ABSTRACT

**Objective:** To study the prevalence of microalbuminuria and its association with more severe diabetic retinopathy in a group of insulin-dependent diabetic patients.

**Materials and methods:** During the period of January 1998 to December 2005 we examined 360 insulin-dependent diabetic patients with at least five years of evolution. We evaluated the presence of microalbuminuria by immunoanalysis. Patients were evaluated by direct and indirect ophthalmoscopy and classified as non-retinopathy, non-proliferative, severe non-proliferative/proliferative, or macular edema.

**Results:** In this study, 24.1% of patients had microalbuminuria. Most of the patients with microalbuminuria and macroalbuminuria were male and had a longer history of diabetes. Microalbuminuria was associated with more severe diabetic retinopathy.

**Conclusions:** All patients with insulin-dependent diabetes of at least five years’ evolution should undergo an evaluation of renal function including tests for microalbuminuria. In the presence of microalbuminuria an ophthalmologic follow-up may be particularly important (Arch Soc Esp Oftalmol 2007; 82: 85-88).

**Key words:** Insulin-dependent diabetes, microalbuminuria, macroalbuminuria, diabetic retinopathy, legal blindness, arterial hypertension.

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RESUMEN

**Objetivo:** Estudiar la prevalencia de microalbuminuria y su asociación con las formas más severas de retinopatía diabética en una población de diabéticos insulinodependientes.

**Material y método:** Se estudiaron 360 pacientes con diabetes insulinodependiente con al menos cinco años de evolución en un periodo comprendido entre enero de 1998 y diciembre de 2005. Se evaluó la presencia de microalbuminuria por inmunonanálisis. Los pacientes fueron estudiados con oftalmoscopia directa e indirecta y clasificados como no retinopatía, retinopatía no proliferante, retinopatía no proliferante severa / proliferante y edema macular.

**Resultados:** En este estudio el 24,1% de los pacientes tenían microalbuminuria. La mayoría de los pacientes con microalbuminuria y macroalbuminuria eran varones con mayor tiempo de evolución de la diabetes. La microalbuminuria se asoció con las formas más severas de retinopatía diabética.

**Conclusiones:** Todos los pacientes diabéticos insulinodependiente con al menos cinco años de evolución deberían ser evaluados en su función renal incluida la microalbuminuria y los pacientes con microalbuminuria deberían ser revisados más frecuentemente.

**Palabras clave:** Diabetes insulinodependiente, microalbuminuria, macroalbuminuria, retinopatía diabética, ceguera legal, hipertensión arterial.
INTRODUCTION

Patients suffering from insulin-dependent diabetes mellitus will develop diabetic nephropathy in 40 percent of cases and a severe diabetic retinopathy after twenty years in up to 50 percent of cases, being responsible for up to 30 percent of blind cases among the working population in industrial countries (1,2). The prevalence of microalbuminuria among diabetic patients is 15-20 percent. Persistence of microalbuminuria in diabetic patients is a risk marker not only for kidney and cardiac disorders but also for severe ocular morbidity (2,3).

The purpose of the present paper is to determine the relation between microalbuminuria and retinopathy in adult, insulin-dependent diabetic patients with more than five-year-long evolutions and to assess its impact on the development of diabetic retinopathies.

SUBJECTS, MATERIAL AND METHODS

The present study was approved by the hospital’s Research and Teaching Commission. Patients were recruited during retinal checkups and family doctor’s visits. The target population included 360 insulin-dependent diabetic patients between the years 1998 and 2005. Table I shows the demographic traits of the target population. Inclusive criteria for patients were as follows:

— Accepting participation in the study by signing an informed consent form.
— Suffering from insulin-dependent diabetes mellitus treated by an endocrinologist, internist or family practitioner for five or more years.
— Having access to the patient’s clinical history.
— Three months prior to the ophthalmologic study, patients could not be treated with corticoids, nephrotoxic drugs and/or surgical procedures.
— Patients must not be undergoing nephrologic treatment in response to chronic kidney failure and/or dialysis.

Table I. Demographic traits

<table>
<thead>
<tr>
<th>Trait</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>360</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>190/170</td>
</tr>
<tr>
<td>Age:</td>
<td>59.2 SD 11.3</td>
</tr>
<tr>
<td>Age at diabetes onset:</td>
<td>39 SD 10 years</td>
</tr>
<tr>
<td>Diabetes evolution time:</td>
<td>19 SD 10 years</td>
</tr>
</tbody>
</table>

H: male; M: female; SD: standard deviation.

All patients were subjected to an eye fundus examination under midriasis performed by the same ophthalmologist, and subsequently classified according to the degree of retinopathy into the following categories: 1) no retinopathy (n= 90); 2) non-proliferative retinopathy (n=90); 3) maculopathy (n=90); 4) advanced non-proliferating retinopathy or proliferating retinopathy (n=90).

Patients were instructed to collect a 24-hour urine sample. Albuminuria was determined at the laboratory by means of radioimmunoassay. Albuminuria values in the micro or macroalbuminuria range were confirmed in a second urine study before being included.

Definitions

Microalbuminuria: the excretion of between 30 and 300mg of albumin a day in the urine, regardless of the urine collection method used.

Macroalbuminuria: the excretion of more than 300mg of albumin a day in the urine, regardless of the urine collection method used.

Legal blindness: whenever best-corrected vision in the better eye is lower than or equal to 0.1.

Hypertension (high blood pressure): whenever the patient is undergoing antihypertensive treatment or scores more than 140/90 mmHg.

Analysis software (SAS/STAT) and chi-square test were used to perform the statistical analysis. The association between microalbuminuria and retinopathy was estimated using the odds ratio (OR) calculation and its corresponding 95% confidence interval. Logistic regression was used to assess the risk dependent on microalbuminuria, considering the presence or absence of retinopathy as a dependent variable or response. Results were deemed significant at a 95% confidence interval.

RESULTS

In the target population of insulin-dependent diabetics (table I), 24.1 percent of patients suffered from microalbuminuria; this rate increased among diabetic patients whose evolution was longer and among men (OR= 4.2; CI 95%: 1.88-6.1) more than women (OR= 3.6; 95% CI= 1.42-5.1) (table II). Patients suffering from albuminuria exhibited more severe retinopathies (maculopathy, advanced
non proliferating or proliferating) and blindness caused by diabetes mellitus (p<.01) (tables III, IV), amounting to 19.72 percent of all legally blind. Out of the 90 patients suffering from severe retinopathies, 37.78 percent (n=34) and 51.11 percent (n=46) exhibited microalbuminuria and macroalbuminuria, respectively. Among those patients with macular edema (n=90), 31.1 percent (n=28) and 40 percent (n=36) exhibited microalbuminuria and macroalbuminuria, respectively. The risk of a proliferating retinopathy increased with the duration of diabetes, although it quickly rose among patients with microalbuminuria and specially with those suffering from albuminuria (OR= 4.2; 95% CI= 1.88-6.1 (p<.001)). The likelihood of sustaining a severe retinopathy increases by 2.6 times versus patients not exhibiting microalbuminuria (CI 95%=1.2-3.6; p<.001). Hypertension was more frequent among patients who had maculopathies and proliferating retinopathies than among the other two groups (p<.001) and was linked to higher systolic pressure levels.

**DISCUSSION**

Blindness is the most dreaded complication of all diseases affecting human beings, only second to death itself. In 2002, 124 million people suffered from low vision and 37 million were blind (4). In western nations, diabetes mellitus is the first cause in loss of vision among younger patients (4,5). Diabetic retinopathy is the most severe of the many complications resulting from diabetes at the eye level, and despite of the progress achieved in its treatment over the past forty years, since the incidence of diabetes mellitus stands at 5-6 percent of the population, retinopathies remain an important medical-social issue (5). Nearly 1 out of 10 diabetics is insulin-dependent and after twenty years almost 100 percent will develop some degree of diabetic retinopathy and up to 50 percent will develop a severe retinopathy (1). Albumin is the most abundant plasma protein, with a molecular weight of approximately 69,000 D, and is mainly responsible for total plasma colloid osmotic pressure. Normal mean value for urine albumin excretion is lower than 30 mg a day, defining microalbuminuria as albumin losses in the urine between 30 and 300 mg a day that are not detected by conventional analytical methods used in the laboratory for protein studies (6). The repeated presence of microalbuminuria in diabetics’ urine samples reveal damage to the glomerular basement membrane and should be considered an early diabetic nephropathy. Medline database features 364 articles referring to diabetic microalbuminuria and diabetic retinopathy, though only a small number refer to insulin-dependent diabetics. In the targeted diabetic population, the prevalence of microalbuminuria stood at 24.1 percent.

**Table II. Albuminuria depending on the time of evolution**

<table>
<thead>
<tr>
<th></th>
<th>NA</th>
<th>MA</th>
<th>MAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>80/106</td>
<td>48/39</td>
<td>50/37</td>
</tr>
<tr>
<td>Time evolution (SD years)</td>
<td>9.2 (SD 2)</td>
<td>16.3 (SD 10)</td>
<td>18.8 (SD 5)</td>
</tr>
</tbody>
</table>

M: male; F: female; NA: no albuminuria; MA: microalbuminuria; MAA: macroalbuminuria; SD: standard deviation.

**Table III. Prevalence of albuminuria depending on the retinopathy involved**

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th>NDR 90</th>
<th>NPDR 90</th>
<th>DM 90</th>
<th>NPDRs+NDR 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>74 (82.22%)</td>
<td>69 (76.67%)</td>
<td>26 (28.89%)</td>
<td>10 (11.11%)</td>
</tr>
<tr>
<td>MA</td>
<td>16 (17.78%)</td>
<td>18 (20%)</td>
<td>28 (31.11%)</td>
<td>34 (37.78%)</td>
</tr>
<tr>
<td>MAA</td>
<td>0 (0%)</td>
<td>3 (3.33%)</td>
<td>36 (40%)</td>
<td>46 (51.11%)</td>
</tr>
<tr>
<td>BP (Yes/No)</td>
<td>6/84</td>
<td>9/81</td>
<td>40/50</td>
<td>50/40</td>
</tr>
</tbody>
</table>


**Table IV. Prevalence of blindness depending on the retinopathy involved and albuminuria**

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th>NDR 90</th>
<th>NPDR 90</th>
<th>DM 90</th>
<th>NPDRs+NDR 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>2 (2.22%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>MA</td>
<td>0</td>
<td>0</td>
<td>6 (6.67%)</td>
<td>12 (13.33%)</td>
</tr>
<tr>
<td>MAA</td>
<td>0</td>
<td>0</td>
<td>13 (14.44%)</td>
<td>29 (32.22%)</td>
</tr>
</tbody>
</table>

NDR: No diabetic retinopathy; NPDR: Non-proliferating diabetic retinopathy; DM: diabetic maculopathy; NPDRs: Severe non-proliferating diabetic retinopathy; PDR: proliferating diabetic retinopathy; NA: No albuminuria; MA: Microalbuminuria; MAA: Macroalbuminuria.
a rate similar to those reported in other papers (6,7). Patients were mainly males with a medical history of early diabetes mellitus of long duration. In the present study, specific retinopathies were correlated to the degree of albuminuria. Patients with microalbuminuria were 2.6 times more likely to suffer from a severe retinopathy than those without microalbuminuria; however, 11.11 percent of patients with severe retinopathies showed normal albumin excretion levels, whereas 20.56 percent of patients with milder retinopathies showed anomalous albumin excretion levels. Thus, the correlation between kidney vascular damage and retinal injury does not always stand, although patients with diabetic nephropathy usually exhibit more severe forms of diabetic retinopathy (2,3). Today, kidney microangiopathy is thought to come before retinal microangiopathy, therefore diabetics suffering from microalbuminuria should be supervised with extra care (7). In spite of the well-known association between the advanced stages of diabetic retinopathy and macroalbuminuria or frank proteinuria, its relation with microalbuminuria is contradictory. In a prospective 5-year study with 104 type-1 diabetic patients, Aroca PR et al (8) found that microalbuminuria was not a good marker for diabetic retinopathy, although in a more recent article (9) they advised repeating eye fundus studies whenever encountering microalbuminuria. Cruickshanks KJ et al. (7) stated that microalbuminuria could be a risk marker for proliferating retinopathy. Microalbuminuria would indicate a generalized vascular dysfunction condition; on the other hand, microalbuminuria and diabetic retinopathy share common determining factors, such as duration of diabetes and blood pressure levels. Hypertension was more frequent among severe cases and was linked to higher levels of systolic pressure. The benefit of the present study is that patients were included based on the criteria set forth under Subjects, Material and Method, in contrast with other hospital studies where patient selection was biased in favor of the most severe forms of diabetes and its complications. This is the reason why the present paper reflects the conditions of a basic rural population.

The study of albumin in the urine among insulin-dependent diabetic patients should be a routine procedure, since the presence of microalbuminuria is a heart and kidney risk factor with bad prognosis and the resulting retinopathies are associated with blindness and mortality (2,6,7). Furthermore, the progression of microalbuminuria may be halted during the initial stages by improving diabetes management, prescribing low protein diets and angiotensin inhibitors, whereas diabetic patients suffering from microalbuminuria could benefit from increased ophthalmologic follow-up.

REFERENCES