ORIGINALS

Characteristics of diabetic patients referred for the first time to the nephrologist

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SUMMARY

Background: Diabetic nephropathy (DN) has become the main cause of end-stage renal disease. In our country, this problem is specially relevant in Canary Islands, where DN is the cause of renal failure in 39% of patients included in dialysis programs. The importance of this situation and the relevance of an adequate referral to the nephrologist, prompt us to study the characteristics of diabetic patients refered to our outpatient clinic.

Subjects and methods: One-hundred and fifty patients with diabetes consecutively referred to the outpatient nephrology clinic at the Hospital Universitario Nuestra Señora de Candelaria were included in the study. We analysed demographic and epidemiologic characteristics, therapeutic strategies, as well as serum and urine biochemical parameters.

Results: Ninety-eight percent of patients suffered from type 2 diabetes, and 90% were referred by the primary physician. Renal insufficiency and proteinuria were the main causes of referral (48% and 30.6%, respectively). Overweight or obesity were present in 82.6% of patients, 97% were hypertensive and 92.6% presented dyslipidemia. Medical history of cardiovascular disease was present 16% of patients. Two-thirds of patients had a creatinine clearance below 60 ml/min. One-third of patients did not receive therapy with blockers of the renin-angiotensin system, and only 37% were treated with statins.

Conclusions: An elevated percentage of diabetic patients referred to nephrologist did not reach the recommended therapeutic goals. These findings prompt us to reflect on the therapeutic approach in these patients and the referral to the nephrologist.

Key words: **Chronic kidney disease. Diabetic nephropathy. Nihilism. Referral.**

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CARACTERÍSTICAS DE LOS PACIENTES DIABÉTICOS REFERIDOS POR PRIMERA VEZ A LAS CONSULTAS DE ATENCIÓN ESPECIALIZADA DE NEFROLOGÍA

RESUMEN

Introducción: *La nefropatía diabética (ND) se ha convertido en la primera causa de insuficiencia renal crónica en nuestro país. Esta patología es especialmente relevante en las Islas Canarias, donde el porcentaje de pacientes en programas de diálisis con ND como enfermedad de base era a 31 de diciembre de 2005 del 39%. Dada la importancia de esta situación, y la trascendencia que en los últimos años ha cobrado la problemática relacionada con la remisión de los pacientes con enfermedad renal a los servicios de Nefrología, el objetivo del presente estudio ha sido analizar las características de la población diabética que es derivada a las unidades de atención especializada de Nefrología.*

Pacientes y Métodos: *Estudio de los 150 primeros pacientes diabéticos que, a partir de octubre de 2001, fueron remitidos de forma consecutiva a las consultas de Nefrología del Hospital Universitario Nuestra Señora de Candelaria de Santa Cruz de Tenerife. Se realizó una historia clínica y exploración física completas, se recogieron datos relativos a las pautas terapéuticas, se realizó una analítica de sangre y orina de 24 horas.*

Resultados: *El 98% de los pacientes eran diabéticos tipo 2, y en el 90% de los casos fueron remitidos por su médico de Atención Primaria. La presencia de insuficiencia renal y de proteinuria fueron los dos motivos más frecuentes de derivación (48% y 30,6%, respectivamente). El 82,6% de los pacientes presentaba sobrepeso u obesidad, el 88% hipertensión arterial y el 92,6% dislipemia. Un 16% de los pacientes 6% presentaba algún antecedente de enfermedad cardiovascular. Dos tercios de los pacientes presentaban un aclaramiento de creatinina inferior a 60 ml/min. Un tercio de los pacientes no recibían tratamiento con bloqueadores del sistema renina-angiotensina, y sólo un 37% estaban tratados con estatinas.*

Conclusiones: *Un elevado porcentaje de los pacientes diabéticos remitidos a los Servicios de Nefrología no presenta un cumplimiento adecuado de los objetivos terapéuticos. Es preciso reflexionar sobre la actitud terapéutica en estos pacientes y su remisión al nefrólogo.*

Palabras clave: **Enfermedad renal crónica. Nefropatía diabética. Nihilismo. Referencia.**

INTRODUCTION

In no more than 25 years, the number of people worldwide suffering from diabetes mellitus (DM) will double; thus, this disease will affect more than 360 million people by the year 2030.[1,2] This implies that even if we may speak today about a true pandemia, particularly regarding type 2 DM, without an effective prevention the incidence and prevalence of this disease will keep on increasing both in developed nations, where a 41% increase is foreseen, and in developing others, where an alarming 170% increase is expected.[3,4]

One of the most important issued in DM is its associated complications, among them renal involvement. Diabetic nephropathy (DN) has become the first cause of chronic renal disease (CRD), with series in which more than 50% of patients included in renal replacement therapy (RRT) programs have DN as the underlying disease.[5] More over, according to recent estimations, if early diagnosis methods and available therapeutic strategies are not consistently applied, by the year 2030 there will be more than one million diabetic patients on RRT programs, only in the USA.[6]

This panorama may be perfectly applied to the Canary Islands. According to the latest data from the Renal Patients Registry of the Canarian Society of Nephrology, corresponding to the year 2005 (not published data), the DN incidence rate was 70 pmp, with a 39% prevalence of DN patients on dialysis

programs. This implies an incidence rate 4 to 5 times higher than the one for the remaining autonomous communities in our country (11-24 pmp), and more than 5-fold higher than that of some European nations.[7]

On the other hand, today we know that renal disease is an independent risk factor for hospitalization, cardiovascular (CV) events and death.[8,9] With diabetes, the development of nephropathy determines a significant impact on these patients' CV risk (CVR). In the first studies, it was already observed that in type 2 DM patients the presence of an increase in albumin urinary output within the microalbuminuria range was associated to a 2.4-fold increase of CV morbi-mortality risk, independently of other CV risk factors, as compared to patients without microalbuminuria.[10]

Although it has been clearly established that early and intensive management of DM may significantly reduce the risk for developing and/or slowing the progression of renal disease, it is paradoxical that the incidence of DN-associated renal failure (RF) has been considerably increasing. From this perspective, the time on the evolutionary course of the disease in relation with the degree of renal failure at which a patient is referred to the Nephrology Specialized Care Units (NSCU) is important. Besides, from our perspective, the situation in which these patients are referred to the NSCU, that is to say, «how», is as important as «when». In this way, the aim of the present study was to analyze from a clinical-epidemiological perspective, the characteristics of the diabetic population referred to the nephrology outpatient clinics, with a special focus on control of CVR factors and the implementation of therapeutic management protocols that have shown to be effective for slowing the progression of renal disease and reducing morbimortality.

MATERIAL AND METHODS

This an observational study including the first 150 diabetic patients consecutively referred to the NSCU of the Nuestra Señora de Candelaria University Hospital between October of 2001 and December of 2002. Our center is the reference hospital for South Tenerife, which includes 20 municipalities, besides covering health care of people from La Gomera and El Hierro islands, which represents a total population of 517,000. All patients gave their informed consent to participate into the study.

At the first visit to the NSCU, each patient had a clinical history taken, which included: a) information on who referred the patient and the reason for the referral; b) demographical and epidemiological data; c)

personal history about the presence of arterial hypertension (AHT), ischemic heart disease, and peripheral vascular disease; d) a specific questionnaire aimed at knowing the treatment received by these patients for arterial hypertension, with a particular interest on renin-angiotensin system blockers, the use of statins, and the use of platelet anti-aggregant agents. A physical examination was carried out including weight and height, calculation of the body mass index (BMI) by the Quetelet index (kg/m^2), overweight being defined as a BMI ranging 25-29.9 kg/m^2, and obesity as a BMI equal or higher than 30 kg/m^2. Blood pressure was measured on two occasions, after a 5-minutes rest, and was computed as the mean value. AHT was defined as the presence of BP equal or higher than 130/80 mmHg or the use of anti-hypertensive medication. The pulse pressure (PP) was defined as the difference between systolic BP (SBP) and diastolic BP (DBP).

A full laboratory work-up was ordered including 24-hour urine collection and electrocardiogram, assessing for the presence of left ventricular hypertrophy by the Sokolov index. Among biochemical variables, we determined serum levels for creatinine, urea, lipid parameters (triglycerides, LDL- and HDL-cholesterol), uric acid, albumin, and high sensitivity C reactive protein (CRP) (N High Sensitivity CRP, Behring, Germany; detection limit 0.16 mg/L). Albumin urinary excretion was measured by nephelometry and creatinine clearance was calculated from the 24-hour urine output not corrected for body surface area. Microalbuminuria was defined as urinary albumin excretion ranging 30-300 mg/day, and when this value was higher than 300 mg/day, it was defined as macroalbuminuria or proteinuria. Creatinine clearance lower than 60 mL/min was a definition of renal failure. Finally, an ophthalmologic examination was ordered, provided it had not been performed within the previous 6 months, in order to assess whether the patient had diabetic retinopathy.

Statistical analysis

The data were analyzed by means of Statistica 7.1 software package (StatSoft 2005, Tulsa, OK, USA). Qualitative variables were expressed as absolute frequencies and/or percentages, and quantitative variables as mean and standard deviation. A p value < 0.05 was considered to be statistically significant.

RESULTS

The laboratory workups ordered were performed in the 150 patients initially included, so that all of them

were valid for final analysis (Table I). Mean age of the patients, 62% males and 38% females, was 65 ± 10 years. One hundred and forty-seven (98%) were type 2 diabetics, and only 3 were type 1 diabetics. Mean known progression time for their diabetes was 14.5 ± 8.1 years, ranging from 3 to 40 years.

The reason for being referred to the nephrology outpatient clinics was the presence of renal failure in 48% of the cases, followed by the proteinuria in 30.6%. Microalbuminuria and AHT were the remaining reasons for referral (Fig. 1). Most of the patients, exactly 90.6%, were referred to our clinics by their primary care physician.

82.6% of the patients had a BMI higher than 25, the overweight prevalence being of 49.3% and that for obesity 33.3%. Thus, only 17.4% of the cases had an adequate weight. Among associated clinical conditions, there was an elevated prevalence of AHT, present in 88% of the cases when a BP value higher than 140/90 mmHg was used to define AHT, this figure going up to 97% when the BP higher than 130/80 mmHg criterion was used. Mean BP values were 154 ± 18 mmHg for SBP and 85 ± 9 mmHg for DBP, whereas the mean PP value was 68 ± 16. Fifty-eight (38.6 %) patients had isolated AHT.

Almost two thirds of the patients had diabetic retinopathy. Thirty-eight percent of the cases had electrocardiographic criteria of left ventricular hypertrophy. About the previous history of CV disease, 37 (24.6%) patients had ischemic heart disease, 21 (14%) patients had peripheral vascular disease, and 13 (8.6%) had suffered from a cerebrovascular accident. The presence of dyslipidemia, defined as serum LDL-cholesterol levels higher than 100 mg/dL, triglycerides levels higher than 150 mg/dL, or the need for hypolipidemic therapy, was present in 92.6% of the cases (Fig. 2).
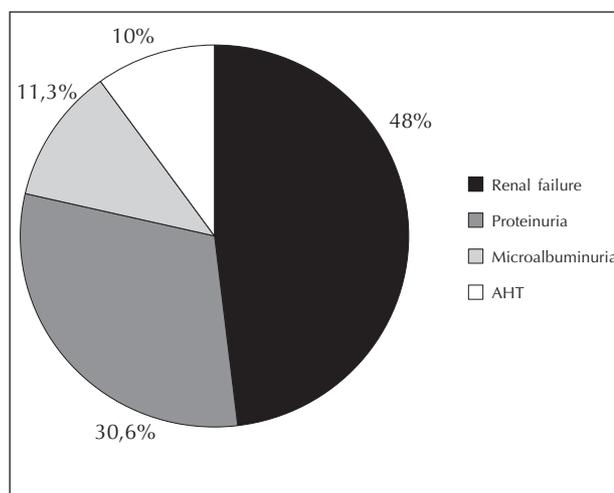

Fig. 1.—*Reason for referral diabetic patients to the nephrologist.*

Table II shows the parameters of renal damage and function for the whole group. Mean creatinine clearance was 64 ± 39 mL/min. According to the CRD classification of the DOQI guidelines,[13] one third of the patients were on stages 1 or 2, whereas the remaining tow thirds had a creatinine clearance lower than 60 mL/min. Mean creatinine clearance for this group of patients was 42 ± 12 mL/min, with 20 patients in whom this parameter was lower than 30 mL/min (Table III).

About the remaining laboratory parameters, we may highlight mean hemoglobin and hematocrit values, of 13.4 ± 1.9 g/dL and 39.8 ± 5.9 %, respectively. According to the European Good Practice Gui-
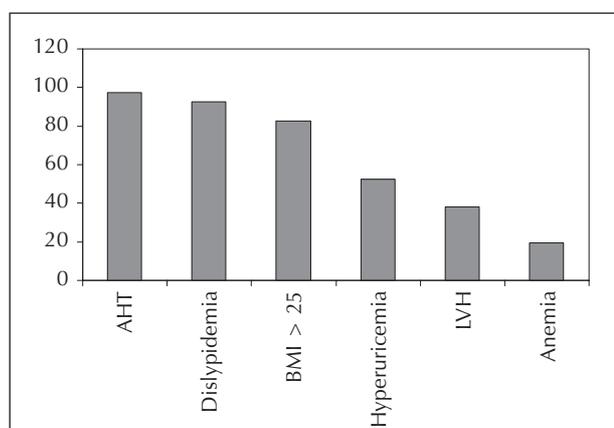
Table I. General data of patients included in the study

Age, years	65.3 ± 10.4
Gender, male/female	93/57
Body mass index, kg/m^2	28.6 ± 4.2
Systolic blodd pressure, mmHg	154.1 ± 18.3
Diastolic blood pressure, mmHg	85.6 ± 9.5
Pulse pressure, mmHg	68.4 ± 16.2
Glycosilated hemoglobin, %	7.9 ± 0.9
Hemoglobin, g/dL	13.4 ± 1.9
Hematocrit, %	39.8 ± 5.9
Uric acid, mg/dL	6.8 ± 1.8
Total cholesterol, mg/dL	228 ± 60
LDL-cholesterol, mg/dL	146 ± 41
HDL-cholesterol, mg/dL	47 ± 11
Triglycerides, mg/dL	197 ± 108
Albumin, g/dL	4 ± 0.5

Fig. 2.- *Associated clinical conditions in diabetic patients referred to the nephrologist. (AHT: arterial hypertension; BMI: Body mass index; LVH: Left ventricular hypertrophy).*

Table II. Renal damage and renal function parameters, and number of patients

Parameter	Mean ± SD (range)	N (%)
Creatinine, mg/dL	1.34 ± 0.62 (0.4-3.4)	150 (100%)
Urea, mg/dL	64.8 ± 27.8 (19-146)	150 (100%)
Creatinine clearance mL/min	64.3 ± 39 (11-311)	150 (100%)
Albumin urinary excretion, mg/day	1,434 ± 2,136 (2-19,720)	150 (100%)
Normoalbuminuria, mg/dL	10 ± 5 (2-18)	6 (4%)
Microalbuminuria, mg/dL	144 ± 81 (32-280)	44 (25.3%)
Proteinuria, mg/dL	2,017 ± 2,344 (310-19,720)	100 (66%)

delines for Anemia Management in Chronic Renal Failure,[14] 19.3% of the patients had anemia. More than half (52.6%) of the patients had hyperuricemia, defined as a serum uric acid level higher than 7 mg/dL in males, and higher than 5.7 mg/dL in females. As for the lipid parameters, mean LDL-cholesterol and triglycerides values were 146 ± 41 mg/dL and 197 ± 108 mg/dL, respectively. Thus, 87.3% of the patients had LDL-cholesterol higher than 100 mg/dL, whereas in 60.6% of the cases triglycerides levels were higher than 150 mg/dL. Besides, more than half (55.3%) of the patients had an HDL-cholesterol value lower than 45 mg/dL. About glycemic control, mean HbA1c concentration was 7.9 ± 0.9%, with 79.3% of the patients having levels higher than 7%. Finally, the mean CRP level was 6.8 ± 8.8 mg/L, this value being higher than 3 mg/L in two thirds of the patients.

The use of several drugs in these patients is shown in Figure 3. We may highlight the use of diuretic agents (49.3%) and dihydropiridinic calcium channel blockers calcioantagonistas (40%). On the other hand, 38.6% of the patients received an ACEI and 25.3% and ARA agent, which means that one third of the patients was not on renin-angiotensin system blockers. Ten patients did not receive any kind of antihypertensive agent, one third of the cases were treated with a monotherapy regimen, whereas 39% received 3 or more antihypertensive agents. Regarding lipid control, although 87% of the patients had LDL-cholesterol higher than 100 mg/dL, only 37.3% were receiving statins. Finally, 67% received treatment with platelet anti-aggregants.

DISCUSSION

It is a well known fact that late referral of CRD patients to NSCUs is associated with deleterious effects: start on RRT in a worse clinical and analytical condition and in a non-programmed way, need of urgent hemodialysis in many cases with vascular access through temporary catheters, avoidable hospital admissions, accelerated loss of renal function, etc. Even this situation has been shown to be an independent risk factor for greater mortality after dialysis onset.[15-21] On the other hand, it is a well known fact that diabetic patients start on RRT with significantly greater comorbidity than non-diabetic patients.[22]

It is estimated that 35% of the patients in Europe are referred late to the nephrologist,[23,24] a percentage that in Spain is 23%, with a mean creatinine clearance in these patients of 30 mL/min.[15,19] In the present study, mean creatinine clearance was 64 ± 39 mL/min, but two thirds of the cases had a creatinine clearance value less than 60 mL/min, with 20 patients (13%) having stage 4 CRD.

Table III. Renal damage and renal function parameters of the patients (mean ± SD and range) classified according to KDOQI renal disease stage

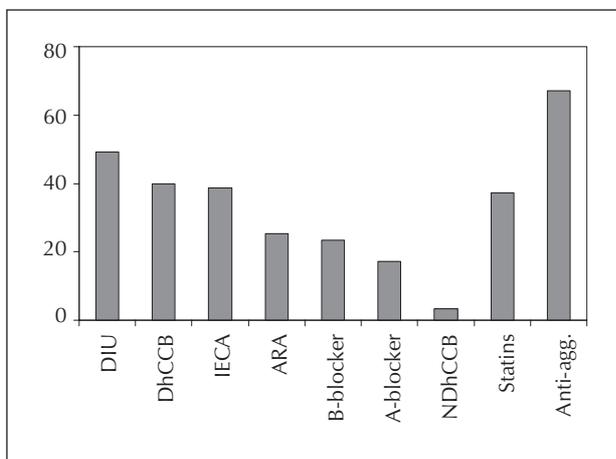|	Creatinine (mg/day)	Urea (mg/dL)	Creatinine clearance (mg/dL)	Albuminuria (mL/min)
Stage 1 N = 27 (18%)	0.85 ± 0.18 (0.4-1.2)	38 ± 11 (19-64)	131 ± 40 (92-311)	1,304 ± 1,251 (32-4,300)
Stage 2 N = 29 (19.3%)	1.21 ± 0.29 (0.7-2)	68 ± 21 (38-109)	73 ± 8.5 (60.7-88)	1,993 ± 1,614 (62-7,600)
Stage 3 N = 74 (49.3%)	1.34 ± 0.57 (0.7-3)	66 ± 29 (31-146)	47 ± 8.7 (30-59)	1,290-2,639 (2-19,720)
Stage 4 N = 19 (12.6%)	2 ± 0,7 (1-3.4)	86 ± 16 (51-130)	23.9 ± 3.5 (18-29)	1,164 ± 1,333 (10-3,800)
Stage 5 N = 1 (0.6%)	3.4	102	11	4.850

Fig. 3.—*Use of several drugs in diabetic patients referred to the nephrologist (DIU: Diuretics; DhCCB: dihydropiridinic calcium channel blockers; ACEI: angiotensin converting enzyme inhibitors; ARA: angiotensin receptor antagonists; B-blocker: beta-adrenergic blocker; A-blocker: alpha-adrenergic blocker; NDhCCB: not dihydropiridinic calcium channel blockers; Anti-agg.: Anti-aggregants).*

Studies carried out so far aiming at analyzing the implications of time of referral to the nephrologist have taken as the reference the time of onset of dialysis therapy in global patient populations. In these studies, the percentage of diabetic patients varies from 10% to 30%.[16,19] Recently, Frimat et al.[25] published a study done between the years 1997-1999 in the French community of Lorraine (2,300,000 population) that included all patients living in this community for at least 3 months and having started RRT during those years. The authors focused their analysis on 148 (29.1%) type 2 diabetics out of 508 included patients, and their most relevant conclusions indicated that more than half of the patients started dialysis under life threatening conditions, one fourth had been referred late to the nephrologist, and almost 40% of the cases had not previously received any kind of nephrologic care. Besides, survival at 3 months since onset of RRT in patients having received regular nephrologic care was 16.4% better than that in those cases that were not sent to the nephrologist, and even in those with late referral the 3-months survival was 9.1% better than those individuals having not received any kind of nephrologic care.

In addition to analyzing patients' characteristics at the time of RRT onset, we believe it is important to know the circumstances under which these patients are referred to the nephrologist. A previous study by Marín et al.[26] on a sample comprising more than 3,500 type 2 diabetics, with clinical follow-up at the primary care setting, showed that a high percentage of them had renal involvement and a deficient control of their arterial hypertension. Particularly, in that study, more than two thirds of the patients had arterial hypertension, a similar proportion had a total cholesterol level above 200 mg/dL, metabolic management was insufficient (HbA1c ≥ 7%) in almost half of the patients (47%), 23.5% of the cases had proteinuria, and finally, serum creatinine was higher than 1.2 mg/L in 15.5% of the patients. Our study has focused on issues related with the clinical condition of patients referred to the nephrologist, by analyzing a group of 150 diabetic patients that were referred for the first time to the NSCU of our hospital. From the analysis undertaken, we may highlight that the most important reason for patient referral in almost half of the cases was the presence of established renal failure (two thirds of the patients had CRD, stage 3 or higher). Among associated risk factors, we may highlight the high prevalence of dyslipidemia (92.6%) and AHT (88%), and about the presence of CV disease, 8-25% of the cases had a personal history of a previous CV event. Finally, from the perspective of therapeutic strategies, the fact that one third of these type of patients did not receive any agent blocking the renin-angiotensin system is alarming, as well as the fact that only 37% were receiving statins in spite the high hypercholesterolemia prevalence.

There are very few studies analyzing the characteristics of the patients attending for the first time the nephrology clinic. Among them, we should highlight the one performed by Kanter et al.[27] that retrospectively analyzed all patients attended for the first time at the nephrology clinic of «Gregorio Marañón» General University Hospital of Madrid between January and December of 2003. Seven hundred and forty-six patients were included in that study, of which 612 were valid for final analysis (28.4% were diabetics). The most striking conclusions from that study were: the reason for consultation, which was the presence of renal failure in 64% of the cases; the high prevalence of AHT (71%); the use of statins in only 22% of the patients having dyslipidemia; the use of renin-angiotensin system blockers in only 42% of hypertensive patients.

The outcomes analysis of the present study, as well as that from previous works, such Kanter's et al., sets up important issues for reasoning. We may point out: 1) the problematic issue of late referral to the nephrologist, particularly when it has been shown that this proceeding is associated with important negative consequences for the patient; 2) the observation that a high percentage of patients do not reach the therapeutic goals recommended by clinical guidelines in issues such as BP management, metabolic manage-

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ment in the case of diabetic patients, or management of lipid serum levels; 3) the existence of an alarming situation of therapeutic nihilism, which is reflected in facts such as the infrequent use of renin-angiotensin system blocking agents or of statins in patients presenting pathologies in which the benefit of these type of strategies has been shown; 4) finally, the disturbing incapacity of translating scientific evidence into the clinical practice, that is to say, to implement intervention strategies with a demonstrated benefit to our patients' care.

Unfortunately, this scenario seems to be quite common in medical care in our country, both at the primary and specialized care levels. In a recent study, Arroyo et al.[28] showed significantly enough data such as 36.9% of type 2 diabetic patients having received pharmacological therapy for more than one year had HbA1c levels below 8%, or that after 6 months of follow-up 45.3% presented an LDL-cholesterol level higher than 130 mg/dL. Similarly, in the PRESCAP study, it was observed that only 10% of diabetic hypertensive patients had a stringent BP control, and that the therapeutic attitude of the practicing physician was very tolerant,[29] whereas in the LIPICAP study, only 31% of dyslipidemic patients had a stringent management of their LDL-cholesterol, a percentage that was reduced to 15% in those cases with high CV risk.[30] Regarding Specialized Care, at the recent Congress of the European Society of Hypertension, celebrated in June of 2006 in Madrid, the results of the DIVA study were presented.[31] In this study, including almost 2,500 individuals suffering from type 2 DM, and followed-up by cardiologists and endocrinologists, 86% of the patients presented a BP level above 130/80 mmHg, 72% had an LDL-cholesterol level above 100 mg/dL, and 53% had an HbA1c level above 7%. In spite of these high percentages of suboptimal control, anti-hypertensive, anti-lipidemic, and anti-diabetic therapies were not modified in 60%, 49%, and 49% of the patients, respectively.

In conclusion, we believe that the results from this and other studies reflect an alarming reality demanding an in-depth analysis seeking the causes and solutions to revert this situation. In this sense, initiatives such as the one undertaken by the Spanish Society of Nephrology by the «Strategic Action Against CRD Program» are highly positive to broadcast the importance of this pathology. We should make an effort to implement the appropriate care for these patients and make people aware of the need of appropriate referral to nephrology departments.

ACKNOWLEDGEMENTS

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