

# CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA: SYSTEMIC RISK FACTORS

## EDEMA MACULAR DIABÉTICO CLÍNICAMENTE SIGNIFICATIVO: FACTORES SISTÉMICOS DE RIESGO

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### ABSTRACT

**Objective:** We examined the influence of non-ophthalmic parameters as risk factors of clinically significant macular edema (CSME).

**Methods:** The authors reviewed clinical records of all clinically significant macular edema between 1995 and 2005. The association between the presence of CSME and HgbA1c, onset and duration of diabetes, blood pressure, body mass index, lipid status, sex, tobacco smoking and urinary albumin excretion was evaluated.

**Results:** 208 eyes met the study criteria. Patients ranged in age from 14 to 82 years (mean, 66 years) and had 8 to 64 years (mean, 47.5 years) of history of diabetes. Significant risk factors for CSME were older age, high levels of HgbA1c, high values of blood pressure, tobacco smoking, high cholesterol and LDL-cholesterol and high levels of proteinuria and microalbuminuria.

**Conclusion:** Independent on the type of diabetes, patients with long standing diabetes have a high risk to develop diabetic maculopathy, but other closely-related risk factors are hypertension, hyperglyce-

### RESUMEN

**Objetivo:** Estudiar los factores de riesgo sistémico del edema macular clínicamente significativo (EMCS) en una población de diabéticos.

**Método:** Se revisaron las historias clínicas de los pacientes diabéticos diagnosticados de edema macular clínicamente significativo entre 1995 y 2005. Se evaluó la asociación entre EMCS y HgbA1c, comienzo y duración de la diabetes, hipertensión arterial, índice masa corporal, nivel de lípidos, sexo, fumar y excreción urinaria de albúmina.

**Resultados:** 208 ojos fueron considerados con los criterios del estudio. Los pacientes tenían un rango de edad entre 15 y 82 años (media, 66 años) y tenían entre 8 y 64 años (media, 47,5 años) de historia de diabetes. Factores de riesgo significativos para desarrollar EMCS fueron edad avanzada, cifras elevadas de HgbA1c, hipertensión arterial, fumar, valores elevados de colesterol y LDL-colesterol y niveles elevados de proteinuria y microalbuminuria.

**Conclusiones:** Independientemente del tipo de diabetes, los pacientes con diabetes mellitus de larga evolución tienen un elevado riesgo de desarrollar

Received: April 26, 2007. Accepted: Feb. 18, 2008.  
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mia, lipids, tobacco smoking and renal status (*Arch Soc Esp Oftalmol* 2008; 83: 173-176).

**Key words:** Diabetes mellitus, diabetic maculopathy, CSME, hyperglycemia, hypertension, albuminuria, dyslipemia, tobacco smoke.

maculopatía diabética, pero otros factores de riesgo asociados son la hipertensión, la hiperglucemia, los lípidos, el tabaquismo y el estado renal.

**Palabras clave:** Diabetes mellitus, maculopatía diabética, EMCS, hiperglucemia, hipertensión, albuminuria, dislipemia, hábito tabáquico.

## INTRODUCTION

Diabetic retinopathy is the first cause of legal blindness among young adults in Western countries. This disease affects about 20 million people the world over (1,2). In Spain the prevalence of DM 2 is between 4.8% and 18.7% and of DM 1 of 0.08% to 0.2%. Diabetes mellitus and its associated pathologies constitute a health problem of the first order, even more at the present time due to the increase in life expectancy and childhood diabetes in developed countries (3,4). Diabetic macular edema is the most frequent cause of severe vision impairment in diabetic patients. Macular edema is secondary to the accumulation of fluid in the retina posterior pole. Its ethiopathogeny is not fully understood and at present there no satisfactory therapy. This enhances the importance of determining its risk factors (5,6). The objective of this study is to describe associated systemic risk factors in a diabetic population diagnosed with clinically significant macular edema (CSME).

## SUBJECTS, MATERIAL AND METHODS

This retrospective study was approved by the Committee of Research and Teaching of our hospital. The medical records of 201 diabetic patients with clinically significant macular edema between 1995 and 2005. Table I shows the demographic cha-

**Table I. Demographic characteristics**

Number	201
Gender (M/F)	81/120
Age	59.2 SD 11.3
Diabetes onset age	39 SD 10 years
Diabetes evolution time	19 SD 10 years

M: Male, F: Female.

racteristics of said population. The inclusion criteria for patients were as follows:

Diabetes mellitus type 1 or type 2 with CSME.

Ability to access clinical records.

No treatment in 3 months prior to the ophthalmological study involving corticoids, nephrotoxic and/or surgery

The diagnostic of CSME was based on slit lamp examination with or without contact lens. The parameters studied were age, sex, mean arterial pressure (systolic and diastolic), obesity, lipids and smoking. The study was completed determining kidney functions (microalbuminuria, proteinuria).

Glycosylated hemoglobin (Hgb A1c) was determined with a range established by the lab between 4.7% and 6.4%.

### Definitions

— CSME was defined according to the ETDRS study (7) as any of the following clinical situations:

Group I: Solid exudate associated to adjacent retinal thickening in the centre of the macula or at 500 microns.

Group II: Retinal thickening at 500 microns or less from the center of the macula.

Group III: Retinal thickening equal to or greater than one papillar diameter with some part thereof inside a region with a papillar diameter having the centre in the fovea.

— Obesity: A clinical situation in which the Body Mass Index exceeds 30.

— Diabetes type 1: diabetes developing in patients aged 30 or less.

— Diabetes type 2: diabetes developing in patients over 30.

— Mean systolic high pressure: the mean of the last three values of systolic pressure.

— Mean diastolic high pressure: the mean of the last three diastolic pressure values.

— Tobacco:

Non-smoker: never smoked.

Ex-smoker: has left the habit completely 1 month prior to CSME diagnostic.

Smoker.

— Kidney study:

Microalbuminuria: concentration of albumina in urine in the range between 30 mg/24 h and 300 mg/24 h, determined by radio immunoassay.

Proteinuria: concentration of proteins in urine > 0.30 g/l.

For the statistical study, the Mantel-Haenszel test was utilized to study the significance of the associations. Student Test was utilized to compare continuous variables. The risk was determined and adjusted with regression models.

## RESULTS

Twenty-two patients were not considered due to incomplete medical records. In all, 208 eyes with CSME were studied, belonging to 179 diabetic patients with an age range comprised between 15 and 85 years (mean 66 years). The diabetes diagnostic age was between 8 and 70 years (mean 49.5 years). Over half (60%) were women while 40% were men. The diabetes duration time ranged between 7 and 46 years (mean 38.7 years). The mean Hgb A1c was of 9.2% (range between 6.4% and 19%). Thirty percent of cases did not have retinopathy against 70% who had, in varying degrees. In 54 eyes (26%) visual acuity was of 1 and in 39.4% (82 eyes) was of 0.1 or less (table II). According to the CSME classification, 29.8% (62 eyes) exhibited a CSME definable within the concepts of group 1, while 38% (80 eyes) were included within group 2, and 21.6% (45 eyes) in group 3 (table 3). The prevalence of CSME was greater in diabetics type 2 in treatment with insulin (56.3% of all CSME) and lower in diabetics type 2 in treatment with oral anti-diabetics (OAD) (15.6%). High levels of Hgb A1c was significantly associated with CSME, with an increase of risk for every 1% of elevation of 2.4 (CI, 1, 45-2.78). In a global manner, the severity of retinopathy and CSME was significantly associated with a risk of 1.6 (CI, 1.16-1.83). The kidney pathology, determined as proteinuria or microalbuminuria, and high arterial pressure (systolic and diastolic) were significantly associated to CSME with a risk of 1.55 (CI, 156-1.78). The age was associated to a risk of 1.8 (CI, 1.24-2.10). Total

cholesterol and LDL cholesterol were associated to a risk of 1.4 (CI, 1.25-1.67). Smoking (former smoker and smoker) was associated to a risk of 1.50 (CI, 1.26-1.45). Gender (0.56, IC= 0.81-1.07) and obesity (0.72, IC= 87-1.5) were not significant factors in the development of CSME.

## DISCUSSION

Diabetes mellitus is a chronic disease affecting the metabolism of carbohydrates which damages the kidneys, blood vessels, peripheral nerves and the eyes. Diabetic retinopathy causes blindness in more people in productive age than any other disease, and is one of the main causes of blindness in young people and adults in developed countries (1,2). The increase of diabetes in said countries matches the reduction of visual health. The rupture of the blood-retina barrier and the ensuing increase of permeability in diabetic retinopathy is the first cause of blindness in said patients (1,2,4,5).

In the instant study, 26% of cases with CSME had visual acuities of 1 against 39% having VAs of 0.1 or less. The onset of CSME is rare before 10 years of evolution of diabetes, although after said period there is a linear cumulative risk of 6.7% per year (8,9). Other studies such as the Wisconsin (10) determined a prevalence between 10-20 years of 3%.

**Table II. Visual acuity at diagnostic time**

VA	No. of eyes
20/20	54 (25,9%)
20/30	32
20/40	19
20/80	21
20/200	45
<20/200	30
HM	4
F	3

VA: Visual acuity; HM: Hands movement; F: fingers.

**Table III. CSME classification**

CSME Group	Eyes (n/%)
1	62 (29.8%)
2	80 (38.4%)
3	45 (21.6%)
Mixed	21 (10.09%)

CSME: Clinically significant macular edema.

Over half of our CSME cases (56.3%) occurred in diabetics type 2 in treatment with insulin against 15.6% of diabetics type 2 in treatment with oral anti-diabetics. This in accordance with other series described in the literature (7,11).

One of the objectives of this study was to study the relationship between CSME and systemic risk factors. In our sample there is a relationship between the age in which diabetes was diagnosed, with CSME being more frequent in older individuals (7,10). In this study, the relationship between HgbA1c levels and macular edema, with risk increasing more than double for each 1% of elevation of glycosylated hemoglobin (7,9). High arterial blood pressure in a diabetic increases almost twofold the risk of CSME. In our patients, the relationship between sub-clinical diabetic nephropathy (microalbuminuria/albuminuria) increases almost twice the risk of macular edema (12). As a frequent metabolic alteration in diabetics, dyslipemia was studied with cholesterol and its LDL fraction and it was seen that its presence increases almost 100% the risk of CSME (13,14). This study establishes a relationship between tobacco addiction (present and past) and CSME, increasing risk almost 100%. However, no association with CSME was found in two variables of the study (sex and obesity), even though other series (8) consider being male an added risk factor for the development of CSME. In a recent study, Knudsen LL et al (15) were unable to establish in type 1 diabetics an association between CSME and the systemic parameters of the study, but in typ2 diabetics a significant association was found with the duration of the diabetes, HgbA1c, neuropathy and albuminuria. In summary, it is probable that the estimated prevalence of CSME is undervalued due to the high percentage of cases appearing in clinical practice with normal visual acuity values and which, due to overburdened ophthalmology services, are not called for an adequate microscopic assessment. It must not be forgotten that the higher percentage arises in type 2 diabetics in treatment with insulin and that the Hgb A1c levels are a risk factor of high magnitude. Therefore, metabolic control, even in advanced stages of diabetes, can modify the risk of developing CSME.

## REFERENCES

1. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. *Ophthalmology* 1984; 91: 1-9.
2. Antonetti DA, Lieth E, Barber AJ, Gardner TW. Molecular mechanisms of vascular permeability in diabetic retinopathy. *Semin Ophthalmol* 1999; 14: 240-248.
3. Ruiz-Ramos M, Escolar-Pujolar A, Mayoral-Sanchez E, Corral-San Laureano F, Fernandez-Fernandez I. Mellitus diabetes in Spain: death rates, prevalence, impact, costs and inequalities. *Gac Sanit* 2006; 20 Suppl 1: 15-24.
4. Lopez-Capape M, Alonso M, Colino E, Mustieles C, Corbaton J, Barrio R. Frequency of the metabolic syndrome in obese Spanish pediatric population. *Eur J Endocrinol* 2006; 155: 313-319.
5. Jousseaume AM, Smyth N, Niessen C. Pathophysiology of diabetic macular edema. *Dev Ophthalmol* 2007; 39: 1-12.
6. Krohne TU, Fauser S, Kirchhof B, Jousseaume AM. Pathogenesis of diabetic macular edema. *Klin Monatsbl Augenheilkd* 2003; 220: 521-525.
7. Early Treatment Retinopathy Study Reserach Group. Photocoagulation for diabetic macular edema. *Early Diabetic Retinopathy Study report number 1. Arch Ophthalmol* 1985; 103: 1796-1806.
8. Kinyoun J, Barton F, Fisher M, Hubbard L, Aiello L, Ferris F 3rd. Detection of diabetic macular edema. *Ophthalmoscopy versus photography-Early. Treatment Diabetic Retinopathy Study Report number 5. Ophthalmology* 1989; 96: 746-751.
9. Vitale S, Maguire MG, Murphy RP, Hiner CJ, Rourke L, Sackett C, Patz A. Clinically significant macular edema in type I diabetes. *Ophthalmology* 1995; 102: 1170-1176.
10. 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.
11. Jeddi Blouza A, Khayati L, Malouche N, Slim B, Azeiz S, Issaoui A, et al. Risk factors for diabetic macular edema. *J Fr Ophtalmol* 2005; 28: 1033-1038.
12. Girach A, Lund-Andersen H. Diabetic macular oedema: a clinical overview. *Int J Clin Pract* 2007; 61: 88-97.
13. Rema M, Srivastava BK, Anitha B, Deepa R, Mohan V. Association of serum lipids with diabetic retinopathy in urban South Indians—the Chennai Urban Rural Epidemiology Study (CURES) Eye Study—2. *Diabet Med* 2006; 23: 1029-1036.
14. Miljanovic b, Glynn RJ, Nathan DM, manson JE, Schaumberg DA. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. *Diabetes* 2004; 53: 2883-2892.
15. Knudsen LL, Lervang HH, Lundbye-Christensen S, Gorst-Rasmussen A. The North Jutland County Diabetic Retinopathy Study (NCDRS). 2 Non-ophthalmic parameters and clinically significant macular edema. *Br J Ophthalmol* 2007; 91: 1593-1595.