

# Chapter 6

## ***Trace microalbuminuria in inflammatory cystoid macular edema.***

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## **Abstract**

### **Purpose**

To assess the role of cardiovascular morbidity, its risk factors, and microalbuminuria in the development of inflammatory cystoid macular edema (CME).

### **Design**

A matched case-control study.

### **Methods**

*Study population:* We included 24 consecutive patients with uveitis and CME. Twenty four uveitis patients without CME, matched for age and duration of uveitis served as controls. *Intervention and observation procedures:* Patients and controls were interviewed for the presence of cardiovascular risk factors and cardiovascular morbidity. All medications were registered. Morning urinary albumin concentration was measured, as well as blood pressure, C-reactive protein, and creatinine in blood. Patients suffering from diabetes mellitus were excluded from this study. *Main Outcome Measures:* The presence of cardiovascular morbidity and its risk factors and microalbuminuria in uveitis patients with and without CME.

### **Results**

We found a positive association between trace- and/or microalbuminuria and inflammatory CME ( $P = .001$ ; odds ratio 13.0, 95 % CI 2.5 to 68.1 and  $P = .015$ ; odds ratio 5.9, 95 % CI 1.6 to 22.6), but no relation between CME and cardiovascular morbidity or its risk factors. No additional association between trace- and/or any microalbuminuria and general characteristics of patients, specific factors related to general disease as a cause of ocular inflammation, location of uveitis, duration of uveitis, and medication was found.

### **Conclusion**

The presence of trace- and/or microalbuminuria in inflammatory CME might indicate the presence of early systemic vascular disease and carry the risk of developing CME. This finding brings new insight into the pathogenesis of CME and could open up new avenues for the treatment of CME.

## Introduction

Cystoid macular edema (CME) is a major cause of visual impairment (41%) and blindness in uveitis (29%).<sup>1,2</sup> Additionally, a large survey on uveitis indicated that 26% of all patients with uveitis develop CME.<sup>1</sup> The treatment of CME is usually initiated when visual acuity drops below 20/40, and consists of causal treatment of underlying disorder and symptomatic treatment of CME. The pathogenesis of CME in uveitis patients is not clear and the groups of patients with uveitis at risk of developing severe CME have not yet been identified.

Cardiovascular diseases and retinal vascular changes are involved in the pathogenesis of CME in patients with diabetes mellitus and retinal vein occlusions, however the underlying mechanism is not yet clarified.<sup>3-7</sup> In particular, the CME in patients with diabetes mellitus is strongly associated with hypertension and the presence of microalbuminuria.<sup>5,7-11</sup> Microalbuminuria reflects the increased permeability of damaged vascular walls. The role of microalbuminuria as a marker of early vascular disease was recently examined not only in diabetes mellitus, but also in non-diabetes mellitus patients.<sup>12-17</sup> In the nondiabetic population, microalbuminuria was an independent indicator for cardiovascular risk factors and cardiovascular morbidity. Microalbuminuria in patients with uveitis could point out the patients with early vascular disease and might be associated with the development of CME.

In this report, we analyze the possible association between microalbuminuria, cardiovascular diseases, and inflammatory CME in patients with uveitis.

## Patients and Methods

This matched case-control study included 24 uveitis patients with CME and 24 uveitis patients without CME, matched for age and duration of uveitis. Consecutive patients with uveitis and CME were selected from the uveitis clinic of the ophthalmologic department of the University Hospital of Utrecht. For each patient, a control patient was selected from the same clinic population with a similar age ( $\pm 5$  years, mean  $\pm 1.8$  years) and duration of uveitis (subdivided in  $0 \leq 2$ ,  $2 \leq 5$ ,  $5 \leq 10$ , and  $10 >$  years) but without CME or previous CME. CME was diagnosed using clinical criteria and fluorescein angiography in all cases.<sup>18</sup> CME

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was graded by a masked ophthalmologist on late phase fluorescein angiography. Patients with no leakage were graded 0, those with leakage less than 25% as grade 1, leakage between 25% and 66% was graded as 2, and leakage of more than 66% was graded as 3.<sup>19</sup> Patients were assessed for inflammation activity and cataract extraction status at time of inclusion.

Patients and controls were interviewed for the presence of cardiovascular disease using a questionnaire, including information on weight, all medications, smoking habits, presence of systemic hypertension, diabetes mellitus, hypercholesterolemia, cerebral vascular accidents, transient ischemic attacks, angina pectoris, myocardial infarction, abdominal aortic aneurysm, thrombosis, and lung emboli. In addition to the patients with systemic hypertension diagnosed in the past and already treated, the patients with 3 independent measurements with an interval of at least 1 week and a diastolic blood pressure of 95 mm Hg or higher were also diagnosed as having hypertension. Cardiovascular morbidity was defined as the presence of or history of cerebral vascular accidents, transient ischemic attacks, angina pectoris, myocardial infarction, and abdominal aortic aneurysm.<sup>20</sup> Cardiovascular risk factors were defined as the presence or a history of hypertension, hypercholesterolemia, and current smoking.<sup>20</sup> Venous thrombo-embolic disease was scored separately. Patients suffering from diabetes mellitus were excluded from this study; so were patients with a non fasting blood glucose level of 7.0 mmol/l at time of uveitis screening.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 11.0). Differences between the patients and controls were compared with the Fisher's exact test and a multivariate logistic regression analysis. A P-value < .05 was considered to be significant.

Blood samples were taken from 46 patients to determine C-reactive protein (CRP) and creatinine. Two patients refused blood sampling.

Morning urinary albumin excretion was determined in all by a commercial immunoturbidimetry assay with a sensitivity of 5.5 mg/l and inter- and intra-assay coefficients of variation of 5.2% and 13.2% respectively (Dade Behring Diagnostics, Liederbach, Germany). Morning urinary albumin excretion  $\leq$  5 mg/l was defined as no

albuminuria, of  $5 \leq 20$  mg/l was defined as trace microalbuminuria and morning urinary albumin excretion of  $20 \leq 200$  mg/l was defined as microalbuminuria.<sup>13,21</sup>

Creatinine clearance was calculated using the serum creatinine levels as a basis with the Cockcroft-Gault equation.<sup>22,23</sup>

## Results

General data from the CME patients and non-CME controls with uveitis are given in Table 1. The average age was 45 years for the CME patients and 45 years for the controls. The male-to-female ratio in the CME group was 3:5, in the non-CME group 1:2. No differences in gender, inflammation activity, and cataract extraction status (cataract extraction  $0 \leq 2$  years before inclusion) were found in both groups ( $P = 1.0$ ;  $P = .77$ ;  $P = .42$ ).

Cardiovascular morbidity was present in 3 patients (6%) (2/24, 8% with CME, 1/24, 4% in non-CME group,  $P = .60$ ). Cardiovascular risk factors were present in 26 patients (54%) (14/24, 58% with CME, 12/24, 50% in non-CME group,  $P = .77$ ). Hypertension was present in 5 patients (10%) (3/24, 12% with CME, 2/24, 8% in non-CME group,  $P = 1.0$ ). Additionally, 19 patients (40%) were current smokers (11/24, 46% with CME, 8/24, 33% in non-CME group,  $P = .56$ ).

**Table 1.** General characteristics of uveitis patients with and without cystoid macular edema (CME).

	CME n = 24	Non-CME n = 24
Average age (range)	45 (11-74)	45 (12-69)
Male-to-female ratio	3 : 5	1 : 2
Location:		
Anterior (%)	1 (4.2)	7 (29.2)
Intermediate (%)	6 (25.0)	2 (8.3)
Posterior (%)	5 (20.8)	7 (29.2)
Pan (%)	12 (50.0)	8 (33.3)
Association with systemic disease (%)	7 (29.2)*	8 (33.3) <sup>+</sup>
Recent systemic medication for uveitis and/or CME (%) <sup>++</sup>	18 (75.0)	9 (37.5)
Medication for cardiovascular diseases or risk factors (%)	4 (16.7)	2 (8.3)

\* 2 patients with sarcoidosis, 1 patient with HLA-B27<sup>+</sup> ankylosing spondylitis, 1 patient with juvenile idiopathic arthritis, 1 patient with Behçet's disease, 1 patient with granuloma annulare, 1 patient with borreliosis; <sup>+</sup> 1 patient with sarcoidosis, 2 patients with HLA-B27<sup>+</sup> ankylosing spondylitis, 2 patients with juvenile idiopathic arthritis, 2 patients with Behçet's disease, 1 patient with multiple sclerosis; <sup>++</sup> Includes acetazolamide, corticosteroids, non-steroidal anti-inflammatory drugs, cytostatics.

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Twenty-seven patients (56%) had systemic medication for uveitis and/or CME during the sampling (18/24, 75% with CME, 9/24, 38% in non-CME group  $P = .019$ ). Six patients (13%) had medication for cardiovascular disease or cardiovascular risk factors.

Trace microalbuminuria was found in 54% of the patients (13/24) with CME in contrast to 8% of the patients (2/24) in non-CME group ( $P = .001$ ; odds ratio 13.0, 95 % CI 2.5 to 68.1); and any microalbuminuria ( $5 \leq 200$  mg/l) was found in 13/24 versus 4/24 patients ( $P = .015$ ; odds ratio 5.9, 95 % CI 1.6 to 22.6) (Table 2 and Table 3). Microalbuminuria ( $\geq 20$  mg/l) was found in 2 patients (8% in non-CME group, not significant); one patient had IgG paraproteinemia with low creatinine clearance of 59 ml/min, the other was treated for 10 years with cyclosporin A; his creatinine clearance was 74 ml/min. Renal function, measured using creatinine clearance was determined in 46 patients and was below 80 ml/min in 12 patients (6 with CME and 6 in non-CME group controls,  $P = 1.0$ ).

**Table 2:** General and laboratory characteristics of uveitis patients with and without microalbuminuria

	No micro- albuminuria $\leq 5$ mg/l n=31	Trace- and any microalbuminuria ( $> 5$ mg/l) n=17	P-value
CME positive	11 (35.5)	13 (76.5)	.015
Gender (male)	8 (25.8)	9 (52.9)	ns
Age >50 years	10 (32.2)	9 (52.9)	ns
Associated systemic disease	11 (35.8)	4 (23.5)	ns
High blood pressure	2 (6.5)	3 (17.6)	ns
Cardiovascular disease	1 (3.2)*	2 (11.8) <sup>+</sup>	ns
Current smoking	11 (35.5)	8 (47.1)	ns
C-reactive protein above 7 mg/L <sup>++</sup>	9 (29.0)	3 (17.6)	ns
Systemic medication			
Acetazolamide	4 (12.9)	5 (29.4)	ns
Corticosteroids	5 (16.1)	6 (35.3)	ns
Non-steroidal anti-inflammatory drugs	8 (25.8)	9 (52.9)	ns
Cytostatics	7 (22.6)	5 (29.4)	ns
Duration of uveitis			ns
>5 years	26 (83.9)	13 (76.5)	ns
>10 years	14 (45.2)	5 (29.4)	ns

CME = cystoid macular edema, ns = not significant

\* Myocardial infarction; <sup>+</sup> Myocardial infarction and abdominal aneurysm aorta; <sup>++</sup> Two patients were not tested.

Trace- and/or microalbuminuria was not related to the presence of cardiovascular risk factors ( $P = .37$ ) and morbidity ( $P = .23$ ), hypertension ( $P = 1.0$ ), smoking ( $P = .54$ ), current and previous treatment with cyclosporin A ( $P = 1.0$ ), current medication with corticosteroids ( $P = .16$ ), acetazolamide ( $P = .25$ ), cytostatics ( $P = .73$ ), NSAID's ( $P = .11$ ) or to elevated CRP ( $p = .49$ ), creatinine clearance  $<80$  ( $n = 46$ ,  $P = .18$ ), age  $> 50$  years ( $P = .22$ ), gender ( $P = .11$ ), specific cause of ocular inflammation, location of uveitis, duration of uveitis, interval between the onset of uveitis and development of CME ( $n = 20$ ,  $P = .16$ ), gradation of CME and presence of systemic diseases ( $P = .52$ ) (Table 2).

The correlation between trace- and/or microalbuminuria and CME was not only found in elderly patients but also in younger patients. Adjustment of gender, age, location of uveitis, activity of uveitis, specific diagnosis, cardiovascular risk factors and morbidity, and cataract extraction status did not change the correlation between trace- and any microalbuminuria and CME.

**Table 3:** General and ocular characteristics of uveitis patients with and without cystoid macular edema (CME)

	CME n = 24	Non-CME n = 24	P-value
Trace microalbuminuria	13 (54.2)	2 (8.3)	.001
Any microalbuminuria	13 (54.2)	4 (16.6)	.015
Gender (male)	9 (37.5)	8 (33.3)	ns
Age $>50$ years	9 (37.5)	10 (41.7)	ns
Associated systemic disease	7 (29.2)	8 (33.3)	ns
High blood pressure	3 (12.5)	2 (8.3)	ns
Cardiovascular disease	2 (8.3)*	1 (4.2)+	ns
Current smoking	11(45.8)	8 (33.3)	ns
C-reactive protein above 7 mg/L **	7 (29.2)	5 (22.7)	ns
Systemic medication	18	9	.019
Acetazolamide	9 (36.0)	0 (0.0)	.002
Corticosteroids	7 (29.2)	4 (16.6)	ns
Non-steroidal anti-inflammatory drugs	13 (54.2)	4 (16.6)	.013
Cytostatics	8 (33.3)	4 (16.6)	ns
Duration of uveitis			ns
$>5$ years	17 (70.8)	22 (91.7)	ns
$>10$ years	8 (33.3)	11 (45.8)	ns

ns = not significant;

\* myocardial infarction; + myocardial infarction and abdominal aneurysm aorta; \*\* two patients without CME were not tested.

## **Discussion**

We report on a positive correlation between trace- and/or microalbuminuria and inflammatory CME (respectively,  $P = .001$ ; odds ratio 13.0, 95 % CI 2.5 to 68.1 and  $P = .015$ ; odds ratio 5.9, 95 % CI 1.6 to 22.6).

The association between microalbuminuria and cardiovascular morbidity, mortality and risk factors, and all-cause death was previously reported for both, diabetic and nondiabetic patients, as well as the associations with diabetes mellitus, nephropathy, endothelial dysfunction, inflammation, increasing age, and malignancies.<sup>12-17,24-29</sup> Additionally retinal micro vascular abnormalities were associated with long term cardiovascular mortality.<sup>30</sup>

Previous studies on microalbuminuria used different excretion values for (trace) microalbuminuria and are therefore difficult to compare. In the general population, 76% of individuals were reported to have urinary albumin excretion of  $0 \leq 10$  mg/l and urinary albumin excretion above 20 mg/l was present in 7% to 15%.<sup>12,29</sup> In our series these percentages were 88% (42/48) and 4% (2/48), respectively. Urinary albumin excretion in the range  $5 \leq 10$  mg/l in the healthy population was to our knowledge not yet reported. In our series, 23% of all uveitis patients (11/48) (10/24 CME patients versus 1/24 non-CME patients,  $P = .004$ ) had urinary albumin excretion of  $5 \leq 10$  mg/l. The majority of discrepancies of trace microalbuminuria between CME and non-CME patients was observed in the excretion range of  $5 \leq 10$  mg/l.

The prevalence of systemic hypertension and myocardial infarction in urinary albumin excretion of  $0 \leq 10$  mg/l found in our series was similar to that reported earlier.<sup>13</sup> However, in our series, the significant associations between cardiovascular morbidity and cardiovascular risk factors with trace- and/or microalbuminuria were not noted, probably because of the limited number of patients included in this study.<sup>12</sup> Furthermore, large recent studies showed that any degree of microalbuminuria (including trace microalbuminuria) was an independent indicator of cardiovascular morbidity.<sup>13,16,29</sup> The risk of cardiovascular morbidity was associated with increasing albumin excretion, which might indicate that our patients with trace- and/or microalbuminuria might develop cardiovascular diseases in the future.

We included a limited, heterogeneous population of consecutive patients with uveitis, with different anatomic locations and specific diagnoses. The sample size is limited and the borderline P-values observed do not exclude significant associations. We performed a multivariate logistic regression analysis controlling for these factors, which showed no influence on our results of the correlation between CME and trace- and/or microalbuminuria. To explore these possible associations and confounders a larger sample size is needed.

In diabetic patients, the presence of microalbuminuria and CVD indicated a greater risk of developing CME and severe retinopathy,<sup>5,7,8,31-33</sup> but the relation between trace microalbuminuria and CME and/ or diabetic retinopathy is not yet known.

The treatment of inflammatory CME includes various combinations of acetazolamide, systemic or periocular corticosteroids, NSAID's and various immunosuppressive drugs, all of which might be associated with significant adverse effects. Despite this therapeutic arsenal the current treatment is often not effective. Since urinary albumin excretion is considered to be a marker of damage to the vascular endothelium and since this damage seems to be present at very low levels of microalbuminuria, it is plausible that the finding of trace- and/or microalbuminuria in patients with uveitis and CME might indicate the presence of (early) systemic vascular disease. This condition, in combination with the pathological changes in the retinal and choroidal vessels induced by uveitis could lead to the increased leakage of fluid in the macula and might explain the correlation between (trace) microalbuminuria and CME. The beneficial effect of early angiotensin-converting enzyme inhibitor (ACE inhibitor) treatment in diabetic patients with microalbuminuria is widely recognized. ACE inhibitors are prescribed routinely for these patients and reduce albuminuria, progression of nephropathy, and hypertension.<sup>34-37</sup> Several reports suggested initiating treatment with ACE inhibitors in diabetic patients even in the absence of microalbuminuria and hypertension.<sup>38-41</sup> The majority of studies reported a beneficial effect of ACE inhibitors in slowing the progression of diabetic retinopathy.<sup>34,39,42-44</sup> The effect of ACE inhibitors on diabetic CME has to our knowledge not yet been systematically studied. Since the use of ACE inhibitors has a low incidence of side effects and diminishes renal vascular

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permeability, we could hypothesize that this type of treatment might be of beneficial influence on inflammatory CME.

In conclusion, we found a positive association between inflammatory macular edema and trace microalbuminuria. The presence of trace microalbuminuria in CME might indicate a presence of early systemic vascular disease and carry a risk of increased permeability of retinal and choroidal vessels and thereby early development of CME. This finding could bring new insights into the pathogenesis of CME and could open up new avenues for the treatment of CME.

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