Published in final edited form as:

Am J Ophthalmol. 2008 April ; 145(4): 700–706.

Clinically Significant Macular Edema and Survival in Type 1 and Type 2 Diabetes

Flavio E. Hirai, MD, MPH^{1,2}, Michael D. Knudtson, MS¹, Barbara E. K. Klein, MD, MPH¹, and Ronald Klein, MD, MPH¹

¹ Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison

² Department of Ophthalmology, Federal University of Sao Paulo, Brazil

Abstract

Purpose—To investigate the association of clinically significant macular edema (CSME) and long-term survival in individuals with type 1 and type 2 diabetes.

Design—Population-based cohort study.

Methods—The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is an ongoing prospective population-based cohort study initiated in 1980–82 of individuals with diabetes diagnosed at either < 30 years (younger-onset, n = 996) or 30 years of age (older-onset, n = 1,370). Stereoscopic color retinal photographs were graded for retinopathy using the modified Airlie House Classification scheme. CSME was defined by the Early Treatment Diabetic Retinopathy Study criteria.

Results—Prevalence of CSME was 5.9% and 7.5% for the younger- and older -onset groups, respectively. After 20 years of follow-up, 276 younger-onset and 1,197 older-onset persons died. When adjusting for age and gender, CSME was not significantly associated with all-cause (hazard ratio and 95% confidence interval: 1.41 (0.96–2.07), P = 0.08) or ischemic heart disease mortality (1.14 (0.61–2.12), P = 0.68) in the younger-onset group. In the older onset group, there was increased all-cause and ischemic heart disease mortality when CSME was present: 1.55 (1.25–1.92), P < 0.01 and 1.56 (1.15–2.13), P < 0.01, respectively, when adjusting for age and gender. After controlling for other risk factors, the association remained significant for ischemic heart disease (1.58 (1.07–2.35), P = 0.02) among those taking insulin. CSME was not significantly associated with stroke mortality in either group.

Correspondence to: Ronald Klein, MD, MPH, University of Wisconsin Madison, Department of Ophthalmology and Visual Sciences, 610 N. Walnut Street, 4th Floor WARF, Madison, Wisconsin 53726 608/263-7758, 608/263-0279 fax kleinr@epi.ophth.wisc.edu.

B. FINANCIAL DISCLOSURES

Authors have no financial conflict of interest.

C. CONTRIBUTIONS OF AUTHORS

Contribution of authors: design and conduct of the study (R.K., B.E.K.K.); collection, management (R.K., B.E.K.K.), analysis and interpretation of the data (F.E.H., M.D.K., R.K., B.E.K.K.); and preparation, review, or approval of the manuscript (F.E.H., M.D.K., R.K., B.E.K.K.).

D. CONFORMITY WITH AUTHOR INFORMATION

Written informed consent for the use and disclosure of protected health information was obtained from all subjects before being enrolled in the study and Institutional Review Board approval was granted by the Health Sciences Institutional Review Board at the University of Wisconsin, Madison.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions—CSME appears to be a risk indicator for decreased survival in persons with older-onset diabetes mellitus. The presence of CSME may identify individuals who should be under care for detection and treatment of cardiovascular disease.

Keywords

macular edema; diabetic retinopathy; diabetes; epidemiology; survival

Introduction

Several studies have investigated and found retinopathy to be a risk indicator of cardiovascular morbidity and mortality in both diabetic^{1–5} and nondiabetic^{4,6} persons. There have been fewer studies examining the relation of diabetic macular edema to these endpoints.^{2,7} Macular edema is one of the major causes of vision loss in individuals with diabetes^{7–10} and its development depends, in part, on the breakdown of the blood retinal barrier. Thus, we hypothesized that macular edema may be a marker of similar microvascular changes that may result in cardiovascular morbidity and mortality. The purpose of this study was to evaluate the association of clinically significant macular edema (CSME) and long-term survival in a population-based study of persons with type 1 and type 2 diabetes.

Methods

Study population

Data are from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).^{11,12} WESDR is an ongoing prospective population-based cohort study initiated in 1980–82 of persons with type 1 and 2 diabetes mellitus living in 11 counties of Wisconsin. Individuals with diabetes diagnosed at age < 30 years were defined as “younger-onset” (n = 996) and those diagnosed at age ≥ 30 years were defined as “older-onset” (n = 1,370). Participants were examined at baseline and every 4–6 years. The longer follow-up, 20 years, provides more cases of ischemic heart disease and stroke mortality than our previous study of these relationships.² Individuals without information about their macular edema status at baseline (42 (4.2%) of younger-onset and 75 (5.4%) of older-onset) were excluded from the analyses. Therefore, our study population had 954 and 1,295 individuals in the “younger” and “older” onset groups, respectively.

Procedures

Detailed protocols used in WESDR were published elsewhere.^{2,11,12} Briefly, baseline and all follow-up examinations included detailed medical history with information about cardiovascular and renal disease, questions about cigarette smoking, measurements of blood pressure, height, weight, and waist and hip circumferences. Laboratory tests included serum glucose, and plasma glycosylated hemoglobin (HbA1c). Urine tests were performed to determine the presence of gross proteinuria at each of the examinations and for microalbuminuria at the 10-year follow-up examination. Nephropathy was defined as presence of gross proteinuria, current or past renal dialysis or kidney transplant. Stereoscopic 7-field color retinal photographs were taken and diabetic retinopathy (DR) was classified according to a modified Airlie House Classification Scheme¹³ into three categories: no DR; mild to moderate non-proliferative DR; and severe non-proliferative to proliferative DR. Those with retinal changes other than DR, e.g. retinal vein occlusion, were excluded from the analysis.

Definition of CSME

CSME was defined according to the Early Treatment Diabetic Retinopathy Study classification protocol¹⁴ as the presence of retinal thickening at or within 500µm of the center of the macula

or hard exudates at or within 500 μ m of the center of the macular if associated with thickening of the adjacent retina and/or zones of retinal thickening 1 disc area in size, at least part of which being within 1 disc diameter of the center.

Deaths were ascertained by contacting family members and physicians, review of newspaper obituaries, and use of vital status records. For cause-specific analyses, any mention on the death certificate was considered an event. Causes of death were defined according to the International Classification of Diseases (ICD) 9th and 10th Revisions. Ischemic heart disease mortality was defined according to codes 410.0–414.9 (ICD-9) and I20.0–I25.9 (ICD-10) and stroke mortality was defined according to codes 430.0–438.9 (ICD-9) and I60.0–I69.9 (ICD-10).

Data analysis

Comparisons of continuous and categorical variables at baseline were done using t-test and χ^2 , respectively. Age and sex adjusted survival curves were calculated using the mean of covariates method. Multivariate analyses were performed with the Cox Proportional Hazards Model. Age and sex were added in all models and covariates were selected using a stepwise procedure, remaining in final models if significant at the 0.05 level. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated and p values less than 0.05 were considered significant. Analyses were performed in SAS (SAS Institute, Cary, NC, USA).

The Institutional Review Board approved the study and consent forms were obtained from all participants. This research was conducted in accordance to the principles of the Declaration of Helsinki.

Results

In the younger-onset group, those who were excluded (n = 42) were older, had longer diabetes duration, and a higher prevalence of hypertension, nephropathy, and DR. In the older-onset group, individuals excluded (n = 75) from the analysis were older, had a longer diabetes duration, smaller body mass index (BMI), and a higher prevalence of nephropathy and DR.

The prevalence of CSME at baseline was 5.9% and 7.5% for the younger-onset and older-onset groups, respectively. Table 1 shows baseline characteristics of both groups stratified by CSME status. In the younger-onset group, individuals with CSME at baseline were older and had longer diabetes duration. Prevalence of hypertension, nephropathy, and more severe DR was also higher in this group. Similarly, in the older-onset group not taking insulin, those with CSME were older, had longer diabetes duration, higher levels of HbA1c, higher prevalence of hypertension, and more severe DR. Among those taking insulin, individuals with CSME at baseline had longer diabetes duration, higher prevalence of nephropathy, and more severe DR.

In the younger-onset group, 276 (28.9%) individuals died after 20 years of follow-up (118 and 18 cases had ischemic heart disease and stroke, respectively, listed as underlying and any mentioned cause of death). Figure 1 shows age- and sex-adjusted survival curves according to CSME status at baseline. In this group, CSME at baseline was not significantly associated with all-, ischemic heart disease, or stroke mortality (Tables 2 and 3).

After 20 years of follow-up, 1,123 (86.7%) individuals from the older-onset group died. In the group not taking insulin (n = 666), ischemic heart disease was listed as underlying or any mentioned cause of death for 255 individuals and stroke was listed for 107 individuals. Among those taking insulin (n = 629), 263 and 86 individuals, respectively, had ischemic heart disease and stroke listed as underlying or any mentioned cause of death.

Figures 2 and 3 show age- and sex-adjusted survival curves according to CSME status at baseline. In the older onset group, when adjusting for age and gender, there was increasing all-cause mortality with the presence of CSME at baseline: Hazard Ratio (HR) and 95% confidence interval (CI) 1.55 (1.25 to 1.92) (Table 2). After controlling for other risk factors, the association remained statistically significant (HR 1.27, 95% CI 1.01 to 1.61). CSME was also associated with ischemic heart disease in the age-sex adjusted model (HR 1.56, 95% CI 1.15 to 2.13). When stratifying according to use of insulin (Table 3), we observed a significant association between CSME at baseline with ischemic heart disease mortality in the group taking insulin (HR 1.58, 95% CI 1.07 to 2.35). CSME was not significantly associated with stroke mortality in the older-onset group. The inclusion of DR (stratified as none; mild/moderate non-proliferative; and severe non-proliferative/proliferative) in the multivariable models decreased the magnitude of the association of CSME and death which was no longer statistically significant: for all-cause mortality, the HR 95% CI was 1.07 (0.83 to 1.37); for ischemic heart disease mortality it was 1.16 (0.81 to 1.67); and for stroke mortality it was 1.02 (0.55 to 1.87).

We also analyzed the associations of any DR with and without CSME at baseline and mortality in the older-onset group. Individuals with both DR and CSME (HR 1.48, 95% CI 1.16 to 1.89) and with DR only (HR 1.30, 95% CI 1.14 to 1.48) had higher risk of death for all-cause mortality compared to individuals without DR. Similar results were found with ischemic heart disease mortality: HR and 95% CI of 1.65 (1.15 to 2.35) and 1.35 (1.11 to 1.65) for those with DR and CSME and DR only, respectively, compared to those without DR. While individuals who had DR and CSME at baseline had higher HR values than those with DR only, the differences in HR were not statistically significantly different.

No interactions between CSME and other factors such as age, diabetes duration, BMI, nephropathy status as measured by presence of gross proteinuria, or glycosylated hemoglobin were observed (data not shown).

Discussion

We report a significant relation of CSME and ischemic heart disease mortality among people with older but not younger onset diabetes, independent of glycemic and blood pressure control, nephropathy, and other risk factors. Breakdown of the blood-retinal barrier, secondary to poor glycemic and blood pressure control, may be a risk indicator of similar microvascular disease in the heart and elsewhere.¹⁵ We were unable to show that the association of CSME to mortality was independent of DR severity.

These findings were consistent with data from some hospital-based studies. Lawson et al.¹⁶ reported higher prevalence of cardiovascular disease among 94 patients with diabetic macular edema compared to general population of similar age and Davies et al.¹⁷ showed that individuals with diabetic macular edema had reduced life expectancy compared to people without diabetes. Neither of these studies reported comparisons with diabetic subjects without macular edema.

Few epidemiological studies have evaluated the association of diabetic macular edema and survival.² One recent clinic-based study analyzed DR and survival in a 10-year follow-up of type 2 diabetes individuals.¹⁸ In that study, sight-threatening retinopathy at baseline, defined as presence of CSME and/or severe non-proliferative retinopathy or proliferative retinopathy, was associated with higher all-cause mortality rates (HR 2.2, 95% CI 1.3 to 3.6) compared to those persons with less severe retinopathy. Interestingly, individuals with no retinopathy at baseline who did not develop sight-threatening retinopathy during the follow-up period had higher risk of death compared to those who developed that condition (HR 3.6, 95% CI 1.1 to 11.8).

In a previous report, after 16 years of follow-up of the same cohort while controlling for other factors, we did not find a statistically significant association of macular edema with survival, possibly due to fewer deaths in the cohort at that time compared to the number in the present analysis. In the current study, we did not find the association of CSME with mortality to be independent of presence of DR in our multivariate models. Inclusion of the severity of DR in the model may result in over controlling because of the high correlation between the severity of DR and CSME. While individuals who had CSME and DR had a 65% higher hazard of dying of ischemic heart disease compared to 35% higher hazard among those with DR but without CSME at baseline, these differences were not statistically significant. Therefore, we cannot conclude that CSME provides additional risk of mortality beyond that found in knowing the severity of retinopathy.

WESDR has many strengths including its population-based design, the use of standard protocols, and long follow-up time. However, our results should be interpreted with caution. We found that CSME was associated with increased mortality among those with older-onset diabetes and using insulin. It could be possible that those treated with insulin had high levels of serum lipids. Serum lipids were not available at baseline but were measured in all participants at the third follow-up visit. We examined the association of CSME and mortality controlling for serum cholesterol levels at the third follow-up visit in a smaller number of persons ($n = 250$) and found that the associations had a similar magnitude of risk (HR 1.58, 95% CI 0.78 to 3.22, $P = 0.20$, for ischemic heart disease mortality in the older onset group taking insulin), although it was not statistically significant (Hirai et al, unpublished data). Similarly, the presence of microalbuminuria was not measured at baseline. Controlling for the presence of microalbuminuria in 150 persons with this measurement at the third follow-up visit the association of CSME with ischemic heart disease mortality remained statistically significant (HR 4.10, 95% CI 1.39 to 12.12, $P = 0.01$, Hirai et al, unpublished data). Individuals at baseline who were excluded from the analysis had characteristics (older age, longer diabetes duration, and higher proportion of nephropathy and diabetic retinopathy) suggesting they had more severe disease. Therefore, their exclusion might have left us with a group at “lower risk” for death, possibly leading us to an underestimation of the association (selective survival). Stroke mortality was low. This may have limited our ability to detect significant relationships. Finally, the assessment of cause of death was based on information from death certificates and misclassification could have occurred.^{19,20}

In summary, older-onset diabetic persons using insulin with CSME at baseline had a higher risk of ischemic heart disease mortality after adjusting for several risk factors when compared to people without CSME. However, the associations between CSME and mortality were not independent of the severity of diabetic retinopathy. It remains to be seen whether more intensive medical care would be of benefit in preventing ischemic heart disease death in these people.

Acknowledgements

A. FUNDING/SUPPORT

This study was supported by the National Eye Institute grant EY015117.

References

1. Juutilainen A, Lehto S, Ronnema T, Pyorala K, Laakso M. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. *Diabetes Care* 2007;30:292–299. [PubMed: 17259497]
2. Klein R, Klein BE, Moss SE, Cruickshanks KJ. Association of ocular disease and mortality in a diabetic population. *Arch Ophthalmol* 1999;117:1487–1495. [PubMed: 10565517]
3. Klein R, Moss SE, Klein BE, DeMets DL. Relation of ocular and systemic factors to survival in diabetes. *Arch Intern Med* 1989;149:266–272. [PubMed: 2916872]

4. van Hecke MV, Dekker JM, Nijpels G, et al. Retinopathy is associated with cardiovascular and all-cause mortality in both diabetic and nondiabetic subjects: the hoorn study. *Diabetes Care* 2003;26:2958. [PubMed: 14514612]
5. Cusick M, Meleth AD, Agron E, et al. Associations of mortality and diabetes complications in patients with type 1 and type 2 diabetes: early treatment diabetic retinopathy study report no. 27 *Diabetes Care* 2005;28:617–625. [PubMed: 15735198]
6. Yu T, Mitchell P, Berry G, Li W, Wang JJ. Retinopathy in older persons without diabetes and its relationship to hypertension. *Arch Ophthalmol* 1998;116:83–89. [PubMed: 9445212]
7. Vitale S, Maguire MG, Murphy RP, et al. Clinically significant macular edema in type I diabetes. Incidence and risk factors. *Ophthalmology* 1995;102:1170–1176. [PubMed: 9097743]
8. Klein R, Moss SE, Klein BE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. XI The incidence of macular edema. *Ophthalmology* 1989;96:1501–1510. [PubMed: 2587045]
9. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV Diabetic macular edema. *Ophthalmology* 1984;91:1464–1474. [PubMed: 6521986]
10. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 2003;26:2653–2664. [PubMed: 12941734]
11. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1984;102:520–526. [PubMed: 6367724]
12. Klein R, Klein BE, Moss SE, DeMets DL, Kaufman I, Voss PS. Prevalence of diabetes mellitus in southern Wisconsin. *Am J Epidemiol* 1984;119:54–61. [PubMed: 6691336]
13. ETDRS report number 10. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991;98:786–806. [PubMed: 2062513]
14. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* 1985;103:1796–1806. [PubMed: 2866759]
15. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet* 2001;358:1134–1140. [PubMed: 11597667]
16. Lawson PM, Hunt B, Kohner EM. Medical conditions in patients with diabetic maculopathy. *Diabet Med* 1985;2:245–250. [PubMed: 2951076]
17. Davies EG, Petty RG, Kohner EM. Long term effectiveness of photocoagulation for diabetic maculopathy. *Eye* 1989;3(Pt 6):764–767. [PubMed: 2630360]
18. Lovestam-Adrian M, Hansson-Lundblad C, Torffvit O. Sight-threatening retinopathy is associated with lower mortality in type 2 diabetic subjects: A 10-year observation study. *Diabetes Res Clin Pract* 2007;77:141–147. [PubMed: 17178168]
19. Smith Sehdev AE, Hutchins GM. Problems with proper completion and accuracy of the cause-of-death statement. *Arch Intern Med* 2001;161:277–284. [PubMed: 11176744]
20. Muhlhauser I, Sawicki PT, Blank M, Overmann H, Richter B, Berger M. Reliability of causes of death in persons with Type I diabetes. *Diabetologia* 2002;45:1490–1497. [PubMed: 12436331]

Figure 1.

Age- and sex-adjusted survival curves by clinically significant macular edema (CSME) status at baseline in younger-onset persons for all-cause and ischemic heart disease mortality.

Figure 2.

Age- and sex-adjusted survival curves by clinically significant macular edema (CSME) status at baseline in older-onset persons NOT taking exogenous insulin for all-cause and ischemic heart disease mortality.

Figure 3.

Age- and sex-adjusted survival curves by clinically significant macular edema (CSME) status at baseline in older-onset persons taking exogenous insulin for all-cause and ischemic heart disease mortality.

Table 1

Characteristics of Individuals in the Younger- and Older-Onset Groups at Baseline According to Clinically Significant Macular Edema (CSME) Status.

CSME status	Younger-onset			Older-onset		
	Non-Insulin-taking			Insulin-taking		
	Absent (n = 898) [*]	Present (n = 56) [*]	P-value	Absent (n = 624) [*]	Present (n = 24) [*]	P-value
Gender, male	51.0	55.4	.52	45.8	33.3	.22
Age, years	28.5 ± 13.1	35.5 ± 11.2	<.01	67.4 ± 11.0	72.9 ± 8.7	<.01
Diabetes duration	13.9 ± 10.4	21.1 ± 8.5	<.01	8.4 ± 6.4	13.7 ± 7.6	<.01
BMI	23.4 ± 4.3	24.3 ± 3.4	.08	29.2 ± 5.5	26.6 ± 3.4	.13
HbA1c	10.8 ± 2.08	11.2 ± 2.08	.15	9.0 ± 1.9	10.1 ± 1.9	.02
CVD history, present	4.4	5.4	.75	26.1	20.8	.56
Hypertension, present	19.1	33.3	.01	61.3	91.7	<.01
Smoking, current	24.6	21.4	.59	13.2	4.2	.19
Nephropathy, present	18.2	49.0	<.01	11.4	20.8	.15
Retinopathy						
Mild to Moderate	47.5	17.8	<.01	37.4	54.2	<.01
NPDR						
Severe NPDR to Proliferative DR	21.7	82.2	<.01	3.1	45.8	<.01

Abbreviations: BMI = body-mass index; HbA1c = glycosylated hemoglobin; CVD = cardiovascular disease; NPDR = non-proliferative diabetic retinopathy; DR = diabetic retinopathy.

^{*} Data are mean ± SD or %.

Table 2
Age-Sex and Multivariable-Adjusted Association of Clinically Significant Macular Edema at Baseline (1980–82) with All-Cause and Cause-Specific Mortality in the Wisconsin Epidemiological Study of Diabetic Retinopathy in Younger- and Older-Onset Groups.

	N	Age-Sex		Younger-onset		Older-onset	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All cause [*]	276	1.41 (0.96, 2.07)	.08	0.67 (0.42, 1.06)	.09		
IHD [*]	118	1.14 (0.61, 2.12)	.68	0.66 (0.32, 1.34)	.25		
Stroke [†]	18	1.35 (0.31, 5.93)	.68	0.92 (0.19, 4.47)	.92		

Abbreviations: IHD = ischemic heart disease

^{*} Multivariable model included age, sex, diabetes duration, glycosylated hemoglobin, history of cardiovascular disease, nephropathy, hypertension, and smoking status.

[†] Multivariable model included age, sex, diabetes duration, body-mass index, glycosylated hemoglobin, history of cardiovascular disease, nephropathy, hypertension, and smoking status.

Table 3
Age-Sex and Multivariable-Adjusted Association of Clinically Significant Macular Edema at Baseline (1980-82) with All-Cause and Cause-Specific Mortality in the Wisconsin Epidemiological Study of Diabetic Retinopathy in the Older-Onset Group Stratified by Exogenous Insulin Use Status.

	Older-onset not taking insulin			Older-onset taking insulin		
	Age-Sex		Multivariable	Age-Sex		Multivariable
	N	HR (95%CI)	P-value	N	HR (95%CI)	P-value
All cause [*]	571	1.38 (0.91, 2.08)	.13	552	1.43 (1.12, 1.85)	.08
IHD [*]	255	1.09 (0.53, 2.21)	.81	263	1.60 (1.12, 2.28)	.02
Stroke [†]	107	0.95 (0.35, 2.60)	.92	86	1.43 (0.73, 2.79)	.29

^{*} Multivariable model included age, sex, diabetes duration, glycosylated hemoglobin, history of cardiovascular disease, nephropathy, hypertension, and smoking status.

[†] Multivariable model included age, sex, diabetes duration, body-mass index, glycosylated hemoglobin, history of cardiovascular disease, nephropathy, hypertension, and smoking status.