.7%)	Ref.	<.001
Present	508 (27.2%)	2.13 (1.63, 2.78)	.
ME ^{††} (Photographs)			.
Absent	1591 (13.3%)	Ref.	<.001
Present	208 (29.8%)	2.36 (1.66, 3.34)	.

* Wisconsin Epidemiologic Study of Diabetic Retinopathy Sensory Neuropathy

[†] Proliferative Diabetic Retinopathy^{††} Macular Edema from Fundus Photography