Association Between Diabetic Macular Edema and Cardiovascular Events in Type 2 Diabetes Patients

A Multicenter Observational Study

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Abstract: Diabetic macular edema (DME) is the main cause of visual loss associated with diabetes but any association between DME and cardiovascular events is unclear.

This study aims to describe the possible association between DME and cardiovascular events in a multicenter cross-sectional study of patients with type 2 diabetes.

Two thousand eight hundred seven patients with type 2 diabetes were recruited from diabetes and nephrology clinical institutional centers participating in the DIAB 2 NEPHROGENE study focusing on diabetic complications. DME (presence/absence) and diabetic retinopathy (DR) classification were based on ophthalmological report and/ or on 30° color retinal photographs. DR was defined as absent, nonproliferative (background, moderate, or severe) or proliferative. Cardiovascular events were stroke, myocardial infarction, and lower limb amputation.

Details regarding associations between DME and cardiovascular events were evaluated.

The study included 2807 patients with type 2 diabetes, of whom 355 (12.6%) had DME. DME was significantly and independently associated with patient age, known duration of diabetes, HbA1c, systolic blood pressure, and DR stage. Only the prior history of lower limb amputation was strongly associated with DME in univariate and multivariate analyses, whereas no association was found with regard to myocardial infarction or stroke. Moreover, both major (n = 32) and minor lower limb (n = 96) amputations were similarly associated with DME, with respective odds ratio of 3.7 (95% confidence interval [CI], 1.77–7.74; $P = 0.0012$) and of 4.29 (95% CI, 2.79–6.61; $P < 0.001$).

DME is strongly and independently associated with lower limb amputation in type 2 diabetic patients.

Abbreviations: CI = confidence interval, DME = diabetic macular edema, DR = diabetic retinopathy, ECG = electrocardiogram, ETDRS = Early Treatment Diabetic Retinopathy Study, GFR = glomerular filtration rate, HbA1c = glycated hemoglobin, IQR = interquartile range, MDRD = modification of diet in Renal disease, OR = odds ratio, SBP = systolic blood pressure, SDs = tandard deviation, VEGF = vascular endothelial growth factors.

INTRODUCTION

The prevalence of diabetes is increasing worldwide, exceeding previous predictions.[1] Patients with diabetes develop macrovascular complications that lead to a doubling of coronary deaths in addition to microvascular consequences with renal, neurological, and visual involvement.[2] Diabetic macular edema (DME) is the main cause of visual loss associated with diabetes. Indeed, DME affects approximately 7% of diabetic patients, resulting in approximately 21 million individuals suffering from visual impairment worldwide.[3,4] Diagnosis of clinically significant DME is important as there are several therapies associated with visual improvement such as laser grid photocoagulation and intravitreal antivascular endothelial growth factors (VEGF) injections.[5,6]

Some clinical (ie, hypertension, nephropathy) and biological parameters (ie. high glycated hemoglobin) are established risk factors for DME and cardiovascular events.[7–9] Although previous studies have suggested that DME may be associated with cardiovascular or vascular events,[10–12] the relationship between DME and the general cardiovascular consequences of diabetes including lower limb amputation requires further investigations. Particularly because none of the studies linking diabetic retinopathy (DR) with cardiovascular events separated ischemic retinal lesions from DME.[13]

The objective of the present study was to describe the association between retinal involvement and cardiovascular events in a multicenter study of type 2 diabetic patients, with special focus on DME and DR.

METHODS

Patient Recruitment

Type 2 diabetic patients were recruited in diabetes and nephrology clinical centers participating in the DIAB 2 NEPHROGENE study (see list in appendix). The aim of this French multicenter cross-sectional study was to explore the contribution of genes and environment to type 2 diabetes complication phenotypes. This ancillary study focuses on clinical or biological associations with DME.

Selection criteria have been previously described[14] and comprised patients with type 2 diabetes with or without DME. The study design was approved by the local ethics committee (CPP Ouest III) and all participants gave written informed consent.

Definition of Cardiovascular Endpoints

Any history of prior cardiovascular events—myocardial infarction, stroke and lower limb amputation—was recorded at inclusion, from the patient record. At inclusion of patients, an electrocardiogram (ECG) was performed to assess any previous myocardial infarction. In cases of multiple lower limb amputations, the most severe level was considered: transtibial or transfemoral amputations were classified as major whereas transmetatarsal or toe amputations were classified as minor amputations.

Ophthalmological Classification

Diagnosis of DME was based on 30° nonmydriatic retinal color photographs interpreted by a senior ophthalmologist and/or on fundus examination after pupillary dilatation performed by a senior ophthalmologist.

Diagnosis of DME was defined as a localized or diffuse thickening of the macular area usually associated with retinal exudates, cysts, and microanevrisms. Patients who could not be assessed for DME, for poor quality of retinal photographs or failure to attend ophthalmological examination during the study, were not considered for analysis in the present study.

DR was defined as absent, nonproliferative (background, moderate, or severe) or proliferative based on 30° retinal color photographs covering the 7 fields and graded according to the Modified Airlie House final classification. In this analysis, 2 groups of patients were classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification[15]: those graded less than stage 53 (group 1) and those graded stage 53 or more (group 2).

Patients were classified according to the eye with the more severe stage.

Biological Determination

Serum creatinine and urinary albumin were measured by nephelometry on a Modular System P (Roche Diagnostics GmbH, Penzberg, Germany). Renal function was estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal disease (MDRD-4) formula. Urinary creatinine was measured on a Hitachi911 automatic analyzer (Roche Diagnostics, Meylan, France). Glycated hemoglobin (A1C) was determined by using a high performance liquid chromatography method with an ADAMS A1C HA-8160 analyzer (normal values 4.0% to 6.0%; Menarini, Florence, Italy).

Statistical Analyses

Statistical analyses were performed with Statview 5.0 (SAS Institute, Cary, NC). Patients' characteristics are expressed as means ± standard deviation or medians (interquartile range) for skewed distributions.

Intergroup comparisons were performed using logistic regression for both univariate and multivariate approaches. Results are given as odds ratio (OR) and 95% confidence intervals (CIs).

Stratification was performed on the presence of significant DR (group 1 vs group 2), due to a significant interaction ($P < 0.001$) between lower limb amputation and DR for the relation between DME and lower limb amputation.

Multivariate logistic regression analyses with DME as the dependent variable were performed using a backward manual procedure; variables with $P < 0.05$ in univariate analysis were selected in the maximal model.

All comparisons were 2 sided with $P < 0.05$ being considered statistically significant.

RESULTS

Demographic Data

The DIAB 2 NEPHROGENE study included 2807 patients with type 2 diabetes after exclusion of patients due to uncertainty about the presence or absence of DME. This study population consisted in 355 patients (12.6%) with DME and 2452 patients (87.4%) without DME. When considering the whole population, history of lower limb amputation was reported in 82/2370 (3.46%) among patient without DME and in 46/309 (12.96%) among patients with DME ($P < 0.001$).

History of stroke and myocardial infarction was reported in 111/2341 (4.53%) and 306/2146 (12.48%) among patients without DME and in 27/328 (7.61%) and 52/303 (14.65%), respectively, among patients with DME ($P = 0.01$ and 0.25, respectively). Their general characteristics are detailed in Table 1.

DME, DR, and Cardiovascular Events—Univariate Analysis

In the study population, DME was significantly associated with age, known duration of diabetes, HbA1c eGFR, and systolic blood pressure (SBP) (Table 1). As expected, DME was significantly more frequent as DR stage became more severe (χ^2 for trend: 696, $P < 0.001$) (see details in Table 2).

In group 1 (patients with DR graded less than stage 53), DME was significantly associated with age, known duration of diabetes, HbA1c, eGFR, SBP, and with a prior history of lower limb amputation (Table 1).

None of the previous clinical or biological variables remained associated with DME when sub-analysis was carried out on group 2 (patients graded stage 53 or more).

We investigated the relationship between DME and DR. In this context, DME was associated with DR. These data are presented in Table 2. We also investigated the relationship between the level of lower limb amputation and DME. No trend was found for an association between DME and severity of lower limb amputation. Indeed, both major and minor lower limb amputations were similarly associated with DME, with

TABLE 1. Comparison of Patients With and Without DME, With Focus on DR Severity Stage: Univariate Analyses for Demographic, Clinical, and Biological Variables

Group	Whole Population Without DME	Whole Population With DME	Group 1 With DME	Group 1 OR (95% CI)	Group 1 P Value	Group 2 Without DME	Group 2 With DME	Group 2 OR (95% CI)	Group 2 P Value
Total no. of patients	2452	355	122	—	—	205	233	—	—
Sex ratio, female/male	959/1493	130/225	82/40	1.31 (0.89–1.93)	0.17	122/83	143/90	1.08 (0.74–1.59)	0.69
Age, yr	63.7±10.5	65.7±8.6	65.7±9.3	1.02 (1.00–1.04)	0.03	64.3±9.7	65.8±8.3	1.02 (0.99–1.04)	0.09
Diabetes duration, yr	14.0±9.7	18.9±9.3	18.3±8.5	1.05 (1.03–1.06)	<0.001	19.1±9.3	19.2±9.7	1.00 (0.98–1.02)	0.95
HbA1c, %	7.7±1.5	8.0±1.6	8.1±1.6	1.18 (1.06–1.31)	0.003	8.1±1.8	8.0±1.5	0.94 (0.84–1.06)	0.31
eGFR, mL/min per 1.73 m^2	77.4±28.1	63.3±31.1	71.8±31.6	0.99 (0.98–1.00)	0.007	63.0±29.1	58.8±30.0	1.00 (0.99–1.01)	0.14
SBP, mm Hg	135.7±18.3	142.7±21.3	143.4±22.5	1.02 (1.01–1.03)	<0.001	141.6±19.8	142.4±20.6	1.00 (0.99–1.01)	0.68
History of amputation, n, no/yes (%)	82/2370 (3.46)	46/309 (12.96)	12/110 (9.8)	3.72 (1.95–7.10)	<0.001	18/187 (8.8)	34/199 (14.6)	1.78 (0.97–3.25)	0.06
History of stroke, n, no/yes (%)	111/2341 (4.53)	27/328 (7.61)	9/113 (7.4)	1.76 (0.87–3.59)	0.12	14/191 (6.8)	18/215 (7.7)	1.14 (0.55–2.36)	0.72
History of myocardial infarction, n, no/yes (%)	306/2146 (12.48)	52/303 (14.65)	14/108 (11.5)	0.93 (0.53–1.65)	0.81	32/173 (15.6)	38/195 (16.3)	1.05 (0.63–1.76)	0.84

Data are n, mean ± standard deviation. Group 1: Patients with diabetic retinopathy graded less than stage 53 from ETDRS classification; Group 2: Patients with diabetic retinopathy graded stage 53 or more from ETDRS classification. CI = confidence interval; DME = diabetic macular edema; DR = diabetic retinopathy; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; OR = odds ratio; SBP = systolic blood pressure.

TABLE 2. Association Between DME and Diabetic Retinopathy

	Patients With DME	Patients Without DME
No DR (ref) (%)	0 (0)	1410 (100)
Background DR	122 (12.7)	837 (87.3)
Severe nonproliferative DR	133 (52.8)	119 (47.2)
Proliferative DR	100 (53.8)	86 (46.2)
Group 1 (ETDRS stage <53)	122 (5.1)	2247 (94.9)
Group 2 (ETDRS >53)	233 (53.2)	205 (46.8)

Data are n (%). DR, diabetic retinopathy graded according to simplified ETDRS classification. Odds ratio for DME group 2 versus group 1: 20.9 (95% CI 15.98–27.43, $P < 0.001$). DME = diabetic macular edema; DR = diabetic retinopathy; ETDRS = early treatment diabetic retinopathy study.

respective OR of 3.7 (95% CI, 1.77–7.74; $P < 0.0012$) and of 4.29 (95% CI, 2.79–6.61; $P < 0.001$) (Table 3).

In the present study, DR was associated with cardiovascular events (Table 4). In fact, when compared to patients with no DR, DR was associated with SBP ($P < 0.001$), lower limb amputation ($P < 0.001$), stroke ($P = 0.0051$), and myocardial infarction ($P = 0.035$).

DME and Cardiovascular Events—Multivariate Analysis

Multivariate analyses carried out on the study population showed that the risk factors identified in univariate analysis remained independently associated with DME. Indeed, as previously observed in univariate analyses, significant associations persisted between lower limb amputation and DME in the whole cohort and in group 1 (Tables 5 and 6), whereas no association was found in group 2 (data not shown).

Interestingly, after full adjustment, history of lower limb amputation remained more than doubled in cases of DME.

DISCUSSION

Association With Cardiovascular Events

In this large-scale cross-sectional analysis, we found an association between cardiovascular risk factors such as age and SBP, and DME. In addition, DME was significantly associated with lower limb amputation in type 2 diabetes patients. In multivariate analysis, SBP and prior history of lower limb amputation were positively and significantly associated with DME. This association between DME and lower limb amputation was independent of DR. The present study did not establish any significant association between myocardial infarction and DME either in our study population or in subgroup analyses. Furthermore, an association was observed between stroke and DME only in univariate analysis performed in the whole population.

A recent retrospective study comparing incidence rates of myocardial infarction and cerebrovascular accident requiring hospitalization in DME patients and in diabetic patients without retinal involvement, found significantly more cardiovascular events, such as myocardial infarction and cerebrovascular events, in patients with DME.[10] Our study did not confirm the hypothesized link between myocardial infarction or stroke

TABLE 3. Association Between DME and Severity of Lower Limb Amputation—Univariate Analysis

	Patients With DME, N = 355	Patients Without DME (Ref), N = 2452	OR (95% CI)	*P* Value
Minor lower limb amputation	35 (9.86)	61 (2.49)	4.29 (2.79–6.61)	<0.001
Toe amputation, n (%)	27 (7.61)	46 (1.88)	4.31 (2.57–7.20)	<0.001
Transmetatarsal amputation, n (%)	8 (2.25)	15 (0.61)	3.75 (1.45–9.47)	0.013
Major lower limb amputation	11 (3.1)	21 (0.86)	3.70 (1.77–7.74)	0.012
Transtibial amputation, n (%)	7 (1.97)	12 (0.49)	4.09 (1.45–11.25)	0.015
Transfemoral amputation, n (%)	4 (1.13)	9 (0.37)	3.09 (0.80–11.02)	0.071

CI = confidence interval; DME = diabetic macular edema; OR = odds ratio.

and DME. This discrepancy may be explained by differences between the 2 populations in terms of age at inclusion and cardiovascular events. DME had previously been associated with lower limb amputation in the Veterans Affairs Diabetes Trial, a study including 1268 patients with type 2 diabetes with different ethnicities, whereas no association could be established with regard to stroke or myocardial infarction in agreement with our findings.[16] In the Veterans Affairs Diabetes Trial study, 7.9% of patients with DME (n = 127) versus 1.8% of patients without DME (n = 1141) had a history of lower limb amputation. Here we report markedly higher rates of lower limb amputation, which was undergone by 12.96% of patients with DME and by 3.8% of patients without DME. These differences may also be explained by differences in the characteristics of patients recruited in the 2 cohorts.

Associations have also been established in our cohort between DR and cardiovascular events. Lower limb amputation was associated with all DR stages, whereas stroke and myocardial infarction were associated primarily with proliferative DR. Previous studies had investigated the presence of DR as a predictor of cardiovascular morbidity and mortality[17–22] and a recent meta-analysis of 20 observational studies established significant associations between DR and all-cause mortality and/or cardiovascular events (such as myocardial infarction, angina pectoris, coronary artery bypass graft, ischemic changes on ECG, transient ischemic attack, nonfatal stroke, or lower limb amputation).[11] However, the study lacks any further information on DME and does not inform on the relationship between DR and lower limb amputation.

As we analyzed the relationship between DME and lower limb amputation, we found that while a relationship between cardiovascular events and DME existed in our study population taken as a whole and in group 1 (patients graded less than stage 53), no such association could be established in group 2 (patients graded stage 53 or more). This is probably due to the strong association existing between DME and DR in this subgroup, which most likely overwhelmed any other potential associations with minor effects. Regarding the clinical criteria of lower limb amputation, all degrees of lower limb amputation were taken into account in our study, without consideration of the pathophysiological mechanisms involved that is peripheral neuropathy, peripheral artery disease, or infection.[23] Interestingly, a sub-analysis taking into account the level of lower limb amputation suggested that DME was similarly associated with both microvascular and macrovascular processes, while a more strongly pronounced relationship between microvascular disease, that is ''minor amputations'' and DME was intuitively expected.

In the Field Study including 9795 type 2 diabetic patients randomized to fenofibrate or placebo, lower limb amputation was more significantly associated with DR than with myocardial infarctions or strokes. Among patients with minor amputations, 36% had DR while among patients with major

TABLE 4. Univariate Analyses for Cardiovascular Events and Biological Variables Associated to Nonedematous Diabetic Retinopathy

Patients Characteristics	No DR	Background DR
n	1410	959
Sex ratio, male/female*	856/554	597/362
Age, y	62.7 ± 10.9	65.2 ± 9.7
Diabetes duration, y	11.3 ± 9.0	17.5 ± 9.3
HbA1c, %	7.5 ± 1.4	8.0 ± 1.5
eGFR, mL/min per 1.73 m^2	81 ± 26	74 ± 30
SBP, mm Hg	133 ± 17	138 ± 20
Lower limb amputation, n (%)	19 (1.3)	57 (5.3)
Stroke, n (%)	50 (3.5)	56 (5.8)
Myocardial infarction, n (%)	158 (11.2)	130 (13.6)

Data are n, mean ± standard deviation. DR = diabetic retinopathy; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; SBP = systolic blood pressure.
* F (female) being the reference gender.

TABLE 5. Multivariate Logistic Regression of DME in the Study Population

	Adjusted OR	95% CI
Lower limb amputation (reference = no)	3.51	2.34–5.28
Diabetes duration, per 1 yr	1.03	1.02–1.04
eGFR, per 1 mL/min per 1.73 m^2	0.99	0.98–0.99
HbA1c, per 1%	1.15	1.07–1.24
SBP, per 1 mm Hg	1.01	1.01–1.02

Only independent factors are shown. CI = confidence interval; DME = diabetic macular edema; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; OR = odds ratio; SBP = systolic blood pressure.

TABLE 6. Multivariate Logistic Regression of DME in Group 1

	Adjusted OR	95% CI
Lower limb amputation (reference = no)	3.27	1.66–6.45
Diabetes duration, per 1 yr	1.04	1.02–1.06
eGFR, per 1 mL/min per 1.73 m^2	0.99	0.99–1.00
HbA1c, per 1%	1.22	1.09–1.36
Sex (reference = female)	1.39	0.93–2.07

Only independent factors are shown. CI = confidence interval; DME = diabetic macular edema; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; OR = odds ratio.

amputations, only 26% suffered from this condition.[24] Our data corroborated these results by underlining the extent to which lower limb amputation is more closely associated with DR than with stroke or myocardial infarction.

One key question arising from the analysis of our data is whether any single unifying mechanism interlinks DR, DME, and lower limb amputation. Biological mechanisms that lead to DME or to DR share many similarities but are also markedly different. DME is produced by alterations of tight junctions, pericyte and endothelial cell loss, retinal vessel leukostasis and increased permeability of retinal capillaries and retinal pigment epithelium cells.[25] On the other hand, the ischemic territories formed by retinal capillary occlusions leading to DR are caused mainly by wall modifications through thickening of basement membranes, pericytes, and endothelial cell loss combined with leukostasis. Extension of the ischemic territories leads to heightened expression of the growth factors (VEGF, IGF-1) that are involved in the retinal neovascular process.[26–28] To explain the interaction between lower limb amputation and severe DR and DME, we can speculate that the occlusive microvascular processes observed in the retina are likely to be stronger determinants than the exudative processes due to VEGF upregulation. The capillary occlusions underlying ischemic DR may also to some extent reflect the peripheral artery disease leading to lower limb amputation. Capillary occlusion might also be involved in the development of diabetic neuropathy, another important contributor to lower limb amputation. On the other hand, a different mechanism entirely could help to explain the association between DME and lower limb amputation. Several disorders associated with central visual impairment that have been shown to increase the risk of fall and traumatic injuries,[29] and it is possible that the visual impairment caused by DME itself may contribute to foot ulcer.

Study Limitations

We acknowledge some limitations regarding the study methodology we used for DME diagnosis, which was based on nonmydriatic color photographs interpreted by senior ophthalmologists. In this context, it is likely that clinically nonsignificant DME with no exudates and without significant visual acuity decrease remained undetected. However, other studies have demonstrated close agreement with regard to DME severity levels ($\kappa = 0.92$)[30] and to DME detection ($\kappa = 0.97$)[31] between nonmydriatic color photographs and the gold standard reference of color stereo-photographs of 7 standard fields. Similarly, a 2001 systematic review concluded that single-field

fundus photographs for screening of DR have sensitivity ranging from 61% to 90% and specificity ranging from 85% to 97% when compared with the stereo-photographs of 7 standard fields.[32]

All of these methods for DME diagnosis rely on en face determination of retinal thickening, and a recent study suggested that color photographs could be a less reliable tool, when compared to optical coherence tomography as a means of detecting DME.[33] However, while this method of DME determination is widely used in interventional clinical trials to assess the effect of molecules on DME during the treatment, it is not currently considered as the gold standard for DME determination in diabetic screening, likely due to the fact that OCT equipment is not as widely used in screening centers as color retinographs. Our study design is cross-sectional, which renders it impossible to establish a causal relationship between DME and lower limb amputation. We were also unable to establish any temporal relationship between visual impairment and lower limb amputation and it is possible that the association observed was produced by recruitment bias as the centers included in the study specialize in diabetes and nephropathy and may have a skewed population of patients with diabetes and severe kidney disease. Our method for establishing the presence of DME was also suboptimal and may have underreported DME as retinal photographs may not pick up DME in the absence of exudates. All of the images and patients were graded by the same clinician but we did not assess the repeatability of those assessments of the diabetes photographs. Four percent of our sample was excluded due to inadequate characterization of the macular status which may have skewed our results. Our method of ascertainment also relied on reported history. Cardiovascular outcomes and stroke while sometimes obvious are less easily characterized than lower limb amputation and these may have been underreported. Nevertheless, we had a large sample size and a cross-sectional approach has high statistical power through which relatively rare events such as amputation can be taken into adequate account.

Our general conclusion following this large-scale study is that DME and proliferative DR are strong and independent risk factors for lower limb amputation. Indeed, the main finding is that in this study people with macular edema had a 3.5-fold increased risk for lower limb amputation. In the context of DR screening, assessment of both retinopathy and macular status may help to identify patients at high risk for amputation. Equally patients with a prior history of amputation should be given special attention. A prospective approach may clarify the prognostic value of DME in relation to the risk of minor or major lower limb amputation in type 2 diabetes patients.

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