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Diabetic retinopathy and dementia in type 1 diabetes

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Abstract

Objective—Retinopathy impacts over one-third of those with diabetes mellitus and is associated with impaired cognitive performance and cerebrovascular lesions in middle-aged adults with type1 diabetes. However, the association between diabetic retinopathy (DR) and risk of dementia in type 1 diabetes is unknown. We investigated the association between DR and incident dementia in a large, elderly population with type 1 diabetes.

Methods—A cohort of 3,742 patients with type 1 diabetes aged ≥50 was followed from 01/01/1996–09/30/2015 for incident dementia. DR diagnoses were identified from electronic medical records. Age as timescale Cox proportional hazard models evaluated associations between time-updated DR and dementia risk. Models were adjusted for demographics, severe glycemic events, glycosylated hemoglobin, and complications of diabetes.

Results—Out of 3,742 patients with type 1 diabetes (47% female, 21% non-white), 182 (5%) were diagnosed with dementia during a mean follow-up of 6.2 years. No significant association was found between DR and incident dementia in the main analyses (aHR=1.12, 95% CI 0.82–1.54), nor among subgroup restricted to those aged ≥ 60 or ≥ 70 years.

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Conclusion—DR was not associated with risk of dementia, suggesting that pathophysiological processes underlying dementia may be different in type 1 versus type 2 diabetes.

Keywords

Type 1 diabetes; dementia; retinopathy; epidemiology; diabetes mellitus; cohort studies

Introduction

Advances in medical care have allowed patients with T1D to reach higher ages than ever before by preventing or delaying severe complications.[1] Unfortunately, the increase in longevity provides new challenges. Recent studies have indicated that patients with T1D may be at increased risk for dementia.[2–4] This is concerning, since T1D treatment relies heavily on the patients' cognitive abilities, and treatment mistakes could potentially be fatal. As there is currently no curative treatment for dementia, exploration of potentially modifiable risk factors is imperative towards better clinical care and preventative measures.

Diabetic retinopathy impacts more than 33% of adult individuals with type 1 diabetes.[5] In diabetic retinopathy, the retinal microvascular circulation is damaged by the effects of diabetes. Recently, the retinal microvasculature has been gaining interest as a possible in vivo marker of brain integrity because of the high correlation with the state of the cerebral microvasculature. Indeed, retinal and cerebral microvasculature have similar embryological origin, similar anatomical features and physiological properties. Furthermore, several studies have found a associations between retinal microvascular changes and dementia risk in the general population, and with poorer cognitive performance and cerebrovascular lesions in younger populations of type 1 diabetes.[6]

The hypothesis of DR being associated with increased dementia risk is supported by previous work in older patients with type 2 diabetes.[7] However, data on type 2 diabetes cannot be extrapolated to type 1 diabetes since there are marked differences in disease origin, onset and treatment between type 1 and type 2 diabetes. To the best of our knowledge, determinants of a relationship between type 1 diabetes and clinically diagnosed dementia have not been studied before, thus it is currently completely unknown whether, and how, DR affects dementia risk in type 1 diabetes.

Exploring processes linking type 1 diabetes and dementia can aid in unraveling the pathogenesis of dementia and its relationship to diabetes. If microvascular changes or other pathophysiological processes involved in the development of DR significantly contribute to development of dementia in older patients with type 1 diabetes, the presence of diabetic retinopathy is expected to be associated with dementia in this cohort. Furthermore, if associated with dementia, diabetic retinopathy could serve as an easily measurable and serially evaluable marker to aid clinicians in targeted dementia prevention and screening. In the current study, we aim to investigate whether diabetic retinopathy is associated with an increased risk of dementia during follow up in a large, well-defined cohort of older patients with type 1 diabetes.

Methods

Study population

For this study, we evaluated all members of Kaiser Permanente Northern California (KPNC) database for eligibility during the study period. KPNC is a large, integrated healthcare delivery system that provides comprehensive medical care to over 30% of the geographical region (3 million members). The population of KPNC generally provide a good representation of the overall regional population, with the exception of extreme tails of the income distribution.[8,9] Senior (≥65+) members of KPNC are similar to seniors residing in the region with respect to history of chronic conditions, including diabetes, hypertension, heart disease and lifestyle factors (e.g. smoking, a sedentary lifestyle and obesity).

Analytic cohort

Members of KPNC with type 1 diabetes, with no prevalent dementia diagnoses, and at least 50 years old at any time within the study period (01/01/1996 until 9/30/2015) were eligible for our dynamic cohort. Patients were considered to have type 1 diabetes if they fit all three of the following criteria[10] : a) had either two International Statistical Classification of Diseases, ninth edition (ICD-9) codes for type 1 diabetes without any type 2 diabetes codes, or a ratio of type 1:type 2 diabetes ICD-9 codes higher than or equal to 0.75 in the Kaiser Permanente electronic database since start of membership; b) filled insulin prescriptions during the study period; and c) did not have filled prescriptions of any hypoglycemic agent other than insulin or metformin. Both insulin prescription and oral hypoglycemic agents were retrieved from the Kaiser Permanente pharmacy databases.

Baseline date was set at entry date into the cohort, which was either I) date at which patients reached the age of 50 for those with type 1 diabetes during the study period, or II) date of first type 1 diagnostic code during the study period for those aged 50 or older. Members were followed until incident dementia diagnosis, lapse in of KPNC membership, death, or end of study (9/30/2015). Lapse in KPNC membership was defined as a membership lapse of ≥90 days. Deaths were captured using information from Kaiser Permanente electronic medical records and the California Automated Mortality Linkage System, an ascertainment method standard for epidemiological studies of KPNC members.[11–13] After exclusion of 42 patients with prevalent dementia, the full cohort consisted of 3,742 patients with type 1 diabetes.

Dementia

Diagnoses of dementia were identified from electronic medical records, using the following ICD-9 diagnostic codes made in primary care, neurology, or memory clinic visits: Alzheimer disease (331.0), Vascular Dementia (290.4x) and nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.1x, 294.2x, and 294.8). Using ICD-9 codes in determining dementia diagnosis has been used successfully in several other publications.[14–17] A similar combination of ICD-9 codes had a sensitivity of 77% and a specificity of 95% compared to a consensus diagnosis of dementia based on a structured interview with informants, neuropsychiatric battery, physical examination and review of medical records.[18] Diagnoses

for frontotemporal dementia (ICD-9 331.1x) and dementia with Lewy Bodies (ICD-9 331.82) were eligible but no cases were identified.

Diabetic retinal disease

To best capture all diagnoses of diabetic retinal disease at baseline and through follow-up period, both ICD-9 diagnostic and Current Procedural Terminology, 4th edition (CPT-4) procedural codes were used. An individual was considered to have DR if they had at least one diagnosis code for proliferative diabetic retinopathy (ICD-9: 362.02; CPT-4: 67228), macular edema (ICD-9: 362.07, 362.53, 362.83; CPT-4: 67208, 67210) or nonspecific diabetic retinopathy (ICD-9: 250.5x, 362.0x). A prior study demonstrated a 88% sensitivity and 75% specificity of a similar set of ICD-9 codes compared to medical record review.[19] To evaluate if there were possible differences by severity, severe diabetic retinopathy (SDR) encompassed codes for proliferative diabetic retinopathy and macular edema. Proliferative diabetic retinopathy (PDR) was also examined separately.

Covariates

These analyses include demographics and comorbidities from the year of cohort entry as potential confounders. Age, sex and race were retrieved from KPNC health plan membership databases. Glycosylated hemoglobin (HbA1c) measurements was obtained from the Kaiser Permanente laboratory, using the last measurement before baseline in tertiles. The following comorbidities that might influence the association between DR and dementia were collected from the KPNC electronic medical records, using the ICD-9 and CPT-4 codes as described in Supplemental Table 1: severe hypo- and hyperglycemic episodes for which hospital admittance or emergency room visit was necessary, diagnoses of neuropathy, diabetic nephropathy, end stage renal disease, cardiovascular disease (heart failure, acute myocardial infarction, and peripheral arterial disease), and stroke.

Statistical analysis

First, the distribution of dementia, sociodemographic variables, and several risk factors or complications associated with diabetes and/or dementia were analyzed by DR status at baseline using $\chi 2$ analyses or Student's T-test. Cox proportional hazards models with age as a time scale were implemented to estimate the effect of DR on dementia risk, with DR as a time-dependent covariate. Three models were examined: no adjustment for covariates except for age as the time scale (model 1), adjustment for sex and race (model 2), and additional adjustment for HbA1c, acute hypo- and hyperglycemia, neuropathy, diabetic nephropathy, end stage renal disease, cardiovascular disease, and stroke (model 3). Since dementia risk is so closely related to age, stratified analyses were also performed on subsets of the cohort aged ≥60 or ≥70. Among the cohort aged ≥ 50, a sensitivity analysis examined the association between DR and dementia risk further adjusting for hypertension. In additional sensitivity analyses, we excluded time-updated DR cases occurring during the 12 months prior to dementia diagnosis to minimize the possibility of reverse causation. Sensitivity analyses also evaluated increasingly severe definitions of baseline DR (SDR and PDR). Associations were considered significant at the level of 0.05. SAS statistical software version 9.3 (SAS Institute Inc, Cary North Carolina) was used for all analyses.

Results

Patients were born between 1900 and 1965 and the mean age at entry was 56.1 (SD=8.5). One hundred eighty-two patients (4.9%) were diagnosed with dementia during follow-up (mean=6.2 years) (Table 1). Fifty-three percent of the cohort was male and 21% of the cohort was non-white. At baseline, 2,294 patients (61.3%) had DR, 1,423 (38.0%) had PDR, and 1,473 (39.4%) had SDR. Individuals with DR at baseline were younger (55.3 versus 57.3 years old) at entry and had longer follow-up time (6.7 versus 5.3 years) than their counterparts without DR. Individuals with DR had higher HbA1c% (8.5% versus 8.0%), and were more likely to have had a stroke, cardiovascular diseases, and hypoglycemic episodes. The subgroup aged ≥60 consisted of 2,021 patients, of which 1,343 (66.5%) had DR, 870 (43.1%) had PDR, 907 (44.9%) had SDR, and 157 patients (7.8%) were diagnosed with dementia during follow up. The subgroup aged ≥70 consisted of 783 patients, of which 548 (70.0%) had DR, 380 (48.5%) had PDR, 394 (50.3%) had SDR, and 99 patients (12.6%) were diagnosed with dementia during follow up.

In models only adjusting for age, patients with diabetic retinal disease had a non-significant increase of 22% in dementia risk compared to those without DR (adjusted Hazard Ratio (aHR)=1.22; 95% Confidence Interval (CI): 0.89–1.67) (Table 2). Further adjustment for individual covariates slightly changed the hazard ratio, but it remained insignificant. In fully adjusted models, the association was insignificant (aHR=1.12, 95% CI: 0.82–1.54). All demographics, comorbidities, and risk factors except neuropathy were associated with elevated risk of dementia in models adjusting for age and DR (Supplemental Table S2). Results were similar, with slightly lower hazard ratios, when excluding cases of DR occurring within a 12-month period prior to dementia diagnosis (Table 3). DR was not associated with dementia risk and had a non-significant trend towards a protective effect as the age of the cohort increased (Table 2 and Table 3).

In sensitivity analyses examining increasing levels of DR severity as baseline variables, comparable hazard ratios were found. In models adjusted for demographics, neither SDR (aHR=1.08, 95% CI: 0.81–1.44) nor PDR (aHR=1.11 95% CI: 0.83–1.49) were associated with dementia risk, and hazard ratios were comparable to that of DR as a baseline variable adjusted for demographics (aHR=1.24, 95% CI: 0.90–1.70). In the main and sensitivity analyses amongst subgroups aged >60 and>70, similar results were seen, albeit with consistently lower hazard ratios in the higher age groups. In sensitivity analyses examining the association between DR and dementia among patients 50 and older, further adjusted for hypertension did not alter the effect estimate.

Discussion

In this large cohort of elderly patients with type 1 diabetes mellitus, there was no evidence DR was associated with an increased risk of dementia. These results were consistently found in unadjusted, minimally adjusted, and fully adjusted cox proportional hazard models. Similar results were found in sensitivity analyses with a 12-month buffer of DR diagnoses before dementia diagnosis, when investigating more severe DR as an exposure variable, and in analyses restricted to older age groups.

Characteristics of the cohort in the present study were comparable to the few previously published large community based cohorts of elderly with type 1 diabetes. Gender distribution, average HbA1c values, and dementia incidence were similar to previous studies amongst older patients with type 1 diabetes.[2,20–22] Self-reported DR in a study amongst patients with type 1 diabetes (n=309, mean age 65.7 ± 8.5) was 71.5%[20] compared to 61.3% (full cohort), and 66.5% (subgroup aged ≥ 60) in the current study. PDR based on fundus photography (n=351, mean age 67.5 ± 7.5) was 48.5% in a previous study, versus 43% (subgroup aged ≥60) in the current study.[21] Furthermore, the relations between other known risk factors of dementia (e.g., stroke[23]) and dementia were as expected and increased risk, supporting the validity of our observations.

The results from the current study can provide important insight into what potentially mediates an increased risk of dementia in type 1 diabetes. The main theoretical basis for an association between diabetic retinopathy and dementia relies on the many similarities between retinal and cerebral small vessels, the latter of which has been greatly supported for its roll in dementia.[24] Indeed, retinal and cerebral microvasculature have similar embryological origin, anatomical features and physiological properties, including barrier functions (blood-brain, and blood-retinal-barrier), auto-regulation and a relatively low-flow and high-oxygen-extraction system. These similarities in anatomy and function are not surprising, as both provide for glia-cells and neurons, and thus have similar functions.[25] Moreover, several studies have found an association between retinal vascular changes and cerebral small vessel disease.[26–29]

Although all analyses were statistically insignificant, it is interesting to see that the hazard ratio for dementia associated with DR and other dementia risk factors is smaller among the older age groups for all analyses. This is in agreement with several other studies amongst type 1 diabetes[2], and all cause diabetes[30], that found that the impact of diabetes on dementia becomes progressively attenuated in the older age groups. This is consistent with diabetes and diabetes related risk factors such as DR accelerating the development of dementia in those prone to the disease, lowering the age of dementia onset, and decreasing the incidence of DR related dementia in older age groups.

Prior studies on the relationship between type 1 diabetes and dementia are in line with a theory of DR related dementia being mainly in younger age groups or during time of onset of DR. Studies amongst younger cohorts with type 1 diabetes found associations between DR and subtle cognitive dysfunction[31,32], diabetes-associated cognitive decrements[33], lower brain volume and more vascular lesions on MRI[34]. However, these studies were conducted in younger patients, thus extrapolation to older groups with regards to dementia risk, retinopathy risk, and type 1 diabetes disease burden is not straightforward. In the older general population, retinopathy was found to be associated with clinically diagnosed dementia in cross-sectional comparisons[35–37] but not longitudinally[38]. Furthermore, a large cross-sectional study (N=2,211) found a significant association only for those without diabetes after stratification by diabetes status (289 patients with diabetes, diabetes types not specified)[39].

Lastly, the contrast between the results of the current study and a comparable study amongst patients with type 2 diabetes aged ≥60 years (N=29,961)[7] which did find DR to increase dementia risk indicates differences between these type 1 and type 2 diabetes cohorts with regards to DR and dementia. The study used similar data collection methods from the KPNC database and found DR to be significantly associated with dementia, with a fully adjusted HR of 1.29 (95%CI 1.14–1.45). Notably, the incidence of SDR diagnoses in the study on type 2 diabetes was much lower than the age-matched subgroup in the current study (7% versus 55.1% in those aged≥60), and the incidence of dementia was higher than that of the current study (17% versus 7.8% aged ≥60). However, caution is needed when interpreting this as an indication of differences in etiological underpinnings of dementia for type 1 versus type 2 diabetes, as other distinctions between the cohorts could explain the contrast. First, attenuation due to selective survivorship could play a larger role in the current cohort. However, as survivorship bias would be expected to affect other risk factors as well, the insignificance of the association between DR and dementia still contrasts the significant association found for other risk factors (Supplemental Table 2). Another explanation could lie in possible differences in DR duration between both cohorts. As stated before, DR might be associated with dementia mainly during onset of the disease, after which the association attenuates. DR might therefore not be associated with dementia in a population that acquired it many years prior to analysis when excluding prevalent dementia cases. This is supported by sensitivity analyses by Exalto et al.[7], which demonstrate an attenuation of the association between DR and dementia with longer time between occurrence of DR and dementia incidence. In the current study, sensitivity analyses censoring DR diagnosis 12 months prior to dementia diagnosis also showed attenuation of the point estimates. Finally, these characteristics from cohorts with the same age, from the same source using similar methods could indicate true differences in etiological underpinnings of dementia for type 1 versus type 2 diabetes, such that the relative impact of DR pathology on dementia is lower in type 1 diabetes compared to type 2 diabetes.

The present study has several strengths. It is the first study investigating the association between diabetic retinopathy and dementia in a large population of older patients with type 1 diabetes. Analyses included information on a wide variety of diabetes specific comorbidities and the longitudinal design of this study allowed for incident dementia to be observed. Furthermore, due to detailed information on date of diagnosis, robust statistical methods using diabetic retinopathy as a time-dependent variable could be used to test the association between diabetic retinopathy and dementia.

There were several limitations to this study. Most importantly, the lack of information regarding age of diabetes and DR onset. Age of onset of diabetes might significantly affect both DR risk[40] and dementia. Type 1 diabetes generally onsets during childhood[41], and several studies have shown that early childhood is a crucial period in which diabetes affects cognition[42]. Furthermore, information on age of onset of DR could illuminate possible close temporal relations between DR and dementia onset. Secondly, this study was performed in a a uniquely large group of patients with type 1 diabetes who survived to older ages, despite being born in a time when mortality for those diagnosed with diabetes was over 50%.[1] This invokes the risk of survivorship bias, as the current study population includes a healthy survivor group that outlived many peers, and may underestimate the relationship between

DR and dementia. However, our sample may also include individuals who were diagnosed with type 1 diabetes later in life, reducing the risk of selective survivorship. Lastly, the use of medical record diagnoses for dementia could be a potential weakness. Although this method has been shown to have a relatively high sensitivity (77%) and specificity (95%) for the diagnosis of dementia compared to a consensus diagnosis[18], it did not allow for stratification by type of dementia as all but a few ICD-9 codes for dementia were unspecified.

In conclusion, in this first study of diabetic retinopathy and dementia in older patients with type 1 diabetes, diabetic retinopathy was not found to be associated with risk of dementia. This study conflicts the hypothesis that pathophysiological processes underlying diabetic retinopathy are also involved in the development of dementia, in older aged patients with type 1 diabetes. Furthermore, the current findings are consistent with different pathophysiological mechanisms involved in the development of dementia in type 1 versus type 2 diabetes. This indicates the need for separation of both types of diabetes when investigating pathophysiology of dementia. As those with type 1 diabetes are living longer than ever before, further investigation of these mechanisms can aid in a broader understanding of dementia and more specific preventative measures for this patient group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of members by diabetic retinopathy diagnosis at baseline

	No DR (N=1,448)	DR (N=2,294)	Total (N=3,742)	P-value
Dementia	55 (3.8%)	127 (5.5%)	182 (4.9%)	0.016
Study characteristics				
Age at baseline *	57.3 (8.9), 53.6 [50.0–61.9]	55.3 (8.1) 50.0 [50.0–58.5]	56.1 (8.5) 51.6 [50.0–60.1]	<.0001
Follow-up duration *	5.3 (5.0) 3.6 [1.2–7.9]	6.7 (5.4) 5.4 [1.9–10.7]	6.2 (5.3) 4.6 [1.6–9.8]	<.0001
Sociodemographic				
Birth year *	1948.5 (12.0) 1951 [1943–1957]	1949.0 (11.7) 1952 [1943–1958]	1948.8 (11.8) 1951 [1943, 1958]	0.2319
Male	762 (52.6%)	1,208 (52.7%)	1,970 (52.6%)	0.98
Race				
Caucasian	1,133 (78.2%)	1,823 (79.5%)	2,956 (79.0%)	<.0001
Black	77 (5.3%)	110 (4.8%)	187 (5.0%)	
Hispanic	81 (5.6%)	127 (5.5%)	208 (5.6%)	
Asian	58 (4.0%)	88 (3.8%)	146 (3.9%)	
Other/mixed	40 (2.8%)	106 (4.6%)	146 (3.9%)	
Missing	59 (4.1%)	40 (1.7%)	99 (2.6%)	
Diabetes complications/control				
Diabetic nephropathy	182 (12.6%)	836 (36.4%)	1,018 (27.2%)	<.0001
Neuropathy	129 (8.9)	527 (23.0)	656 (17.5)	<.0001
End stage renal disease	27 (1.9%)	281 (12.2%)	308 (8.2%)	<.0001
Severe diabetic retinopathy	0 (0%)	1,473 (64.2)	1,473 (39.4)	<.0001
HbA1c% †*	8.0 (2.0) 7.5 [6.7–8.7]	8.5 (1.8) 8.0 [7.2–9.4]	8.3 (1.9) 7.9 [7.0–9.1]	<.0001
Hyperglycemia‡	167 (11.5%)	306 (13.3%)	473 (12.6%)	0.11
Hypoglycemia‡	175 (12.1%)	524 (22.8%)	699 (18.7%)	<.0001
Comorbid diseases				
Stroke	84 (5.8%)	178 (7.8%)	262 (7.0%)	0.022
Heart failure	104 (7.2%)	285 (12.4%)	389 (10.4%)	<.0001
Acute Myocardial infarction	51 (3.5%)	144 (6.3%)	195 (5.2%)	0.0002
Peripheral arterial disease	111 (7.7%)	354 (15.4%)	465 (12.4%)	<.0001
Reason for censoring				
Death	280 (17.9%)	458 (21.0%)	738 (19.7%)	0.02
Membership lapse	477 (30.5%)	514 (23.6%)	991 (26.5%)	<.0001

Data presented as number (column %) unless indicated differently. P-values were calculated using chi-square test or student T-test. DR: diabetic retinopathy.

* mean (SD), median [lower interquartile range, upper interquartile range].

† HbA1c%: percentage glycosylated hemoglobin.

Table 2

Diabetic retinopathy and risk of dementia from a cox proportional hazards model using age as the timescale

	Full cohort (≥50) **HR (95% CI)**	**Cohort aged ≥60** **HR (95% CI)**	**Cohort aged ≥70** **HR (95% CI)**
N	3,742	2,021	783
Model 1: age-adjusted	1.22 (0.89,1.67)	1.13 (0.85,1.59)	0.91 (0.59,1.42)
Model 2: model 1 further adjusted for sex and race	1.24 (0.90,1.69)	1.17 (0.83,1.64)	0.95 (0.61,1.47)
Model 3: model 2 further adjusted for baseline glycosylated hemoglobin and comorbidities	1.12 (0.82,1.54)	1.02 (0.72,1.45)	0.91 (0.58,1.44)

*Baseline comorbidities include neuropathy, diabetic nephropathy, end-stage renal disease, cardiovascular disease, stroke, and hyperglycemic or hypoglycemic episodes.

Table 3

Diabetic retinopathy and risk of dementia from a cox proportional hazards model excluding cases of diabetic retinopathy diagnosed < 1 year before dementia

	Full cohort (≥50) HR (95% CI)	Cohort aged ≥60 HR (95% CI)	Cohort aged ≥70 HR (95% CI)
N	3,742	2,021	783
Model 1: age-adjusted	1.04 (0.76–1.41)	0.91 (0.65–1.26)	0.67 (0.45–1.02)
Model 2: model 1 further adjusted for sex and race	1.06 (0.78–1.43)	0.94 (0.67–1.31)	0.70 (0.46–1.07)
Model 3: model 2 further adjusted for baseline HbA1c tertiles and comorbidities *	0.97 (0.71–1.33)	0.85 (0.61–1.21)	0.66 (0.42–1.03)

Note: Estimates obtained from Cox proportional hazards models with age as time scale.

*Baseline comorbidities include neuropathy, diabetic nephropathy, end-stage renal disease, cardiovascular disease, stroke, and hyperglycemic or hypoglycemic episodes.