Study on the level of adherence to the 2002 Consensus Document on Diabetic Nephropathy Management at the outpatient clinic in Catalonia (ECCODIAB)

N. Fontseré*, J. Bonal, F. Torres***, X. de las Cuevas* and J. Fort******
*Nephrology Department. Hospital of Terrassa. **Nephrology Department. University Hospital Germans Trias I Pujol. ***Biostatistics and Epidemiology Laboratory. Autonomous University of Barcelona. ****Nephrology Department. Vall D'Hebrón Hospital.

[5] Collaborative Group of the ECCODIAB study (Catalonian Society of Nephrology):
J. Bonal (Hospital Universitari Germans Trias i Pujol); J. Soler (Manresa Althaia); JMª. Mauri (Hospital Trueta de Girona); E. Andrés (Fundación Puigvert); A. Martínez Castelao (Hospital de Bellvitge); MªJ. Soler (Hospital del Mar); JMª. Galcerán (Hospital de Palamós); Prim (Clínica Girona); M. Ramírez de Arellano (Hospital de Terrassa); R. Sanz (Hospital de Figueres); J. Viladoms (Hospital de Mollet); X. Borrellas (Hospital Vall d'Hebrón); R. Ramos (Hospital Arnau de Vilanova); E. Poch (Hospital Clínico); A. Pelegrí (Hospital Sagrado Corazón de Barcelona); J. Oliver (Hospital Joan XXIII de Tarragona); E. Ponz (Hospital Parc Taulí de Sabadell); L. Pérez (Hospital de Vic); E. Fernández (Hospital Arnau de Lleida); J. Mallafré (Hospital Cruz Roja de Barcelona); P. Angelet, MªT. Compte (Hospital de la Sta. Tecla); Sese (Hospital de Granollers) y A. Sans (Hospital de Manresa).

SUMMARY

Objective: *To evaluate the level of compliance with the 2002 consensus document (Spanish Society of Nephrology) on guidelines for the detection, prevention and treatment of diabetic nephropathy in Catalonia.*

Subjects and methods: *Multicenter (23 hospitals), observational, cross-sectional, descriptive study conducted in 413 diabetic patients (61.7% men, 38.3% women) with a median age of 66.2 ± 11.5 years (26-93 years). The ANOVA test (post-hoc analysis; p value < 0.05) was used to study the relationships between the stages of diabetic nephropathy and different variables.*

Results: *90.3% of the patients had type 2 DM. The following anthropometric parameters were observed: BMI 29.8 ± 5 kg/m^2 (BMI > 30 kg/m^2: 48.7%) and waist circumference 104.1 ± 14 cm (48.6% men > 102 cm and 78.9% women > 88 cm). Serum creatinine 1.9 ± 1.3 mg/dl and simplified MDRD equation 45.3 ± 25.0 ml/min/1.73 m^2 [65.8% with CKD stages 3 and 4]. 80% of patients had ophthalmologic examination and 52.8% antiplatelet treatment. Hb A1c was 7.3 ± 1.3%, but the percentage of patients with glycated hemoglobin > 7% and 8% was 54.9 and 28.6% [only 50.2% had been seen by an endocrinologist in the last 6 months]. 52.8% of patients were treated with insulin and 44.1% with anti-diabetic drugs, although only 19.6% used the new anti-diabetic drugs. 61% of patients had an LDLc > 100 mg/dl (61% treated) and 44% had triglycerides (TG) > 150 mg/dl (72% treated). 95% of patients presented with hypertension (BP ≥ 130/80 mmHg), 91% were undergoing antihypertensive treatment (79.7% with angiotensin-converting enzyme inhibitors and / or angiotensin receptor blockers). 81% with microalbuminuria and 78% with established proteinuria were receiving antiproteinuric treatment. Of the patients considered to be refractory to BP (>3 drugs), only 28.9% underwent ambulatory BP monitoring. Significant differences were observed between stages of diabetic nephropathy and glycated hemoglobin (HBA1c; p = 0.048), systolic blood pressure (SBP; p = 0.024), lipidic*

Correspondence: Dr. Néstor Fontseré
Hospital de Terrassa
Carretera de Torrebonica s/n
08227 Terrassa
E-mail: 34989nfb@comb.es

control (HDLc; p = 0.015 and TG; p = 0.034), anemia (Hb; p = 0.010) and CKD (creatinine and sMDRD; p = 0.000). The levels of compliance with the therapeutic objectives regarding lipid control (LDL ≤ 100 mg/dl and TG ≤ 150 mg/dl), BP ≤ 130/80 mmHg and HbA1c ≤ 7% were 1 objective: 68%, 2 objectives: 21.8% and 3 objectives: only 4% of patients.

Conclusions: *According to the results of our study, only a reduced proportion of patients fulfilled the different therapeutic end-points indicated. Future measures will be directed at improving physician-patient relationships with the main aim of intensifying the therapeutic measures to attain better metabolic and blood pressure control, nephroprotection and prevention in the appearance of cardiovascular events.*

Key words: ***Diabetic patients. 2002 diabetes consensus document. Glycated hemoglobin. Blood pressure. Lipidic control. Nephroprotection.***

ESTUDIO SOBRE EL GRADO DE CUMPLIMIENTO AMBULATORIO DEL DOCUMENTO DE CONSENSO 2002 PARA EL CONTROL DE LA NEFROPATÍA DIABÉTICA EN CATALUÑA (ECCODIAB)

RESUMEN

Objetivo: *Evaluar el grado de cumplimiento del documento de consenso 2002 (SEN) sobre pautas de detección, prevención y tratamiento de la nefropatía diabética en Cataluña.* ***Pacientes y métodos:*** *Estudio multicéntrico de corte transversal (23 centros hospitalarios), observacional y descriptivo, realizado sobre un total de 413 pacientes diabéticos (61,7% hombres y 38,3% mujeres) con una edad media de 66,2 ± 11,5 años (26-93 años). Para el análisis estadístico entre los diferentes grados de nefropatía diabética y las variables del estudio, se utilizó un test de ANOVA con valoración* post-hoc *(p < 0,05).*

Resultados: *El 90,3% de los pacientes eran DM2. Entre los parámetros antropométricos observados: IMC 29,8 ± 5 kg/m² (IMC > 30 kg/m²: 48,7%) y perímetro de cintura 104,1 ± 14 cm (48,6% hombres > 102 cm y 78,9% mujeres > 88 cm). El valor de la creatinina sérica 1,9 ± 1,3 mg/dl y el GFR estimado con la ecuación MDRD simplificada (MDRDs) 45,3 ± 25,0 ml/min/1,73 m² [65,8% con ERC estadios 3 y 4]. El 80% de los pacientes tenían examen oftalmológico y el 52,8% recibía tratamiento antiagregante. La Hb A1c fue 7,3 ± 1,3%, pero el porcentaje de pacientes con glicadas > 7% y 8% resultó del 54,9 y 28,6% respectivamente [tan sólo el 50,2% había sido visitado por el endocrinólogo en los últimos 6 meses]. El 52,8% de los pacientes se encontraban en tratamiento con insulina y el 44,1% con ADOs, pero tan sólo un 19,6% con antidiabéticos de metabolización hepática. El 61% de la muestra tenia un LDLc > 100 mg/dl (61% tratados) y el 44% triglicéridos (TG) > 150 mg/dl (72% tratados). El 95% de los pacientes presentaban antecedentes de hipertensión arterial (≥ 130/80 mmHg) y de estos el 91% se encontraban con tratamiento hipotensor (79,7% con IECAS y/o ARA tipo II). El 81% de los microalbuminúricos y el 78% de los macroalbuminúricos recibía algún tipo de tratamiento antiproteinúrico. Entre el grupo de pacientes considerados con HTA refractaria (>3 fármacos), tan sólo el 29% tenía un MAPA. Se obtuvieron relaciones significativas entre los diferentes estadios de nefropatía diabética y el control glucémico (HBA1c; p = 0,048), tensión arterial sistólica (TAS; p = 0,024), perfil lipídico (HDLc; p = 0,015 y TG; p = 0,034), anemia (Hb; p = 0,010) y grado de ERC (creatinina sérica y MDRDs; p = 0,000). El grado de cumplimiento terapéutico sobre el control lipídico (LDL ≤ 100 mg/dl y TG ≤ 150 mg/dl), TA ≤ 130/80 mmHg y HbA1c ≤ 7%; fue 1 objetivo: 68%, 2 objetivos: 21,8% y 3 objetivos: sólo el 4% de la muestra.*

Conclusiones: *Según los resultados obtenidos en nuestro estudio, tan sólo un reducido porcentaje de pacientes cumplieron los diferentes «end points» terapéuticos marcados. Futuras acciones deberán ir encaminadas a potenciar la relación entre médico-paciente, con el principal objetivo de intensificar aquellas medidas terapéuticas encaminadas a un mejor control metabólico y tensional, nefroprotector y prevención de los eventos cardiovasculares.*

Palabras clave: ***Diabetes mellitus. documento consenso 2002. Hemoglobina glicosilada. Tensión arterial. Perfil lipídico. Nefroprotección.***

INTRODUCTION

Diabetes mellitus (DM) represents today a important socio-sanitary problem worldwide since its estimated prevalence is around 140 million people[1]. Some recent studies have reported that it may affect up to 4.4% of the world population by 2030, accounting for a prevalence of about 366 million people[2]. Diabetic nephropathy is the first cause of end-stage chronic renal failure requiring renal replacement therapy in developed countries. In the United States, this figure is around 44.4%, whereas according to current data of the Catalonian registry, the prevalence and incidence in our setting is around 20% and 11%, respectively[3].

Aiming at establishing early detection, prevention, and management proceedings of diabetic nephropathy, on 2002 several Spanish medical societies elaborated a consensus document (table I)[4]. There are very few previous studies evaluating the level of adherence to several therapeutic and health care «end-points» in diabetic patients without renal replacement therapy referred to the nephrology outpatient clinics.

PATIENTS AND METHODS

Study population

The main goal of our multicenter (23 hospital-based centers), cross-sectional, observational, and descriptive study was to assess the level of adherence to the 2002 Consensus Document on Diabetic Nephropathy in Catalonia[4]. Thus, between November and December of 2004, we evaluated 413 diabetic patients referred and followed-up at the nephrology outpatient clinics (61.7% male and 38.3% female patients) with a mean age of 66.2 ± 11.5 years (range: 26-93 years). The study group was comprised by 90.3% of type 2 diabetic patients, 7.3% type 1 diabetic patients, and 2.4% Mody type diabetic patients. All of them met the classification criteria established by the American Diabetes Association[5].

All the participants included into this study were referred for the first time to the nephrology outpatient clinics or were preventively followed-up at the participating centers. The different data analyzed were collected by each center by using the card designed for this study.

Methods

Arterial hypertension has been defined as the existence of blood pressure levels > 130/80 mmHg or >125/75 mmHg in patients with proteinuria > 1g/24h. Refractory arterial hypertension has been defined as blood pressure levels > 140/90 mmHg in patients on anti-hypertensive therapy with at least 3 drugs, adequately combined, at maximal doses, and one of them being a diuretic.

Blood samples were analyzed at the laboratory of each participating center. According to urinary albumin excretion rate (UAER), patients were classified as normo-albuminuric (< 30 mg/24h), micro-albuminuric (30-299 mg/24h), and macro-albuminuric (≥ 300 mg/24h).

Table I. Therapeutic measures for renal and cardiovascular protection in diabetic nephropathy. 2002 Consensus Document on Prevention and Treatment of Diabetic Nephropathy[4]

Objectives
Strict control of blood pressure (< 130/80 mmHg)
– Most of the patients will need 2 or more antihypertensive agents.
– With proteinuria > 1 g/24h, a blood pressure level < 125/75 mmHg may be useful (the decrease must be gradual, especially in the elderly, and orthostatic hypotension must be ruled out).
Reducing proteinuria (< 1 g/24 hours)
Glycemic control (Hb A1c ≤ 7%)
– With severe renal failure, use insulin. With glomerular filtration rate 70-30 mL/min (Creatinine 2-5 mg/dL) gliquidone (other sulphonilureas may accumulate and biguanides are contraindicated), thiazolindiones (troglitazone, pioglitazone), repaglinide, nateglinide, and acarbose may be used.
Stop cigarette smoking
Dyslipidemia control (LDL-cholesterol < 100 mg/dL, HDL-cholesterol > 45 mg/dL in men and > 55 mg/dL in women, triglycerides < 150 mg/dL)
Anti-clotting agents
Low doses of ASA as primary and secondary cardiovascular prevention.
Therapeutic
Non-pharmacological measures
– Appropriate diet for metabolic control and salt restriction (< 6g/day).
– Control of overweight.
– Protein restriction in case of renal failure
– Physical activity (at least a 60-minute walk, 4-5 days per week).
Antihypertensive drugs
• First step:
– ACEI (preferred for type 1 diabetes) or ARA-II (preferred for DM2). Alternative use in case of intolerance.
– Control of serum creatinine and potassium 1-2 weeks after implementation.
• Second step:
– thiazidic diuretics (12.5-25 mg/24h).
– Loop diuretics for moderate-severe renal failure.
• Third step:
– Calcium channel blockers or b-blockers or a-blockers.
– Non-dihydropiridinic calcium channel blockers are first choice agents in case of contraindication of ACEI or ARA-II (verapamil and diltiazem have greater anti-proteinuric capacity than dihydropiridines).
• Fourth step:
– Calcium channel blockers or a-blockers or b-blockers if not used before.
– Other alternatives: central action agents (moxonidine).

ASA: acetyl salicylic acid; ACEI: angiotensin converting enzyme inhibitors; ARA II: angiotensin receptor antagonists-II.

Serum creatinine was determined by the Jaffé's method (range: 0.6-1.5 mg/dL) and estimation of glomerular filtration rate by the simplified MDRD [the Modification Diet in Renal Disease] (sMDRD) adjusted at 1.73 m^2 of body surface area[6]. All study patients were classified by different chronic renal disease stages established by the American Society of Nephrology[7].

Simplified MDRD[6]: 186 x $(SCr)^{-1.154}$ x $(age)^{-0.203}$ x (0.762) female gender x (1.212) Afro-American origin.

SCr: serum creatinine (mg/dL).

Statistical Analysis

The statistical analysis for the ECCODIAB study has been essentially descriptive. The percentage of adherence to the different Consensus Document therapeutic end-points[4] has also been calculated. Besides, we have considered of interest to analyze the main relationships between the different quantitative variables of the study. For this, we have used the ANOVA test with post-hoc analysis for statistical significance ($p < 0.05$). The SPSS® Software, version 12.0 (SPSS Inc.) was used for statistical analysis.

RESULTS

The main socio-demographic, anthropometrical, and laboratory characteristics of the study group are shown in Table II. Of anthropometrical data, we should highlight that 48.7% of the patients had a BMI > 30 kg/m^2 (42.7% male and 51% female patients). Besides, 48.6% of male patients had a waist circumference > 102 cm and 78.9% of female patients had a waist circumference > 88 cm at physical examination.

Plasma creatinine value for the study group was 1.9 ± 1.3 mg/dL (0.4-11 mg/dL) and the glomerular filtration rate estimated by the sMDRD equation was 45.3 ± 25 mL/min/1.73m^2 (4.2-171.6 mL/min/1.73m^2). Most of the patients (20.8%) were classified as stage 2 CRF [GFR: 89-60 mL/min/1.73m^2], stage 3 (45.6%) [GFR: 59-30 mL/min/1.73m^2], and stage 4 (20.2%) [GFR: 29-15 mL/min/1.73m^2]. About the level of proteinuria, 11.8 were classified as normo-albuminuric (≤ 30 mg/24h), 30.0% as microalbuminuric (31-299 mg/24h), and 58.1% as macroalbuminuric (≥ 300 mg/24h).

Mean Hb A1c value was 7.3 ± 1.3% (5.5-14.5%). Fifty two point eight percent of the patients were on insulin therapy, and 44.1% on oral anti-diabetic agents. Among patients treated with anti-diabetic agents, the most frequently used drugs were biguanides (45.6%), sulfonylureas (43.4%), and acarbose-miglitol (13.7%). The use of oral liver-metabolized anti-diabetic agents was the least since only 9.3% of the patients were treated with thiazolindiones (rosiglitazone and pioglitazone), 9.8% with repaglinide, and 0.5% with nateglidine. There were no significant differences by use among patients in 4 and 5 CRF stages [GFR < 30 mL/min/1.73m^2]. However, about the metabolic control obtained, 54.9% of the patients had Hb A1c values > 7% and 28.6% > 8% (fig. 1a). Of these patients, only half of them (50.2%) had been referred to the endocrinologist within the last 6 months.

Table II. Socio-demographic, anthropometrical, and laboratory characteristics of the 431 diabetic pactients

Variable	Mean ± SD
Age (years)	66.2 ± 11.5 (26-93)
Weight (kg)	79.7 ± 14.5 (41.5-123.8)
Height (cm)	163.3 ± 8.6 (142-192)
BMI (Kg/m^2)	29.8 ± 5 (16.3-45.2)
Waist perimeter (cm)	104.1 ± 14 (60-150)
Hb A1c (%)	7.3 ± 1.3 (5.5-14)
SBP (mmHg)	145.8 ± 20.7 (90-250)
DBP (mmHg)	77.4 ± 11.6 (46-130)
Cholesterol (mg/dl)	190.6 ± 45 (50-556)
HDLc (mg/dl)	47.7 ± 20.3 (13.5-95)
LDLc (mg/dl)	111.1 ± 39.3 (27.8-406)
Triglycerides (mg/dl)	162.4 ± 98.5 (30-825)
Proteinuria (g/24 h)	1.1 ± 1.8 (0-12)
Serum Creatinine (mg/dl)	1.9 ± 1.3 (0.4-11)
sMDRD (ml/min/1,73 m^2)	45.3 ± 25 (4.2-171.6)

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; sMDRD: simplified MDRD equation.

Ninety-five point two percent of the study patients were hypertensive, among which 91% were receiving some kind of hypotensive medication. The most frequently used drugs were renin-angiotensin-aldosterone system blockers (79.7% of the patients) [43.1% ACEIS, 48.2% type II ARA, and 11.6% both drugs], diuretics (56.9%), and calcium-channel blockers (48.4%). In spite of the fact that the mean number of agents per patient was 2.4 ± 1.1 (0-6), 75.3% of them had systolic blood pressure (SBP) values > 130 mmHg, 31.1% diastolic blood pressure (DBP) values > 80 mmHg, and 28.4% had systolic-diastolic hypertension (BP > 130/80 mmHg) (fig. 1b). Only 28.9% of the patients with refractory arterial hypertension had a MAPA done. In spite of this, 81.4% of the patients with a history of hypertension, 81.2% of microalbuminuric patients, and 78% macroalbuminuric patients were on therapy with renin-angiotensin-aldosterone system blockers.

About the lipid profile, 61% of the subjects had LDLc values > 100 mg/dL [61% treated with hypolipidemic agents], 45.5% HDLc < 45 mg/dL (males), and 34.1% < 55 mg/dL (females), and 44.1% had triglycerides > 150 mg/dL [72% treated with hypolipidemic agents] (figs 1c and 1d).

About the personal history of cardiovascular disease, 21.5% of studied patients had ischemic heart disease, 19.4% peripheral vasculopathy, and 10.4% cerebrovascular disease. Only 52.8% of the sample had some kind of anti-aggregant therapy, with a mean dose of ASA of 125 ± 60 mg/24h (75-300 mg/24 h). About the smoking status, 10.7% were current smokers, 34.6% were ex-smokers, and only 23.6% had had access to some smoking cessation unit.

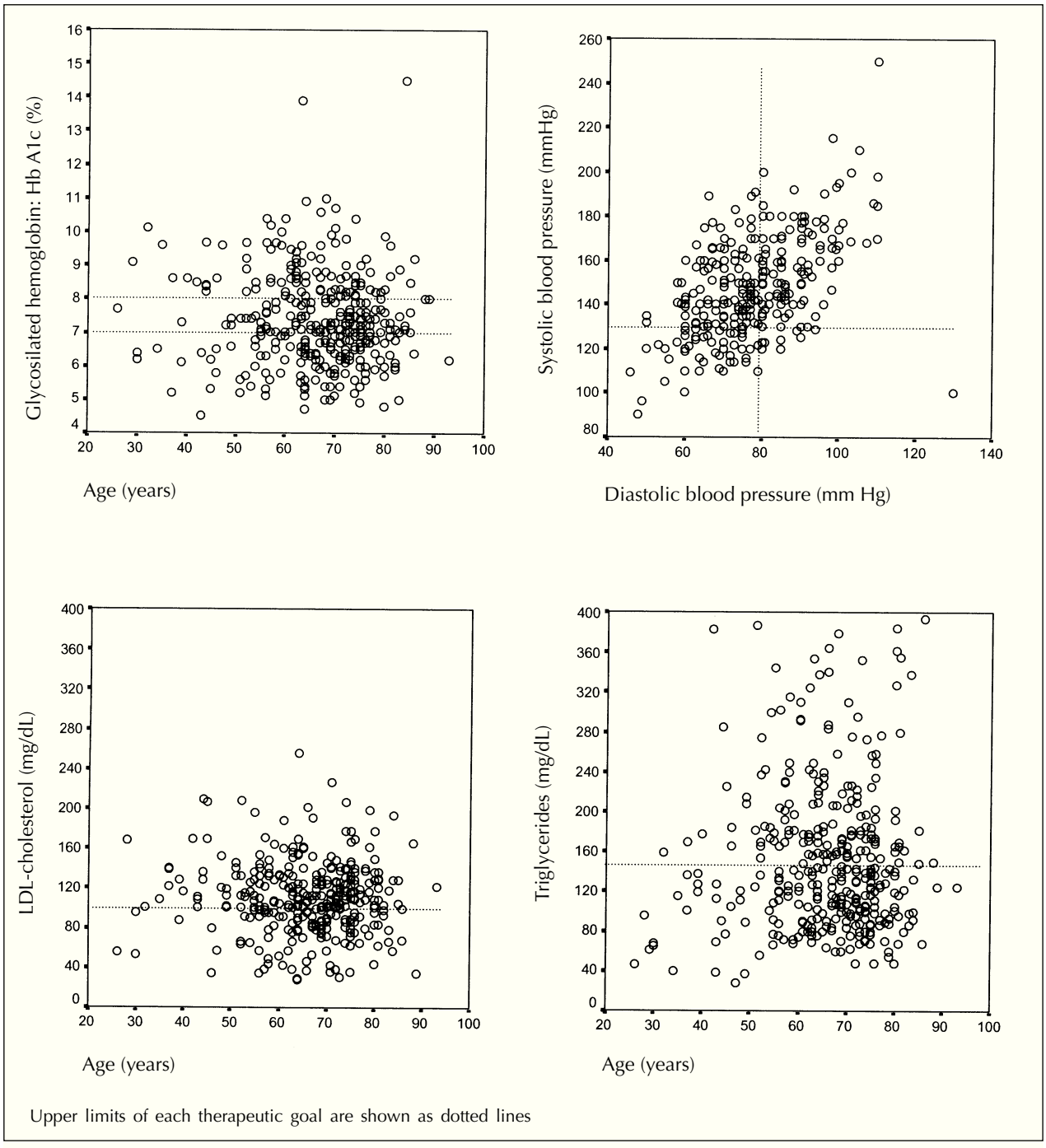

Fig. 1.—Level of adherence to the main therapeutic goals in the sample of 413 diabetic patients from the ECCODIAB study. A) glycosilated hemoglobin [%] (Hb A1c > 7%: 54.9% and Hb A1c > 8%: 28.6%); B) Blood pressure [mmHg] (SBP > 130 mmHg and DBP > 80 mmHg; Systolic AHT: 75.3%, Diastolic AHT: 31.1% and systolic-diastolic AHT: 28.4%). C) LDL cholesterol [mg/dL] (LDLc > 100 mg/dL: 61%); D) Triglycerides [mg/dL] (TG > 150 mg/dL: 44.1%).

About health care parameters, 80.6% had a fundus examination done, and 70% had received diabetes education. About controls performed within the last 6 months, 71.8% of the sample had visited his/her primary care doctor, 50.5% the endocrinologist, 21.8% the diabetes-specialized nurse, and 15.8% the diabetes trainer.

Table III. Statistical analysis by ANOVA Test with *post-hoc* evaluation between the different Diabetic Nephropathy stages and the different study variables.

	Normo-albuminuric	Microalbuminuric	Macroalbuminuric	p value[a]
Patients	49	124	240	
Age (years)	62.9 ± 14.2	66.6 ± 11.3	66.1 ± 11.3	NS
Weight (kg)	78.3 ± 13.4	78.6 ± 13.9	80.6 ± 14.8	NS
Height (cm)	163.2 ± 8.8	161.7 ± 8.6	164.1 ± 8.5	NS
BMI (kg/m^2)	29.4 ± 5.0	30.0 ± 4.8	30.4 ± 5.3	NS
BSA (m^2)	1.8 ± 0.1	1.8 ± 0.2	1.9 ± 0.2	NS
Waist perimeter (cm)	104.5 ± 16.7	104.3 ± 16.5	95.5 ± 23.7	0.0180*
SBP (mmHg)	140.5 ± 18.9	143.6 ± 21.5	148.3 ± 19.6	0.0246*
DBP (mmHg)	76.9 ± 11.0	77.4 ± 11.3	77.4 ± 11.3	NS
LDLc (mg/dl)	108.2 ± 24.1	113.4 ± 35.71	110.3 ± 44.7	NS
HDLc (mg/dl)	53.7 ± 24.8	48.9 ± 13.8	45.0 ± 19.3	0.0159*
Triglycerides (mg/dl)	135.0 ± 47.01	54.4 ± 94.91	174.5 ± 110,1	0.0343*
Cholesterol (mg/dl)	184.6 ± 28.7	193.1 ± 57.0	190.8 ± 40.8	NS
Creatinine (mg/dl)	1.5 ± 1.6	1.5 ± 0.8	2.2 ± 1.4	0.0000**
Hemoglobin (g/dl)	13.7 ± 1.7	13.3 ± 1.8	12.9 ± 1.7	0.0106*
Hb A1c (%)	6.9 ± 1.2	7.3 ± 1.1	7.5 ± 1.4	0.0482*
Proteinuria (mg/24 h)	10.0 ± 10.0	140.0 ± 7.0	2,000 ± 2,130	0.0000**
sMDRD (ml/min/1,73 m^2)	58.4 ± 28.1	49.1 ± 21.0	39.2 ± 24.4	0.0000**

BMI: Body mass index; BSA: Body surface area; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; sMDRD: simplified MDRD equation.
[a] Test de ANOVA with *post-hoc* evaluation; p value < 0.05* y < 0.01**.
Normo-albuminuric: < 30 mg / 24 h. Microalbuminuric: 30-299 mg/24 h. Macroalbuminuric: ≥ 300 mg/24 h.

The main causes for referral to the nephrology outpatient clinic were CRD (50.2%), uncontrolled arterial hypertension (34.7%), the onset of macroalbuminuria (24.5%), and the increase of microalbuminuria (16.5%).

Table III shows the main relationships between the different diabetic nephropathy stages and the main quantitative variables of the study. We essentially highlight the observation of a statistically significant relationship with glycemic control (Hb A1c; p = 0.048), systolic blood pressure (SBP; p = 0.024), lipid profile (HDLc; p = 0.015 and TG; p = 0.034), anemia (Hb; p = 0.010) and CRD (serum creatinine and sMDRD; p = 0.000).

Table IV shows the percentages of different therapeutic end-points obtained in the study group. Considering the level of adherence by the Hb A1c value (≤ 7%), lipid profile (LDLc ≤ 100 mg/dL and TG ≤ 150 mg/dL), and blood pressure control (BP ≤ 130/80 mmHg) 68% of the sample met at least one of the target therapeutic end-points, 21.8% two, and only 4% three.

Table IV. Level of adherence to the main therapeutic goals in the sample of 413 diabetic patients

Therapeutic criterion	% of adherence
1. Anthropometrical parameters	
BMI ≤ 30 Kg / m^2 (male/female)	57.3% / 49%
Waist perimeter (male ≤ 102 cm	
/ female ≤ 88 cm)	51.4% / 29.3%
2. Control Hb A1c ≤ 7%	45.1%
3. Blood pressure control	
Without proteinuria (BP ≤ 130/80 mmHg)	21.8%
Proteinuria > 1 g/24 h	
(BP ≤ 125/75 mmHg)	10.0%
4. Lipid profile control	
LDLc ≤ 100 mg/dl	39%
HDLc < 45 mg/dl (male)	
o < 55 mg/dl (female)	45.5% / 34.1%
Triglycerides ≤ 150 mg/dl	55.9%
5. Anti-aggregants	52.8%

DISCUSSION

The main goal of the ECCODIAB study (Study of Adherence to the Consensus Document) done on diabetic patients followed-up at the outpatient nephrology clinic was to assess the level of adherence to the different clinical and

health care indicators achieved in daily clinical practice. Unfortunately, there were a high percentage of patients that did not obtained the different goals indicated on the consensus document. The elaboration and planning of future actions should be directed to: (i) improved collaboration with the different implicated specialists, especially general practitioners and endocrinologists; (ii) early detection of associated complications; and (iii) a reinforcement of medical recommendations based on lifestyle and early implementation of different therapeutic measures.

There are currently a great number of studies described in the literature analyzing the beneficial effect of strict blood pressure, glycemia, and lipids control as for the onset and progression of proteinuria. In spite of all this, there are very few previous studies[8,9] analyzing the level of therapeutic adherence in patients with diabetic nephropathy without renal replacement therapy.

Independently of the beneficial effects of strict glycemic control on micro-and macrovascular complications[10], management of lipid profile is also of paramount importance as shown by the MRFT study (Multiple Risk Factor Intervention Trial)[11]. That study shows how the existence of dyslipidemia increases 2-4 fold the risk for the onset of cardiovascular pathology.

Hypertension represents the most relevant risk factor not related with metabolic impairment for prevention and development of diabetic nephropathy. It is estimated that 35-75% of vascular complications of the diabetic patient (including progression to renal failure) are a consequence of hypertension, which is the most relevant predictive factor for cardiovascular mortality. Microalbuminuria (30-299 mg/24 h) represents the earliest risk marker of the development of evolutionary diabetic nephropathy[12]. It is not only by itself an excellent marker of renal risk but also of cardiovascular events (ischemic heart disease and cerebrovascular accident), especially in type DM patients[13]. A relationship has particularly been found between microalbuminuria and hypercholesterolemia with a decrease of high density lipoproteins, an increase in Von Willebrand's factor and of homocysteine, which is considered by itself an independent risk factor[14]. Oxidative stress and endothelial dysfunction are factors mediated by the renin-angiotensin system, both in renal and cardiovascular diseases. Several studies have shown that the use of pharmacological agents blocking the RAAS (ACEIS and/or type II ARA) decreases the level of albuminuria and the risk for cardiovascular pathology. Such an anti-proteinuric effect has been shown both in type I[15,16] and type II[17] DM patients, hypertensive or normotensive, normo-albuminuric[18,19], microalbuminuric[20,21], and also in patients with established diabetic nephropathy and associated renal failure[22,23,24], leading to a delay in glomerular filtration loss and lower incidence of cardiovascular events. For all these reasons, it is important to establish albuminuria determination as an early screening method of diabetic nephropathy after 5 years of disease progression in type I DM and readily in type II DM. For the case of microalbuminuria or established proteinuria, this parameter should be done 3-4 times yearly because of the potential progressive course[25].

Regarding cardiovascular risk prevention, virtually almost all studies (UKPDS[26], CAPP[27], HOPE[28], ABCD[29], SIST-EUR[30], and FACET[31]) have shown a reduction in this sub-group of patients by optimizing blood pressure control. In this sense, the MICRO-HOPE study[32] is one of the most important ones, with a special emphasis on the analysis of the subgroup of diabetic patients with negative proteinuria, concluding and reassuring both the cardio- and renoprotective feature, as well as antiproteinuric, of ACEIS. Besides, the HOT study (Hypertension Optimal Treatment)[33] has shown that the addition of low-dose aspirin (75-125 mg/day) acts together with strict blood pressure control as primary and secondary prevention mechanism of myocardial infarction in type 2 diabetes mellitus patients.

The existence of non-treated arterial hypertension, defined as BP > 140/90 mmHg, is seldom seen, especially in patients with microalbuminuria or established proteinuria. In spite of all this, controlled arterial hypertension, defined as BP < 130/85 mmHg in type 1 diabetics with anti-hypertensive therapy, is only achieved in 33% and 19% of the patients with microalbuminuria and established nephropathy, respectively[8]. In our study mainly done on type 2 diabetes mellitus patients, that blood pressure control was achieved in 25.8% of microalbuminuric patients and in 20.5% macroalbuminuric patients. N. Joss *et al.*[9] analyzed 170 patients with diabetic nephropathy, mean serum creatinine of 170 µmol/L and 3 g proteinuria. In this sense, mean blood pressure initially obtained was 159/85 mmHg and the number of antihypertensive drugs used was 1 (range: 0-3). Forty-six percent of the patients were on ACEIS, 7% on β-blockers, 36% on calcium channel blockers, and 36.5% on diuretics. Besides, 49% of the patients were receiving aspirin and only 15% hypolipidemic agents.

Anemia is another paramount factor, since its management and early correction may improve the situations of hemodynamic angina, slow the progression of associated left ventricular hypertrophy, nephropathy, and retinopathy, as well as substantially increasing quality of life of diabetic patients[34].

Recent studies[35] have shown that cigarette smoking acts as an independent risk factor for reducing glomerular filtration rate in diabetic patients with normal renal function. Therefore, smoking cessation should be encouraged and, if necessary, make easier to have access to specialized smoking cessation units.

Several studies have shown that early referral to the nephrologist decreases the associated morbimortality in type 2 diabetic patients with associated chronic renal disease[36]. This beneficial effect is essentially obtained by managing anemia and calcium-phosphorus metabolism, as well as an early planning and implementation of renal replacement therapy. Therefore, referral to the nephrologist should be done when microalbuminuria is present or increases, proteinuria develops, sub-optimal blood pressure control occurs, or with the presence of chronic renal disease at stages 3, 4, and 5 (estimated by the MDRD equation or the Cockcroft-Gault formula).

To conclude, we may state that the main health care goal should be directed towards promoting the patient-doctor relationship with the aim of preventing and early diagnosing the onset of diabetic nephropathy. In order to achieve this premise, a multidisciplinary and interdisciplinary ap-

proach would be necessary between the different specialists implicated aiming at intensifying those therapeutic measures directed to improve metabolic and blood pressure control, renal protection, and preventing the onset of cardiovascular events.

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