Renal Function Changes in Microalbuminuric Normotensive Type II Diabetic Patients Treated With Angiotensin-Converting Enzyme Inhibitors

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OBJECTIVE — To determine the effects of captopril on microalbuminuria and renal function in normotensive type II diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 26 patients were randomized in two homogeneous groups for clinical and analytical data in a 6-mo follow-up study. Group A received captopril (initial dose: 12.5 mg daily, increased according to tolerance); group B was untreated.

RESULTS — Microalbuminuria decreased only in the treated group at 6 mo ($P = 0.044$) and a significant ($P = 0.027$) mean percentage change on microalbuminuria excretion between the groups was observed. Filtration fraction decreased in group A (baseline: 0.23 ± 0.03; 6 mo: 0.22 ± 0.04) and increased in group B (baseline: 0.22 ± 0.04; 6 mo: 0.25 ± 0.04) with a significant mean percentage change between the groups at 6 mo ($P = 0.032$). The mean percentage change in microalbuminuria was significantly correlated with a mean percentage change in diastolic blood pressure throughout the trial. Neither metabolic control nor sodium or protein intake changed in either group during the trial.

CONCLUSIONS — These results suggest that captopril can help arrest microalbuminuria in normotensive type II diabetic patients, with a decrease in diastolic blood pressure and filtration fraction after a 6-mo treatment.

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TYPE II DIABETES, NON-INSULIN-DEPENDENT DIABETES MELLITUS; ACE, ANGIOTENSIN-CONVERTING ENZYME; TYPE I DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS; BP, BLOOD PRESSURE; DBP, DIASTOLIC BLOOD PRESSURE; SBP, SYSTOLIC BLOOD PRESSURE; WHO, WORLD HEALTH ORGANIZATION; CV, COEFFICIENT OF VARIATION; HDL, HIGH-DENSITY LIPOPROTEIN; LDL, LOW-DENSITY LIPOPROTEIN; GFR, GLOMERULAR FILTRATION RATE; RPF, RENAL PLASMA FLOW; FF, FILTRATION FRACTION; PRA, PLASMA RENIN ACTIVITY; ANOVA, ANALYSIS OF VARIANCE; CI, CONFIDENCE INTERVAL; BMI, BODY MASS INDEX.

Microalbuminuria is accepted as an index of incipient diabetic nephropathy. Of patients with type I diabetes mellitus and microalbuminuria, >80% develop nephropathy (1). The course of nephropathy in type II diabetes is poorly documented, possibly because its follow-up is usually shorter because of increased cardiovascular mortality (2–4). Early antihypertensive treatment can improve the course of albumin excretion and renal function in diabetic nephropathy. Recent studies (5,6) suggest that the use of ACE inhibitors may arrest the progression of diabetic nephropathy in normotensive type I diabetic patients with microalbuminuria (7–11). This effect has been studied less in normotensive type II diabetic patients (12). The aim of this study was to measure the effect of captopril in normotensive type II diabetic patients with microalbuminuria.

RESEARCH DESIGN AND METHODS

— A total of 26 normotensive type II diabetic patients with increased urinary albumin excretion accepted enrollment in the study. Baseline clinical data are shown in Table 1. Microalbuminuria was diagnosed when the urinary albumin excretion in three 24-h urine collections, performed during the previous 6 mo, was between 30 and 300 mg/daily. None of the patients had clinical or laboratory evidence of cardiac disease, nor liver or renal disfunction. No drugs (except insulin or oral hypoglycemic agents) were given at least 8 wk before randomization. All followed a qualitative constant diabetic diet (1200 Kcal/day) with neither protein nor sodium restriction. Patients were told not to change their physical activity during the study or engage in vigorous exercise. Patients' supine BP was within normotensive values (WHO criteria: <140/90 mmHg) on three consecutive monthly visits to the outpatient clinic before beginning the study, although 2 patients in each group had sBP between 140 and 150 mmHg at baseline. BP was calcu-

Table 1—*Clinical characteristics of microalbuminuric normotensive type II diabetic patients*

	GROUP A	GROUP B
N	13	13
AGE (YR)	53.2 ± 7.1	52.5 ± 15.1
SEX (F/M)	4/9	6/7
DURATION OF DIABETES (YR)	11.3 ± 5.5	12.8 ± 9.6
BMI (KG/M^2)	27.5 ± 4.4	26.8 ± 5.5
RETINOPATHY	10	8
POLYNEUROPATHY	4	4
HYPERLIPEMIA	4	5
TREATMENT		
INSULIN	7	8
SULFONYLUREAS	6	5

Data are means ± SD. Group A was treated with captopril, and group B was untreated.

lated as a mean of two determinations recorded after 5 min rest in a sitting position. dBP was recorded with disappearance of the Korotkoff sounds (phase V). The mean BP was calculated as dBP plus 33% of the pulse pressure. Patients were distributed aleatorily into two groups. In group A, 13 type II diabetic patients were treated with captopril at an initial dose of 12.5 mg twice a day, which was gradually increased according to tolerance, until the patient reported hypotensive symptoms. In group B, 13 untreated patients were included. Clinical control involved measuring BP and weight monthly and evaluating the glycemic controls obtained once or twice a day by the patient at home.

At the start of treatment and at 3 and 6 mo of follow-up, glycemia, total cholesterol, triglycerides, albumin, and creatinine in serum were determined with a CHEM-1 Thecnicon autoanalyzer (TerryTown, NY). The 24-h microalbuminuria was measured by nephelometry (CV: interassay 5%, intra-assay 3%, sensitivity 1.9 mg/L) only when sediment in fresh urine, assayed at the same time, was normal. HDL-cholesterol fraction was determined by precipitation, and LDL fraction was calculated with the Friedewald formula. HbA_{1c} was quantified by a chromatographic method (Biosystem, Barcelona, Spain) (normal range: 5–6.7%). At baseline and 6 mo, GFR was determined from 10 venous blood samples drawn 5–240 min after a bolus intravenous injection of 40 μCi ^{125}iothalamate, and RPF was determined from venous blood samples drawn 5–60 min after a bolus intravenous injection of 50 μCi ^{131}I-labeled hippuran (13,14). The patients fasted overnight before measurement of kidney function, and no insulin was given the morning of the investigation. FF was calculated as the ratio of GFR and RPF. The estimated daily protein intake was calculated from the excretion of urinary nitrogen according to Maroni (15), at the beginning and end of treatment. A renal echography discounted any kidney or urinary tract pathology. At 6 mo, PRA (Biodata Renin MAIA, Serono, Roma, Spain) was measured at least 12 h after the intake of the last dose of captopril.

Data obtained were assessed statistically with one-way ANOVA for repeated measurements in both groups. Microalbuminuric excretion was logarithmically transformed before analysis because of the positively skewed distribution (Fisher coefficient). Microalbuminuria geometric means with 95% CIs are given at baseline and 3 and 6 mo. Remaining data are presented as means ± SD. The mean percentage change of renal function (GFR, RPF, and FF) and BP was compared between the two groups during the trial. Microalbuminuria variations were calculated after logarithmic transformation as follows: microalbuminuria increase = [(microalbuminuria log 6 mo − microalbuminuria log baseline)/ microalbuminuria log baseline] × 100. Student's *t* test for comparing paired and unpaired data and finally Pearson's linear test for correlations between variables were used. $P < 5\%$ was considered significant.

RESULTS— At baseline the two groups were homogeneous as regards age, sex, duration of diabetes, chronic complications of the disease, BMI, and analytical data (Tables 1 and 2). During the study, sBP did not change in either group. A significant decrease in dBP ($P = 0.015$) and mean BP was observed only in group A ($P = 0.02$) when the

Table 2—*Laboratory data of microalbuminuric normotensive type II diabetic patients*

	GROUP A		GROUP B	
	BASELINE	6 MO	BASELINE	6 MO
GLUCOSE (MM)	9.1 ± 1.9	10.0 ± 3.4	9.0 ± 3.1	8.8 ± 3.7
HbA_{1c} (%)	8.5 ± 2.0	8.0 ± 1.7	9.3 ± 2.1	8.0 ± 1.7
CHOLESTEROL (MM)	5.4 ± 1.2	5.9 ± 1.2	5.4 ± 1.1	5.6 ± 1.0
TRIGLYCERIDES (MM)	1.4 ± 0.5	1.5 ± 0.7	1.4 ± 0.9	1.2 ± 0.5
HDL CHOLESTEROL (MM)	1.1 ± 0.3	1.1 ± 0.3	1.3 ± 0.3	1.3 ± 0.2
LDL CHOLESTEROL (MM)	3.8 ± 1.3	4.1 ± 1.2	3.5 ± 1.0	3.7 ± 0.9
CREATININE (MM)	96.4 ± 25.1	96.7 ± 22.4	97.3 ± 28.5	96.9 ± 23.2

Data are means ± SD. No significant differences were found between groups. Group A was treated with captopril, and group B was untreated.

Table 3—*Baseline and 3- and 6-mo follow-up values of renal function and microalbuminuria in microalbuminuric normotensive type II diabetic patients*

	Group A			Group B		
	Baseline	3 mo	6 mo	Baseline	3 mo	6 mo
sBP (mmHg)	132 ± 14	130 ± 10	127 ± 9	126 ± 19	129 ± 14	129 ± 28
dBP (mmHg)	75 ± 9	77 ± 4	68 ± 8*	71 ± 11	71 ± 9	72 ± 10
Mean BP (mmHg)	94 ± 10†	95 ± 4	89 ± 5‡	89 ± 12	90 ± 9	91 ± 15
Microalbuminuria (mg/24 h)§	93 (70–144)	67 (35–125)	60 (35–104)†	81 (55–119)	87 (54–125)	91 (58–141)
Captopril dose (mg/24 h)	—	50 ± 10	61 ± 19	—	—	—
GFR (ml/min)	124 ± 29	—	119 ± 25	117 ± 38	—	122 ± 48
RPF (ml/min)	532 ± 112	—	577 ± 188	535 ± 165	—	497 ± 179
FF	0.23 ± 0.03	—	0.22 ± 0.04	0.22 ± 0.04	—	0.25 ± 0.04

Data are means ± SD. Significance was determined by repeated-measure ANOVA. Group A was treated with captopril, and group B was untreated.
*$P = 0.015$.
†$P = 0.04$.
‡$P = 0.02$.
§Data are geometric means (95% CI).

captopril dose was increased (50.10 ± 10.21 to 61.54 ± 19.41 mg; paired Student's t test $P < 0.01$) (Table 3). Microalbuminuria excretion in group A decreased significantly ($P = 0.044$), whereas it increased in group B, but not significantly. A significant correlation was noted between the mean percentage change in microalbuminuria and mean percentage change in dBP throughout the trial in both groups ($P = 0.033$; $r = 0.4201$). The mean percentage change on microalbuminuria excretion between both groups was significantly different ($P = 0.027$) at 6 mo. The mean percentage change in FF decreased in group A and increased in group B (group A, −6.32% vs. group B, 12.0%; $P = 0.032$) (Fig. 1). No significant differences were observed in estimated daily protein intake (group A, 104 ± 49 vs. 91 ± 37 g/24 h; group B, 99 ± 28 vs. 82 ± 33 g/24 h). PRA was different, although not significantly, between both groups at 6 mo (group A, 0.94 ± 0.65 vs. group B, 3.71 ± 4.71 ng · $ml^{-1} \cdot min^{-1}$; $P = 0.058$). No side effects were observed in the treated group.

CONCLUSIONS — This study shows that in normotensive type II diabetic patients, ACE inhibition by captopril decreases BP, arresting an increase of microalbuminuria over a 6-mo period. Few studies on ACE inhibition have been done in type II diabetic patients with microalbuminuria. In Marre et al.'s (8) study, enalapril significantly reduced microalbuminuria in 16 type I diabetic and 4 type II normotensive diabetic patients. In a multicentric study with normotensive and hypertensive diabetic patients (type I and type II) with persistent microalbuminuria, perindopril and nifedipine significantly reduced mean BP in both normotensive and hypertensive patients, but decreased microalbuminuria only in hypertensive patients (16). In contrast, a previous study suggested that different antihypertensive drugs could not have the same effect on microalbuminuria excretion (9). These contradictory results could, at least in part, be explained by the different clinical characteristics of patients involved in the studies and the different follow-up. Mathiensen obtained a 9% reduction of microalbuminuria in normotensive diabetic patients treated with captopril versus an 8% increase of microalbuminuria in the control group (11). These are similar to our results, which showed an increase of 3.39% in the untreated group and a decrease of 10.15% in the treated group.

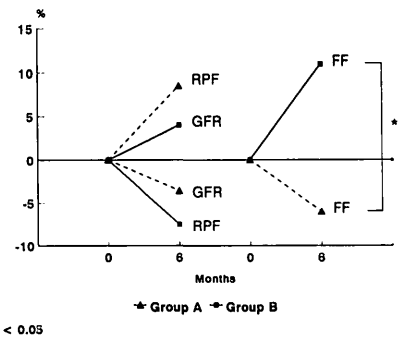

Figure 1—*Mean percentage variation of RPF, GFR, and FF during the 6-mo follow-up of microalbuminuric normotensive type II diabetic patients. Group A was treated with captopril, and group B was untreated.*

Mechanisms by which antihypertensive drugs reduce microalbuminuria are not totally understood. BP seems to be an important determinant of urinary albumin excretion (9,18). In our study, mean BP and dBP decreased in the treated group, suggesting that microalbuminuria is almost partially pressure dependent, as has been observed by other authors (8,17). However, direct effects of ACE inhibitors on glomerular resistances (19,20) could explain the decrease of microalbuminuria without changes in systemic BP, as has been reported in normotensive type I diabetic patients treated with ACE inhibitors

(11,21). It has been reported (22) that during antihypertensive treatment, BP decrease is only associated with proteinuric decrease if the drug lowers FF. We, as have other authors (9,10,21), observed a nonsignificant decrease in FF in the captopril-treated group, but with a significantly different mean percentage change of FF between both groups at 6 mo. In the same way, although in Marre et al.'s (8) study the FF did not change, total renal resistances declined in the enalapril-treated group. On the other hand, Slomowitz (17) observed in 6 type II diabetic inpatients, that microalbuminuria was normalized with enalapril treatment in 4 wk without any change in GFR and RPF, but with a significant drop in systemic BP. Unfortunately, these opposing results cannot be contrasted with other studies because very few had measured RPF to assess FF analysis. Because HbA_{1c}, protein, and sodium intake did not change in either group, these factors could not affect microalbuminuria excretion during the study. Finally, although the treated group complied with the use of medication, we did not find significant difference in PRA between both groups, in accordance with other published results (9,17), perhaps because of the anomalous renin secretion described in diabetic patients (23).

In conclusion, in normotensive type II diabetic patients, captopril arrested microalbuminuria, whereas an increase of microalbuminuria was observed in the control group. Although this event could be explained by the drop in BP, intraglomerular hemodynamics changes induced by captopril could have a synergic effect. Further comparative studies with a large follow-up are necessary to establish whether the ACE inhibitors could prevent progression of incipient diabetic nephropathy in type II diabetic patients.

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