Effect of Intensive Glycemic Control on Microalbuminuria in Type 2 Diabetes

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OBJECTIVE — Microalbuminuria can reflect the progress of microvascular complications and may be predictive of macrovascular disease in type 2 diabetes. The effect of intensive glycemic control on microalbuminuria in patients in the U.S. who have had type 2 diabetes for several years has not previously been evaluated.

RESEARCH DESIGN AND METHODS — We randomly assigned 153 male patients to either intensive treatment (INT) (goal HbA_{1c} 7.1%) or to standard treatment (ST) (goal HbA_{1c} 9.1%; $P = 0.001$), and data were obtained during a 2-year period. Mean duration of known diabetes was 8 years, mean age of the patients was 60 years, and patients were well matched at baseline. We obtained 3-h urine samples for each patient at baseline and annually and defined microalbuminuria as an albumin:creatinine ratio of 0.03–0.30. All patients were treated with insulin and received instructions regarding diet and exercise. Hypertension and dyslipidemia were treated with similar goals in each group.

RESULTS — A total of 38% of patients had microalbuminuria at entry and were evenly assigned to both treatment groups. INT retarded the progression of microalbuminuria during the 2-year period: the changes in albumin:creatinine ratio from baseline to 2 years of INT versus ST were 0.045 vs. 0.141, respectively ($P = 0.046$). Retardation of progressive urinary albumin excretion was most pronounced in those patients who entered the study with microalbuminuria and were randomized to INT. Patients entering with microalbuminuria had a deterioration in creatinine clearance at 2 years regardless of the intensity of glycemic control. In the group entering without microalbuminuria, the subgroup receiving ST had a lower percentage of patients with a macrovascular event (17%) than the subgroup receiving INT (36%) ($P = 0.03$). Use of ACE inhibitors or calcium-channel blockers was similarly distributed among the groups.

CONCLUSIONS — Intensive glycemic control retards microalbuminuria in patients who have had type 2 diabetes for several years but may not lessen the progressive deterioration of glomerular function. Increases in macrovascular event rates in the subgroup entering without albuminuria who received INT remain unexplained but could reflect early worsening, as observed with microvascular disease in the Diabetes Control and Complications Trial.

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Abbreviations: INT, intensive treatment; ST, standard treatment; UKPDS, U.K. Prospective Diabetes Study; VA, U.S. Department of Veterans Affairs.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Recently, the final results of the U.K. Prospective Diabetes Study (UKPDS) were published (1). This long-term trial evaluated the progression of complications in newly diagnosed patients with type 2 diabetes beginning at a stage in which many patients were responsive to treatment with diet or oral hypoglycemic agents. However, we know of no reports in Western populations regarding the effects of initiating intensive glycemic control in patients with known diabetes of several years' duration in whom glycemia no longer responds to diet or oral hypoglycemic agents and for whom initiation of insulin therapy is required.

In 1990, 5 medical centers in the U.S. Department of Veterans Affairs (VA) initiated an intervention trial (2,3). The study was designed to test whether a significant difference could be achieved in glycemic control in 2 groups of randomly allocated male patients: 1 group maintained within the range accepted in observed community practice (standard treatment [ST]) and the other group maintained with a glycemic pattern close to ranges in nondiabetic individuals (intensive treatment [INT]). Insulin was used in both of these groups because glycemic control could not be achieved with diet or oral hypoglycemic agents.

As part of this 3-year feasibility trial, we collected data on various clinical parameters, including urinary albumin measurements. This report summarizes the effects of 24 months of INT on microalbuminuria and associated clinical parameters in men with type 2 diabetes.

RESEARCH DESIGN AND METHODS

These methods have also been detailed in previous publications (2–7).

Patients

Male veterans between 40 and 69 years of age (mean ± SD 60 ± 6) who had diabetes for a duration of <15 years (mean 7.8 ± 4) participated in this study. They had failed to obtain optimal glycemic control with maximal doses of sulfonylurea therapy or various insulin regimens. The mean HbA_{1c} value for the entire group at screening was 9.8 ± 1.9%, which is >7 SD above the upper limits of normal (6.05%) for the central gly-

cosylated hemoglobin laboratory at the University of Minnesota (Minneapolis, MN).

Exclusion and inclusion criteria have been previously described (2,3). Briefly, the study required the ability to cooperate with an intensive glycemic control regimen and the absence of incapacitating cardiovascular or other medical conditions that would preclude participation. The diagnosis of type 2 diabetes was substantiated by fasting C-peptide levels >0.21 pmol/ml in the laboratory of Dr. A. Rubenstein at the University of Chicago.

The protocol and informed consent procedures were approved by institutional review boards at each of the 5 VA medical centers participating in this study and by the Cooperative Studies Program Coordinating Center Human Rights Committee in Hines, Illinois.

Randomization and stratification were done separately for each participating medical center and took into consideration previous cardiovascular or cerebrovascular events (2,3).

Standard treatment

ST patients (n = 78) (2,3) received a regimen that consisted of good general medical care and avoidance of excessive symptomatic hyperglycemia or hypoglycemia. Physicians were not informed of the HbA_{1c} levels for this group unless the value reached an alert range (12.9%) established as >2 SD of the mean of a random sample of 100 nonparticipating type 2 diabetic outpatients from the 5 VA medical centers.

ST patients were seen quarterly and were usually treated with 1 insulin injection/day, including long- or intermediate-acting insulin or mixtures of intermediate-acting and regular insulin. If patients were symptomatic or glycemic goals could not be attained, then a maximum of 2 injections/day could be prescribed. A total of 5 patients (6%) in this group took 2 injections/day. Home glucose monitoring was not mandatory, but ~70% of the patients in this group performed this activity once a day 3–7 times/week. Insulin doses were not changed according to glucose monitoring results.

Intensive treatment

The goal for this group (n = 75) was to achieve HbA_{1c} levels that were as close to the nondiabetic range as possible (5.05 ± 1%) (2,3). Home blood glucose monitoring was mandatory and was performed twice daily at variable times and once weekly at 3:00 A.M. Visits to the clinic to adjust glycemia were made monthly, and telephone calls for adjustment of glycemia were made once or twice weekly.

The patients were treated with a stepped regimen (2,3,7) that began with a bedtime dose of intermediate- or long-acting insulin (phase 1). The goal of morning fasting glycemia was a level within 80–150 mg/dl. After a 6-week trial, if a subsequent HbA_{1c} level was not reduced, then patients were moved into phase 2, which consisted of bedtime insulin plus daytime glipizide. If those goals were not met, then phase 3 consisted of 2 insulin injections/day without glipizide. Finally, phase 4 involved multiple daily injections of insulin.

Hypertension, dyslipidemia, smoking, and obesity were managed similarly in both groups in accordance with the guidelines available at the time of planning (8). All patients were similarly oriented to dietary, exercise, and smoking cessation programs.

Measurements of urinary albumin and creatinine

During the screening phase and then annually, a morning 3-h urine sample was obtained at each study center under the observation of the study coordinators.

Specimens were obtained and processed as follows. Patients maintained their dietary and medication schedule before the test and avoided strenuous activity on the day before the collection. On the morning of the collection, patients were instructed not to eat, exercise, or smoke. Patients voided, and 200 ml water was ingested to initiate a "0" time. All urine up to 3 h was collected, and the volume was recorded. No preservatives were added, and the urine was not acidified. Urine was mixed gently and frozen at −20°C for subsequent shipment to the central biochemical laboratory at the Edward Hines Jr. VA Medical Center (Hines, IL). Routine and microscopic urinalyses were performed in each hospital laboratory using a portion of the fresh urine.

Determinations of microalbuminuria were performed according to the method of Brodows et al. (9). This method uses a double antibody kit (Diagnostic Products Corp., Los Angeles, CA). Briefly, a standard curve using human albumin is set up for comparison of isotope counts with the unknown samples after precipitation with a second antibody (polyethylene glycol mixture). Basic analytical solutions include ^{125}I-albumin and 200 µl albumin antisera. Counting was performed in the antibody-bound fraction. Renal criteria that excluded patients from entering the study were 24-h urinary albumin levels >500 mg, an albumin:creatinine ratio of >0.5, or a serum creatinine level >1.6 mg/dl.

Blood pressure readings were determined at each visit. Standardized measurement guidelines were as previously described (10).

To define microalbuminuria, we used a ratio of albumin to creatinine (11–16). Microalbuminuria was indicated with a urinary albumin:creatinine ratio (both reported in milligrams per 100 ml) of 0.03–0.30. Overt nephropathy was defined as an albumin:creatinine ratio >0.30.

Renal end points in the intervention phase were a change in urine albumin:creatinine ratio from baseline or a change in creatinine clearance, serum creatinine, and blood pressure. Patient data were excluded from analysis if either baseline or follow-up specimens were missing or if hematuria was present. By using these criteria, at least 91% of all patients were included in the analysis.

Treatment for hypertension was similar in both groups and applied guidelines from multiple sources (8,11,12,16–18). Treatment of lipoprotein disorders was also similar in both groups (3).

Creatinine clearance was calculated according to the method of Cockcroft and Gault (19) as follows:

$$\frac{(140 - \text{age [years]})\ (\text{lean body weight [kg]})}{72 \times \text{serum creatinine (mg/dl)}}$$

where lean body weight = 50 kg + 2.3 kg/inch over 5 ft.

Statistical analysis

Comparison of baseline characteristics between patients entering the trial with and without microalbuminuria was done using the unpaired t test for quantitative variables and the χ^2 test for categorical variables. Changes in the albumin:creatinine ratio and in serum creatinine levels over time were assessed within therapy arms using the paired t test and between therapy arms using the unpaired t test. Comparison of therapy arms for the 24-month albuminuria category and for macrovascular events was done using the χ^2 test. Comparison of ST patients resistant to increases in urinary albumin and INT patients who progressed in microalbuminuria was done using the unpaired t test for quantitative variables and the χ^2 test for categorical variables. Changes over time in

Table 1—*Baseline characteristics: relationship to microalbuminuria*

	No microalbuminuria	Microalbuminuria	*P*
n	95	58	—
Age (years)	60.0 ± 0.7	60.3 ± 0.8	0.78
Known duration of diabetes (years)	7.6 ± 0.4	8.2 ± 0.5	0.32
Blood pressure (mmHg)			
Systolic	133.4 ± 1.5	138.3 ± 2.1	0.06
Diastolic	80.0 ± 0.8	82.3 ± 1.1	0.11
BMI	30.8 ± 0.5	31.2 ± 0.7	0.65
Recent history of			
Insulin therapy	61.0	56.9	0.61
Sulfonylurea therapy	51.6	50.0	0.85
Current smokers	11.6	27.6	0.01
Taking ACE inhibitors	23.2	32.8	0.19
Taking calcium-channel blockers	14.7	29.3	0.03
HbA_{1c}	9.2 ± 0.2	9.7 ± 0.2	0.08
Triglycerides (mg/dl)	180.5 ± 11.1	336.3 ± 111.6	0.17
Serum creatinine (mg/dl)	0.92 ± 0.02	0.94 ± 0.03	0.59
Cholesterol (mg/dl)	213.9 ± 4.7	239.5 ± 17.3	0.16
Urine albumin:creatinine ratio (mg/dl)	0.01 ± 0.0008	0.103 ± 0.01	0.0001
History of myocardial infarction	14.7	12.1	0.64
History of cerebrovascular accident	4.2	10.3	0.14

Data are means ± SEM for continuous variables or %. No microalbuminuria = urinary albumin:creatinine ratio <0.03; microalbuminuria = urinary albumin:creatinine ratio 0.03–0.3.

the percentage of patients taking ACE inhibitors or calcium-channel blockers were tested using the McNemar χ^2 test. All tests were performed 2-sided, and any *P* values ≤0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the groups

The presence of microalbuminuria at baseline was significantly associated with current smoking, use of calcium-channel blockers, and a trend toward higher systolic blood pressure levels (Table 1).

At baseline, for the entire cohort, the urinary albumin:creatinine ratio for the patients who were to be randomized to the INT group was 0.039 vs. 0.046 for those randomized to the ST group (*P* = 0.44). Creatinine clearance in the INT group was 86.6 ml/min and was 91.4 ml/min in the ST group (*P* = 0.23). At baseline in the INT group, 28 patients (37%) had microalbuminuria, and 47 patients did not. In the ST group, 30 patients (38%) had microalbuminuria, and 48 patients did not. Patients in ST and INT groups were well matched regarding other variables at baseline (2,3).

Effect of the intervention

As previously reported (3), patients in the ST group entered with HbA_{1c} and fasting blood glucose levels of 9.5 ± 0.2% and 227 ± 7.3 mg/dl, respectively. For the 24-month period of follow-up, these figures were essentially unchanged. The INT group had similar starting figures (9.3 ± 0.2% and 206 ± 6.8 mg/dl, respectively). However, the mean HbA_{1c} level for the INT group was significantly lower than that of the ST group from the third month and ≤7.3% from the sixth month onward (*P* < 0.001). At 24 months, the mean HbA_{1c} level was 7.1 ± 0.1% for the INT group (*P* < 0.001, entry versus final value). The mean HbA_{1c} for the ST group was 9.1% at 24 months (*P* = 0.0001 vs. INT).

Table 2 compares the change in albumin:creatinine ratio between both treatment groups divided into assigned glycemic control groups (INT versus ST). Significant differences existed between these groups with INT intervention retarding but not eliminating microalbuminuria progression. By 12 months, albuminuria in both groups had approximately doubled, and this increase was significant by paired analysis in the ST group. At 24 months, the albumin:creatinine ratio in the INT group remained at the level seen a year earlier, whereas the level in the ST group continued to rise to >4 times the basal level. The doubling at 2 years for the INT group was also significant. The increase in albumin:creatinine ratio from baseline to 24 months was significantly higher in the ST group than in the INT group (*P* = 0.043).

When data were analyzed regarding the presence versus absence of microalbuminuria at entrance into the study, further differences between the INT and ST regimens were observed. Figure 1 shows microalbuminuria data for the glycemic control groups at 12 and 24 months. In the subgroup entering without microalbuminuria, INT tended to retard the progress of microalbuminuria. After 1 year, the ST group had a mean increase in ratio of 0.041 (*P* = 0.02) and an increase of 0.09 at 2 years (*P* = 0.06). The increase was 0.015 in the INT group at 1 year (*P* = 0.02) and tended to be less at 2 years (ratio change = 0.045 vs. 0.090, respectively; *P* = 0.4). Thus, the no microalbuminuria group experienced an increased microalbuminuria ratio regardless of intensity of glycemic control, and this was significant at 1 year for both INT and ST interventions. A trend toward lessening of the rate of increase was observed in the INT group.

In patients entering with microalbuminuria, Fig. 1 demonstrates that INT clearly slowed the progress of microalbu-

Table 2—*Effect of the intervention for the entire cohort*

Therapy	*n*	Baseline	12 months	24 months	*P* for baseline vs. follow-up within treatment group	*P* for magnitude of changes (INT vs. ST)
INT	70	0.038 ± 0.006	0.090 ± 0.036	—	0.132	0.87
ST	74	0.042 ± 0.007	0.098 ± 0.020	—	0.0016	
INT	66	0.037 ± 0.006	—	0.083 ± 0.022	0.03	0.043
ST	74	0.042 ± 0.007	—	0.183 ± 0.044	0.0009	

Data are means ± SEM albumin:creatinine ratios. *n* indicates the number of patients who could be evaluated by paired *t* test because they had a baseline sample that was paired with another sample at the indicated time.

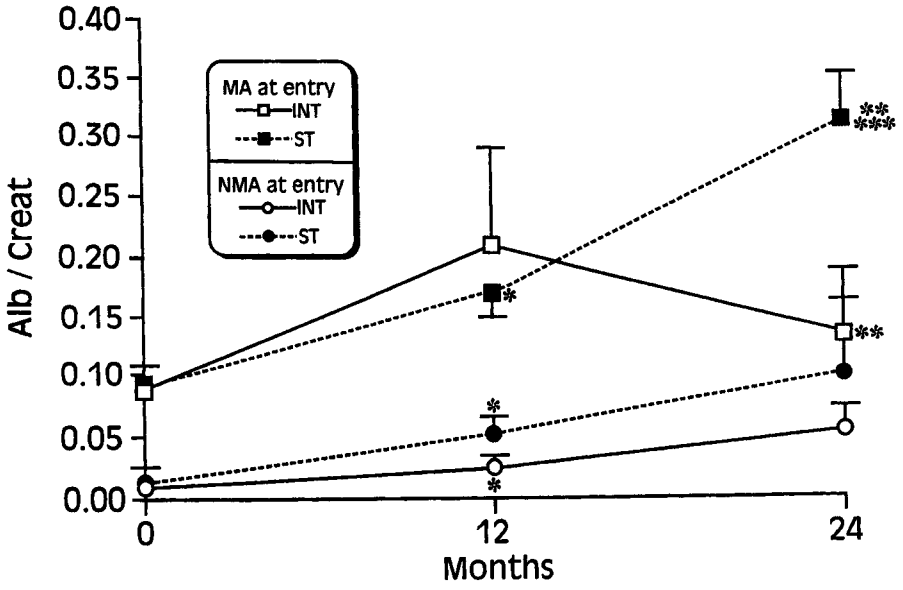

Figure 1—*Effect of glycemic control on microalbuminuria (MA) with the entire cohort divided into 4 subgroups: microalbuminuria at entry, no microalbuminuria (NMA) at entry, INT, and ST. The number of patients at each interval differed slightly based on the availability of both basal and sequential specimens at that interval. At 12 months: NMA/INT,* n = *44; ST,* n = *46; MA/INT,* n = *26; ST,* n = *28; NMA/INT,* n = *42; and ST,* n = *46. At 24 months: MA/INT,* n = *42; ST,* n = *46; MA/INT,* n = *24; and ST,* n = *28. Reasons for exclusion of specimens for analysis included hematuria and inadequate collection.* *P = *0.02 by paired* t *test;* **P = *0.048 by unpaired* t *test;* ***P = *0.006 by paired* t *test. (Paired* t *test represents comparison with entry value.) Alb/Creat, albumin:creatinine ratio.*

minuria. At 1 year, the microalbuminuria had almost doubled for the ST group (P = 0.03) and tripled at 2 years (P = 0.006). In contrast, the INT group showed a trend toward an increase at 12 months, but by 2 years, their mean values had returned to entry level in this subgroup.

In the group entering without microalbuminuria, 35 patients (83%) in the INT subgroup remained without microalbuminuria at 24 months. However, in the ST subgroup, 30 patients (65%) had deteriorated to microalbuminuria or worse. This difference was significant (P = 0.05).

For the group entering with microalbuminuria, 7 patients (29%) from the INT subgroup and 10 patients from the ST subgroup were without microalbuminuria at 24 months (NS). Three patients (12%) in the INT subgroup and 10 patients (36%) in the ST subgroup had progressed to overt nephropathy (ratio >0.3) (P = 0.04).

Blood pressure control

By using appropriate treatment (3,5) for blood pressure, systolic blood pressure was kept similar to entry level in patients entering the study without microalbuminuria (baseline 132 ± 3 to 135 ± 3 mmHg at 24 months in the ST group and baseline 132 ± 3 to 134 ± 3 mmHg at 24 months in the INT group). This was also true for those entering the study with microalbuminuria who were in the INT group (140 ± 3 mmHg at baseline and 140 ± 3 mmHg at 24 months). However, the ST microalbuminuria group had a small but significant increase from 135 ± 3 mmHg at baseline to 142 ± 4 mmHg at 24 months (P = 0.01).

Diastolic blood pressure throughout the study did not differ among the groups. With appropriate therapy, it was in the low 80s at 24 months.

Table 3 indicates that a considerable number of patients throughout the study were taking medications used for hypertension control. ACE inhibitors were the most frequent single class, although a considerable number of patients took calcium-channel blockers, and a small number of patients took a combination of these 2 drugs. A total of 29 patients took diuretics regularly. Thus, no difference was evident between the treatment groups in antihypertensive medication administration. However, when combining ST and INT groups, 31.8% (28 of 88) of patients with no microalbuminuria at entry were taking ACE inhibitors at 24 months, whereas 52.8% (28 of 53) of patients with microalbuminuria at entry were taking ACE inhibitors at 24 months (P = 0.00006).

Creatinine and creatinine clearance

At 24 months, the serum creatinine levels in the group that did not have microalbuminuria at study entry did not rise to >1.5 mg/dl for any patients. At 24 months, for those entering with microalbuminuria, this degree of serum creatinine was reached in 2 patients in the INT group and 2 patients in the ST group. Table 4 shows that all 4 groups had significant increases in serum creatinine by 24 months. Despite increased serum creatinine in all 4 subgroups, only the group entering with microalbuminuria had a significant reduction in creatinine clearance at 2 years. Figure 2 demonstrates

Table 3—*Medication for blood pressure*

	Patients taking ACE inhibitors (%)	Patients taking calcium-channel blockers (%)
No microalbuminuria at entry		
ST		
Baseline	27.1	14.6
24 months	34.8	19.6
INT		
Baseline	19.2	14.9
24 months	28.6	21.4
Microalbuminuria at entry		
ST		
Baseline	30.0	30.0
24 months	53.6	32.1
INT		
Baseline	35.7	28.6
24 months	52.0	36.0

Table 4—*Serum creatinine*

	n	Baseline (mg/dl)	24 months (mg/dl)	*P*
Entering without microalbuminuria (ratio <0.03)				
INT	42	0.92 ± 0.03	1.00 ± 0.03	0.013
ST	46	0.90 ± 0.03	0.97 ± 0.03	0.024
Entering with microalbuminuria (ratio 0.03–0.3)				
INT	24	0.96 ± 0.05	1.16 ± 0.07	0.0006
ST	28	0.90 ± 0.04	1.04 ± 0.05	0.0019

Data are means ± SEM.

that the INT/no microalbuminuria group had a 5% reduction ($P = 0.18$), and clearance in the ST subgroup fell 8% ($P = 0.065$). In contrast, the group entering with microalbuminuria had a 17 and 12% reduction of creatinine clearance in the INT and ST groups, respectively—both of which reflect a significant fall. Smokers and nonsmokers in the microalbuminuria group had reductions in creatinine clearance that equaled ~12 ml/min during the 2 years.

Macrovascular events

Table 5 indicates macrovascular events related to baseline microalbuminuria and treatment group. In the group without microalbuminuria at entry, significantly fewer macrovascular events were evident in the ST group versus the INT group. In subjects entering with microalbuminuria, about one-fourth underwent at least 1 of these events regardless of intensity of glycemic therapy.

CONCLUSIONS — The main purpose of the first 3 years of this study was to examine whether intervention with insulin could result in successful intensive glycemic control in half of the patients participating in the study. This goal was achieved (3). As another essential part of the study, we obtained data assessing the progress of eye (4), neurological (20), macrovascular (5), and renal disease. The current study, in which completed data for 2 years are available, focused on renal disease.

We found in these patients, who were mostly obese (3) and who had failed to maintain normal glycemia with oral hypoglycemic therapy (sulfonylureas) and nonintensive insulin regimens, that intensive glycemic control retards the progression of microalbuminuria. Reduction of microalbuminuria was most pronounced at 24 months in the subgroup that entered with microalbuminuria and was randomized to INT. In patients who were microalbuminuric when they entered the study, creatinine clearance deteriorated during the 2-year period, regardless of whether microalbuminuria was retarded.

Other studies of patients with type 1 (21) and type 2 (22) diabetes have also shown that intensive glycemic control slows the progression of microalbuminuria. For the Diabetes Control and Complications Trial, in which the criteria for microalbuminuria based on a 4-h collection was an albumin excretion rate of >28 µg/min (21,23), only 75 patients (5%) in the entire 1,441-patient cohort entered with microalbuminuria. A total of 73 of these patients were in the secondary prevention cohort (715 patients), in which mean duration was slightly <9 years. In the present study, 38% of subjects entered with microalbuminuria. In the study by Ohkubo et al. (22), the percentage of patients with microalbuminuria at entry in the combined cohort was not specifically reported but appeared to be quite low. Thus, even in the secondary intervention group (mean duration of diabetes 10 years), which had the highest cumulative percentage of patients developing a progression of microalbuminuria, 30% developed such progression at the end of 6 years of observation. In our study in Western patients with type 2 diabetes, even with an equivalent duration of disease, microalbuminuria was present in a greater proportion of patients than other populations studied prospectively for effects of glycemic control. Nevertheless, we found that the progression of microalbuminuria is ameliorated by INT in those patients who have it at entry. The high frequency of complications in type 2 diabetes, even at diagnosis, is apparent: the UKPDS reported 18% microalbuminuria at entry (24). Studies in type 2 diabetes, therefore, will often evaluate the effects of interventions on complications that are already evident.

Intensive glycemic control was associated with less worsening of microalbuminuric categories. On the other hand, about one-third of our patients with microalbuminuria at entry moved into nonmicroalbuminuric status at 24 months regardless

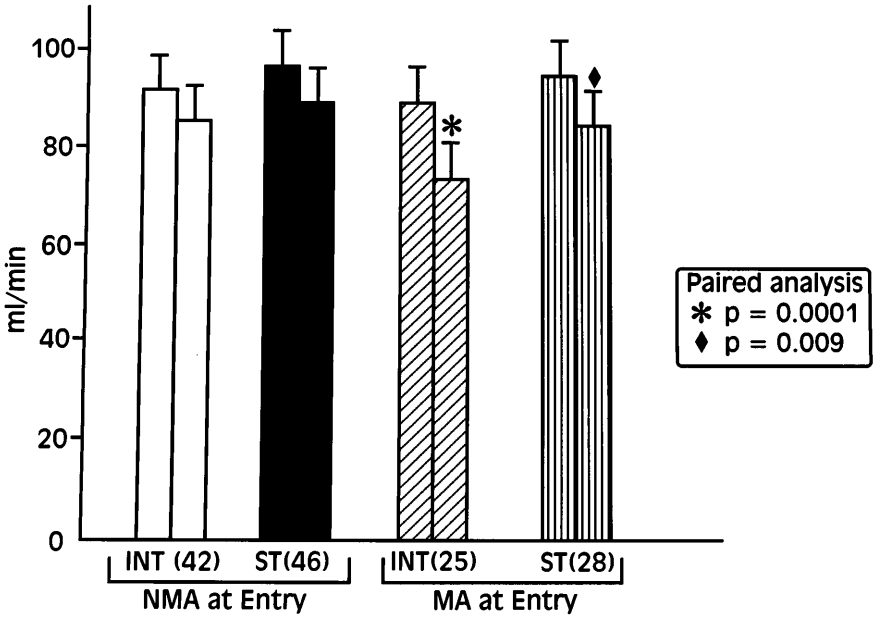

Figure 2—*Creatinine clearance at baseline and after 24 months. Numbers in parentheses indicate the number of patients in subgroups. MA, microalbuminuria; NMA, no microalbuminuria.*

Table 5—*Macrovascular events*

	With event	Total patients
No microalbuminuria at entry (ratio <0.03)		
INT	17 (36.2)*	47
ST	8 (16.7)	48
Microalbuminuria at entry (ratio 0.03–0.3)		
INT	7 (25)	28
ST	8 (26.7)	30

Data are *n* (%) or *n*. Macrovascular events included myocardial infarction, stroke, congestive heart failure, amputation for gangrene, cardiovascular death, coronary artery bypass graft, coronary angioplasty, transient ischemic attack, ischemic ulcer, and new intermittent claudication. *P = 0.03, INT vs. ST.

of the intensity of glycemic control. In addition to day-to-day variations in individuals, multiple factors that influence albumin in the urine may account for this improvement (e.g., control of preexisting hypertension during the study and improvement of glycemia in some individuals in the ST group) (3,5,25).

The reason for the greater deterioration in creatinine clearance in the microalbuminuria subgroup compared with the nonmicroalbuminuria subgroup, regardless of intensity of glycemic treatment, is not clear. The method we used to calculate creatinine clearance compares reasonably with that which uses urinary creatinine concentration as a measure of the glomerular filtration rate (26). Although creatinine clearance may be reduced in extreme aging (26), the degree of deterioration in our patients with >7 years of type 2 diabetes is greater than that which would be seen as a result of aging during a 2-year period (15,27) or to differences in ACE inhibitor usage. At baseline, significantly more smokers were in the microalbuminuria group. Smoking has been shown to accelerate a decline in glomerular filtration rate and to promote the progression of nephropathy in type 2 diabetes (28). This could be a possible explanation for the greater decline in the microalbuminuria group compared with the nonmicroalbuminuria group. However, we were unable to see a predominance in the fall in creatinine clearance in the smoking versus nonsmoking patients who entered with microalbuminuria during the 2-year observation period.

In contrast with the UKPDS, which incorporated an intensive and nonintensive blood pressure control policy (29), all of our patients were included in an attempt to bring blood pressure within recommended guidelines (3). This was done to focus on the effects of glycemic control. Blood pressure (and lipids) did not differ between the groups, and mean systolic and diastolic values met standards established more recently (25). Elevated systolic blood pressure may contribute to the decline in glomerular filtration rate (30). The subgroup with microalbuminuria that was randomized to ST did have a slightly higher but significant rise in systolic blood pressure during the study. However, the INT patients in this subgroup also had a deterioration in creatinine clearance without a change in systolic blood pressure throughout the 24 months. Recently, genetic determinants of microalbuminuria have been implicated (31), and these could be linked to greater susceptibility to renal damage.

ACE inhibitors can also arrest the progression of renal dysfunction and albuminuria in type 2 diabetes (32,33). We found no difference in the usage of ACE inhibitors or calcium-channel blockers among the groups at 2 years. However, the effects of euglycemia and ACE inhibitors may be at least additive.

The study by Ohkubo et al. (22) found that intensive glycemic control ameliorated the progression of stages of nephropathy. However, they excluded patients with hypertension and abnormal lipid values. Their patients were lean and insulin sensitive. Our present study represents typical North American patients with type 2 diabetes. Most patients were obese (3) and insulin resistant. At baseline, about half of our patients had been treated for hypertension (3), which was defined at the time of the planning phase of the study as >140/90 mmHg (2). At the end of the 2 years, blood pressure was controlled in most patients, two-thirds of whom were treated for hypertension. Average systolic and diastolic blood pressures at the end of the 2 years were within recommended limits (3) and were not different in the INT and ST groups. Hypertension could not have accounted for the progression of albuminuria in the groups even though systolic blood pressure was slightly but significantly increased during the 24 months in the ST group with baseline microalbuminuria.

A recent overview of many aspects of microalbuminuria in type 2 diabetes summarizes several aspects of the presence of microalbuminuria as predictive of macrovascular events (34). Our group with microalbuminuria had ~25% of such events during the relatively brief 2-year duration of this study. Our data demonstrated an unexpected finding: use of insulin alone to achieve intensive glycemic control was associated with more episodes involving large vessels in subjects who entered without microalbuminuria. This occurred despite comparable blood pressure, triglyceride, and LDL cholesterol levels in INT and ST groups (3). We have previously found that, when entering any baseline cardiovascular abnormality into the analysis, a regression model indicated a lower HbA_{1c} level before the event as the only correlate for new cardiovascular events (5). In considering INT and macrovascular disease, our overall findings included a nonsignificant excess of nonfatal cardiovascular events in the INT group and a borderline correlation of new cardiovascular events with lower attained HbA_{1c} levels (35). In contrast, Kuusisto et al. (36) demonstrated a correlation between glycemia and coronary artery disease; however, <10% of their patients used insulin.

Researchers believe that the effect of high endogenous or exogenous insulin levels on macrovascular disease needs to be more fully examined (37,38). Large doses of insulin were used to attain the levels of control described in our patients. At the end of the study, 64% of the INT patients were receiving ≥2 insulin injections/day with a mean insulin dosage of almost 100 U/day (3,7). One potentially adverse effect of INT on macrovascular outcomes in our patients is a significant rise in fibrinogen levels after 1 year that returned to baseline at 2 years (39). This and other factors could produce early worsening of macrovascular diseases as observed for microvascular events in the Diabetes Control and Complications Trial (40).

The UKPDS has demonstrated that intensive control of glycemia improves health status in type 2 diabetic patients observed for up to 20 years (1,41). Overall, the study indicated that intensive glycemic control with sulfonylureas or insulin reduced the risk of microvascular but not

macrovascular complications. Thus, the issue of which therapeutic strategies are most beneficial in terms of macrovascular disease remains unsettled (42).

Several differences were evident between the UKPDS and our study. In our study, no patients entered with newly diagnosed diabetes, and the patients were older. Most patients were obese, and lipids and blood pressure were controlled to a normal mean and equal in both of our groups (3), which allowed us to focus on the effects of glycemia. All patients were at a stage when oral hypoglycemic agents no longer controlled their glycemia. Our patients had a requirement for higher insulin doses, even in the ST control group, when compared with insulin-receiving overweight patients in the UKPDS. On initiation and at 2 years, all of our patients took insulin, and 23% (17 patients) took insulin in combination with a sulfonylurea (glipizide) in the INT group (3). The UKPDS INT group took 20–50% less insulin on a weight basis than did our group. Despite these differences, INT, especially with insulin, did not protect against or reverse macrovascular outcomes (1).

In future studies examining whether intensive glycemic control prevents complications of type 2 diabetes in patients who require exogenous insulin, combining insulin with drugs that enhance insulin action and spare the dosage of insulin may provide information about optimal ways to minimize both microvascular and macrovascular disease (43).

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APPENDIX — The following individuals and institutions participated in the VA Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial. Study Chairman's Office, Edward Hines Jr. VA Hospital: Study Chairman Carlos Abraira, MD, and Study Administrator Hae Sook Lee, BA. Boston, MA, VA Medical Center: Principal Investigator Clark T. Sawin, MD; Co-Investigator Cynthia K. Silbert, MD; and Nurse Coordinator Roberta Cxypoliski, RN, MEd. Edward Hines Jr. VA Medical Center, Hines, IL: Principal Investigator Nicholas V. Emanuele, MD, and Nurse Coordinator Diane Keman, RN, BSN. Houston, TX, VA Medical Center: Principal Investigator John P. Comstock, MD, and Nurse Coordinator Mirian Vazquez, RN. Minneapolis, MN, VA Medical Center: Principal Investigator Frank Q. Nuttall, MD, PhD; Co-Investigator Catherine Niewoehner, MD; and Nurse Coordinator Marie Backes, RN. West Los Angeles VA Medical Center, CA: Principal Investigator Seymour R. Levin, MD; Co-Investigator Mark Bradley, MD; and Nurse Coordinator Micheline Bradley, RN, CDE. Data Monitoring Board: Chairman F. John Service, MD, PhD; Barbara Howard, PhD; Emily Chew, MD; Byron Hoogwerf, MD; and Daniel Seigel, ScD. Policy Advisory Board: Charles M. Clark, Jr., MD; Jerrold M. Olefsky, MD; Daniel Porte, Jr., MD; and Karl F. Sussman, MD. Hines, IL, VA Cooperative Studies Program Coordinating Center: William G. Henderson, PhD, Director; Barbara Christine and Kelly Tir. Cooperative Studies Central Research Pharmacy, Albuquerque, NM: Research Pharmacists Chief Mike Sather, MS; Philip Day, MS, RPh; and Nancy Morgan, MS, RPh. VA Headquarters: Chief of the Cooperative Studies Program John Feussner, MD; Staff Assistant Ping Huang, PhD; and Program Analyst Joe Gough, MA.

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