

Rise in Albuminuria and Blood Pressure in Patients Who Progressed to Diabetic Nephropathy in the Diabetes Control and Complications Trial

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Abstract. The Diabetes Control and Complications Trial (DCCT) enrolled 1441 participants to address the role of intensive therapy for type 1 diabetes mellitus on the onset and progression of microvascular complications. To examine the timing of elevated systolic BP (SBP) and diastolic BP (DBP) and increased albumin excretion rate (AER) in the progression to clinical diabetic nephropathy (AER > 300 mg/24 h on two consecutive visits from a baseline of <100 mg/24 h) and, importantly, to control for initial values of hemoglobin A_{1c}, a retrospective case-control study was assembled from the records of the publicly released DCCT data. Participants who progressed to clinical diabetic nephropathy—progressors—were matched with participants of the same gender and treatment group who had similar baseline values for DBP, SBP, AER and hemoglobin A_{1c}, but who did not progress to clinical diabetic nephropathy—matched controls. In the conventional treatment group, the 21 progressors exhibited a significant rise

in mean AER (above their own baseline levels and above values in the matched controls) at year 2 of the DCCT. In contrast, the progressors' mean DBP and SBP were not significantly higher than baseline until year 3 (DBP) or year 4 (SBP) and not significantly higher than the matched controls until year 4 (both DBP and SBP). On the individual level, 19 of 21 (90%) progressors reached clinical diabetic nephropathy before the diagnosis of hypertension (140/90 mmHg). In the intensive treatment group, however, the rise in DBP preceded the rise in AER by 1 to 2 yr among the six progressors. Both intensively treated progressors who experienced hypertension reached this before AER > 300 mg/24 h. These results underline the early and prognostic rise in AER in diabetic patients, but only in those who received conventional treatment. The evolution of diabetic renal disease may follow a different course in patients who receive intensive diabetic treatment.

The Diabetes Control and Complications Trial (DCCT) demonstrated the effectiveness of intensive management of type 1 diabetes mellitus in preventing or ameliorating the microvascular and neurologic complications of the disease (1). To monitor progress toward diabetic nephropathy, the DCCT Research Group measured albumin excretion rate (AER) and creatinine clearance yearly, BP quarterly, and GFR two or three times in the course of the trial (2–4). However, the DCCT was designed to address primarily the efficacy of glycemic control on diabetic retinopathy (5). Thus, there was only modest power to evaluate its effects on the development of clinical diabetic nephropathy, *e.g.*, AER > 300 mg/24 h, because the participants' durations of diabetes mellitus were generally too brief. As a result, the DCCT Research Group found no differences between treatment groups for systolic

(SBP) or diastolic BP (DBP), creatinine clearance, or GFR (4). Nevertheless, the relative risk of microalbuminuria at several different levels, regarded as a harbinger of clinical diabetic nephropathy (6–8), was consistently reduced by about 50% in the intensive treatment group (4).

Advances in therapy directed specifically toward diabetic nephropathy, such as angiotensin-converting enzyme inhibitors, permit effective intervention in the course of nephropathy (9,10) and heighten interest in possible predictive and predisposing factors, such as a rising or elevated BP or AER (7,8). However, the DCCT failed to show a significant difference in mean BP between treatment groups, perhaps because fewer than 5% of participants progressed to hypertension (2–4).

Mathiesen *et al.* (11) reported that an increase in mean AER preceded an increase in mean DBP in a group of type 1 diabetic patients who were receiving conventional therapy and progressed to AER >30 mg/24 h. However, this conclusion was drawn from a group of patients who started the study with significantly higher baseline AER and hemoglobin A_{1c} (HbA_{1c}) levels than the remainder of the participants. Thus, the subgroup that showed the early rise in AER started with significantly higher values for both AER and HbA_{1c}, so the effects of higher HbA_{1c} confounded the higher initial levels of AER.

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We examined these questions in a retrospective, case-control study from the publicly released DCCT data. We identified participants who progressed to clinical diabetic nephropathy (AER >300 mg/24 h on two successive annual measurements from a baseline <100 mg/24 h) and matched them with participants of the same gender and treatment group who had similar baseline values for DBP, SBP, AER, and, importantly, HbA_{1c} but who did not progress to clinical diabetic nephropathy. This allowed comparisons over 6 yr of the AER and BP trajectories of those who progressed to clinical diabetic nephropathy with similar participants who did not. In addition to assessing mean behavior, we examined the order in which individuals crossed thresholds of hypertension and AER >300 mg/24 h.

Materials and Methods

Data

This study used the publicly released data sets from the final nephropathy, retinopathy, and neuropathy manuscripts of the DCCT Research Group (4,5,12) and the comprehensive publicly released data set. The study design and methods of the DCCT have been reported previously (1–5). These data sets include baseline and up to nine annual measurements/summaries of AER, HbA_{1c}, baseline and poststimulation c-peptide levels, DBP and SBP, grades for retinopathy, and demographic information for the 1441 participants in the DCCT. Because many patients participated fewer than 9 yr in the DCCT, we report values through 6 yr to provide sufficient numbers of observations for valid comparisons among the patients.

DCCT Measurements

Procedures used in the DCCT to measure BP, AER, HbA_{1c}, and other factors have been summarized previously (1–4,13). Briefly, SBP and DBP were measured with a random-zero sphygmomanometer twice in a sitting position at quarterly visits in the clinic. Recorded BP was used in all analyses whether or not the subject was treated for hypertension. With a 4-hr collection of urine, AER was determined annually by a fluorescence immunoassay and expressed in milligrams per 24 h (4,13). HbA_{1c} was measured by HPLC, quarterly in participants in the conventional treatment group and monthly for those in the intensive treatment group (1,2). Retinopathy was evaluated twice yearly with stereo fundus photographs graded by a modification of the Early Treatment Diabetic Retinopathy Study scale (1,2,5). A neuropathy classification was given to each participant, based on a combination of neural function tests and a carefully administered questionnaire (12). Finally, several anthropomorphic measurements were completed annually (percentage of ideal body weight and body mass index), with others (natural waist-to-hip ratio and iliac waist-to-hip ratio) measured only at closeout of the study. Because the more rapid growth during puberty may affect these parameters, values were separately compared in the DCCT participants who were older than 17 yr at entry.

Patients

There were 1441 participants in the DCCT: 711 in the intensive treatment group and 730 in the conventional treatment group. Because of the transient increase in AER during pregnancy, all participants who became pregnant during their participation in the DCCT were omitted from this analysis, leaving 617 in the intensive treatment group and 644 in the standard treatment group, for a total of 1261. Participants were treated for hypertension when DBP exceeded 90

mmHg and/or SBP exceeded 140 mmHg on two consecutive readings 1 mo apart (2). The annual visit when hypertension was first diagnosed was recorded in the DCCT database.

Selection of Progressors and Matched Control Subjects

DCCT participants who progressed to clinical diabetic nephropathy—progressors—were identified by the DCCT criteria: AER > 300 mg/24 h on at least two consecutive visits as designated in the DCCT database (NPH5PFLG) with the first annual visit when clinical diabetic nephropathy began. We included only progressors whose baseline AER was <100 mg/24 h. There were 6 progressors in the intensively treated group and 21 in the conventional group.

A matched control participant was selected for each progressor by the following criteria: match the progressor's gender and DCCT treatment group, within 10% of the progressor's baseline AER, and within 2 mmHg of the progressor's baseline DBP. Among nonprogressors who satisfied these four criteria, the nonprogressor with baseline HbA_{1c} closest to the progressor was selected as the matched control.

Statistical Analyses

The progressors and matched control subjects were compared with the remainder of their treatment group with respect to continuous variables by two-sample *t* tests or χ^2 tests for proportions. Paired *t* tests and McNemar's test were used to compare progressors to matched controls and to compare both groups to their own baseline values. All comparisons were first completed on data summarized on an annual basis. In all analyses, AER was transformed to the logarithmic scale to correct for marked skewness. Medians and ranges for AER are shown on the original scale (mg/24 h), but listed *P* values derive from analysis of means on the logarithmic scale.

Results

Baseline values for AER, DBP and SBP, HbA_{1c}, gender, and other factors were similar for progressors and matched control subjects (Table 1), reflecting effective matching. Baseline comparisons among progressors, matched control subjects, and the remaining participants (excluding those who became pregnant during the trial) demonstrated the following: In both conventional and intensive treatment groups, progressors experienced a longer duration of diabetes mellitus and a higher incidence of mild retinopathy. In both treatment groups, progressors and matched control subjects together had higher AER (more than double the value of the remainder of their group) and lower levels of stimulated c-peptide. In the conventional treatment group, 8 of 21 progressors and 8 of 21 matched control subjects had baseline values of AER >30 but <100 mg/24 h. Similarly, two of six progressors and two of six matched control subjects in the intensive treatment group had baseline values of AER >30 but <100 mg/24 h. In the conventional treatment group, progressors and matched control subjects had higher HbA_{1c} levels and higher rates of neuropathy than the remainder of the group. There were no significant differences in mean age, racial composition, or mean percentage of ideal body weight among the subgroups.

For the conventional treatment group, Figure 1 shows mean levels of AER, DBP, SBP, and HbA_{1c} for the progressors, matched control subjects, and the rest of the participants during the first 6 yr of the DCCT. Figure 1 indicates significant

Table 1. Summary of baseline values for the progressors, matched control subjects, and the remaining members of both DCCT standard and intensive therapy groups who did not become pregnant during the DCCT^a

Parameter	DCCT Standard Therapy Group			DCCT Intensive Therapy Group		
	Progressors	Matched Controls	Remainder	Progressors	Matched Controls	Remainder
Number	21	21	602	6	6	605
Age	26 (7)	28 (8)	27 (7)	21 (7)	28 (3)	28 (7)
Female <i>n</i> (%) ^b	7 (33%)	7 (33%)	235 (39%)	2 (33%)	2 (33%)	247 (41%)
Nonwhite <i>n</i> (%)	0 (0%)	1 (5%)	21 (3.5%)	1 (17%)	0 (0%)	19 (3.1%)
IDDM duration (yr)	9.4 (3) ^c	6.5 (4) ^d	5.1 (4) ^d	9.4 (3) ^c	8.6 (6) ^{cd}	5.7 (4) ^d
Diastolic BP mmHg ^b	76 (8)	76 (8)	73 (9)	72 (7)	71 (5)	73 (8)
Systolic BP mmHg	117 (10)	115 (9)	115 (12)	107 (11)	116 (8)	115 (11)
Albumin excretion mg/24 hr ^b	23 (1–59) ^c	22 (3–79) ^c	10 (1–287) ^d	17 (14–98) ^c	17 (14–71) ^c	10 (1–187) ^d
Hemoglobin A _{1c} ^b	10.3 (1.4) ^c	9.8 (1.7) ^c	8.8 (1.6) ^d	10.0 (1.1)	9.7 (0.9)	8.8 (1.5)
Stimulated C-peptide	0.05 (.06) ^c	0.07 (.09) ^c	0.12 (.12) ^d	0.04 (.02) ^c	0.04 (.02) ^c	0.11 (.12) ^d
Percent ideal body weight	102 (15)	107 (16)	105 (13)	95 (8)	110 (19)	104 (12)
Body mass index	23.3 (3)	24.2 (3)	23.7 (3)	22.8 (2)	25.0 (4)	23.4 (3)
Retinopathy status						
none <i>n</i> (%)	2 (10%) ^c	10 (48%) ^d	331 (55%) ^d	1 (17%) ^c	2 (33%) ^d	296 (49%) ^d
mild <i>n</i> (%)	19 (90%) ^c	11 (52%) ^d	271 (45%) ^d	5 (83%) ^c	4 (67%) ^d	309 (51%) ^d
Neuropathy status (clinical diagnosis)						
none <i>n</i> (%)	10 (48%) ^c	13 (62%) ^d	414 (69%) ^d	2 (33%) ^c	4 (67%) ^d	413 (69%) ^d
possible <i>n</i> (%)	6 (29%)	4 (19%)	140 (23%)	0 (0%)	2 (33%)	126 (21%)
definite <i>n</i> (%)	5 (24%) ^c	4 (19%) ^c	46 (8%) ^d	4 (67%) ^c	0 (0%) ^d	63 (10%) ^d

^a The numbers are given as mean (standard deviation), or frequency (percent) indicated by *n* (%); albumin excretion is given as median (range). IDDM, insulin-dependent diabetes mellitus.

^b Basis of matching between progressors and matched control subjects.

^{c,d} Where group means or percentage differ significantly (*P* < 0.05), the groups with the same letter are indistinguishable; where there are no letters, none of the means are significantly different. Comparisons are within DCCT therapy groups.

differences between pairs of the three subgroups at each year of the DCCT and also identifies the years in which progressors and matched control subjects were significantly different from their respective baseline values for AER, DBP, SBP, and HbA_{1c}. The progressors' mean AER at year 2 was significantly above their own baseline, as well as the matched control subjects, and continued to rise for the duration of the study. In contrast, the progressors' mean DBP and SBP levels reached a significant increase over their baseline values only at years 3 and 4, respectively, and they were not significantly higher than the matched control subjects until year 4. Thus, on average, the conventional therapy progressors' rise in AER preceded the rise in DBP by 1 to 2 yr and SBP by 2 yr. Among the matched control subjects, mean AER and DBP remained essentially constant throughout the study, with no significant increases above baseline mean values. In fact, the matched control subjects' mean AER fell significantly below baseline at year 2.

We also examined the priority of increases in AER and DBP in individual records of progressors and matched controls. Numbers of participants who were first diagnosed with hypertension or first experienced AER > 300 mg/24 h are given in Table 2. In the conventional treatment group, 7 (33%) progressors reached AER > 300 mg/24 h with no hypertension, 12 (57%) progressors experienced AER > 300 mg/24 h before

hypertension, and only 2 (10%) progressors reached hypertension before AER > 300 mg/24 h. Altogether, 19 (90%) progressors in total demonstrated AER > 300 mg/24 h before hypertension.

Regarding the intensive treatment group, Figure 2 shows mean AER, DBP, SBP, and HbA_{1c} for the progressors, matched control subjects, and the rest of the participants in the same format as Figure 1. The order of significant increases in mean AER and DBP was reversed from that in the conventional treatment group: An increase in DBP at year 2 was followed in year 3 by a rise in AER above baseline levels. Importantly, these were also the points when the levels for the intensively treated progressors were first significantly higher than their matched control subjects. There were no differences in SBP until year 6. The increase and variability in DBP were consistent among the six progressors: Five of six experienced increases in DBP of 10 to 20 mmHg between years 1 and 2. The progressors' early spike in DBP did not reach the level indicating hypertension; only two of six (33%) progressors reached hypertension before AER > 300 mg/24 h, as shown in Table 2. No matched control subjects received a diagnosis of hypertension in the intensive treatment group.

Comparing progressors in the conventional and intensive treatment groups, mean AER during the DCCT was indistin-

Table 2. Numbers and percentages of participants among progressors and matched control subjects who first experienced AER > 300 mg/24 h at two consecutive annual visits (persistent nephropathy) were first diagnosed with hypertension or experienced neither event. There were no ties.^a

Therapy	Progressors	Matched Controls
Conventional		
AER > 300 mg/24 h first	19 (90%)	None by selection
hypertension diagnosis first	2 (10%)	3 (15%)
neither event	0	18 (85%)
Intensive		
AER > 300 mg/24 h first	4 (67%)	None by selection
hypertension diagnosis first	2 (33%)	0
neither event	0	6 (100%)

^a Difference in percentage reaching AER >300 mg/24 h before the diagnosis of hypertension among conventional treatment progressors (90%) versus intensive treatment progressors (67%) was not significant ($P = 0.148$).

guishable; however, the intensively treated progressors had significantly higher DBP in year 2 ($P = 0.027$). In both treatment groups, the progressors showed consistently poorer glycemic control. In the conventional treatment group, the progressors' mean HbA_{1c} remained approximately 1% higher than corresponding values for their matched control subjects and the remainder of the treatment group from years 1 through 5 (Figure 1) and never decreased significantly from baseline. A similar pattern occurred in the intensive treatment group during years 1 through 3 (Figure 2). Mean HbA_{1c} in both intensive treatment progressors and matched control subjects fell significantly from baseline after 1 yr, yet both remained higher, on average, than the remainder of the intensive treatment group throughout the study (Figure 2).

In both treatment groups, progressors, matched control subjects, and the remaining participants all experienced substantial increases in percentage of ideal body weight and body mass index from baseline to DCCT year 6, as shown in Tables 1 and 3. However, there were no significant differences among the groups either at baseline or at year 6. Natural and iliac waist-to-hip ratios were measured only at the end of the DCCT; the groups were indistinguishable (Table 3). Although the pubertal increase in growth may affect these measures, the groups were still indistinguishable after omitting participants who were younger than 18 yr at baseline. Finally, comparing intensive progressors versus matched control subjects, there were no differences for family history of diabetic nephropathy or of hypertension, and there were no differences for current or past record of smoking.

As noted above, there were significantly more progressors than matched control subjects with mild retinopathy at baseline. Among the conventional treatment progressor-matched control pairs, in 8 of the 21 pairs, the progressor had mild

retinopathy at baseline and the matched control subject had none; there was only one such pair of six in the intensive treatment group.

Discussion

These analyses demonstrated a marked increase in AER before an increase in DBP and SBP, but only in the conventional treatment group. Because most diabetic patients (both types 1 and 2) achieve glycemic control no better than that in the DCCT conventional treatment group, these results will apply to many diabetic patients. Surprisingly, the relationship between rising AER and DBP in the intensive treatment group was reversed, although present in fewer DCCT participants. Nevertheless, sustained efforts to improve glycemic control in diabetic patients may increase the proportion who confront a different pattern of response to insulin treatment, *i.e.*, weight gain and the possibility of an early increase in BP.

Many studies that examined changes in AER in types 1 or 2 diabetes mellitus have been unable to eliminate the differences in glycemic control among normo-, micro-, and macroalbuminuric participants (11,18–23). Of particular importance to the present study, Mathiesen *et al.* (11) observed significantly lower baseline HbA_{1c} differences of 8.5% versus 9.6% in patients who remained normoalbuminuric, compared with those who progressed to microalbuminuria in their study. Thus, initial differences in HbA_{1c} and AER may have influenced the outcome. Therefore, we strove to eliminate these confounding factors in our retrospective case-control study, the conclusions of which extend the findings of Mathiesen *et al.* (11). Despite the care in matching control subjects for the progressors, there were several important differences among the progressors, matched control subjects, and the remaining study participants, as well as between treatment groups. In both treatment groups, progressors had longer duration of type 1 diabetes mellitus and a higher incidence of mild retinopathy. It was not possible to match progressors and controls for all characteristics, *e.g.*, duration of diabetes mellitus and stimulated c-peptide levels, that may affect the progression of diabetic nephropathy.

That only 30% as many participants progressed to AER > 300 mg/24 h in the intensive treatment group suggests that strict glycemic control was highly effective in preventing the progression of nephropathy even in those with elevated baseline AER. This observation is similar to the differences in treatment effects found in the expression of the familial or genetic influences on the development of the microvascular complications of diabetes mellitus in the DCCT population (24). In other words, intensive diabetic management may reduce or ameliorate the effects of nondiabetic factors on the appearance and progression of the microvascular complications. Yet the small number of intensively treated DCCT participants who did progress to advanced or clinical diabetic nephropathy seem to have different characteristics underlying the development of diabetic nephropathy.

To evaluate other factors that affect the progression of diabetic renal disease, especially in the intensively treated participants, we assessed several anthropomorphic parameters. In general, the intensively treated participants gained more

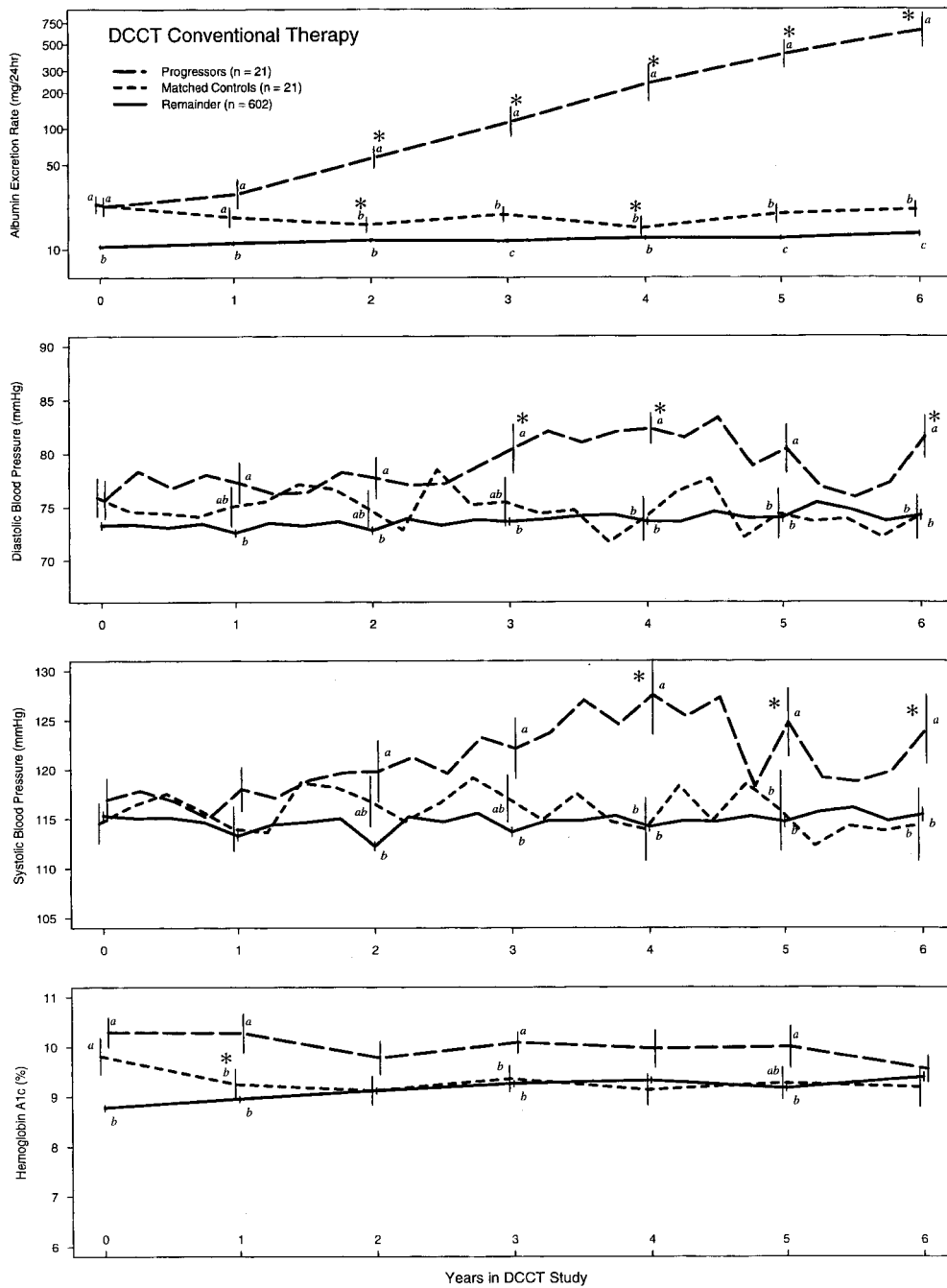


Figure 1. DCCT conventional treatment group: mean albumin excretion rate (mg/24 hr), diastolic and systolic BP (mmHg), and hemoglobin A_{1c} (%), for the 21 progressors, 21 matched controls, and 602 other participants who did not become pregnant during the DCCT. Values for AER are presented on a logarithmic scale. The vertical bars indicate one standard error above and below the mean. Means are compared annually between groups at each year of the DCCT. Where some of the means are significantly different ($P < 0.05$), the means with the same letter are indistinguishable; where there are no letters, the means were not significantly different. Within the progressors and within the matched controls, means were also compared annually to baseline (year 0) levels. Significant change from baseline is indicated with an asterisk (*)

weight, and many had a lipid profile suggestive of the metabolic syndrome and thus had a greater risk to develop hypertension (25,26). In fact, the top quartile of intensively treated DCCT participants who gained weight clearly had increased BP (26). However, we found no anthropomorphic differences in our six intensively treated progressors versus their matched control subjects and remaining participants. Perhaps with more

intensively treated participants progressing to diabetic nephropathy, the anticipated changes in anthropomorphic features may be seen.

Whether albuminuria is an indicator of structural diabetic nephropathy or an important factor in promoting its further progression (27) cannot be determined retrospectively. In other studies comparing structural and functional measures of dia-

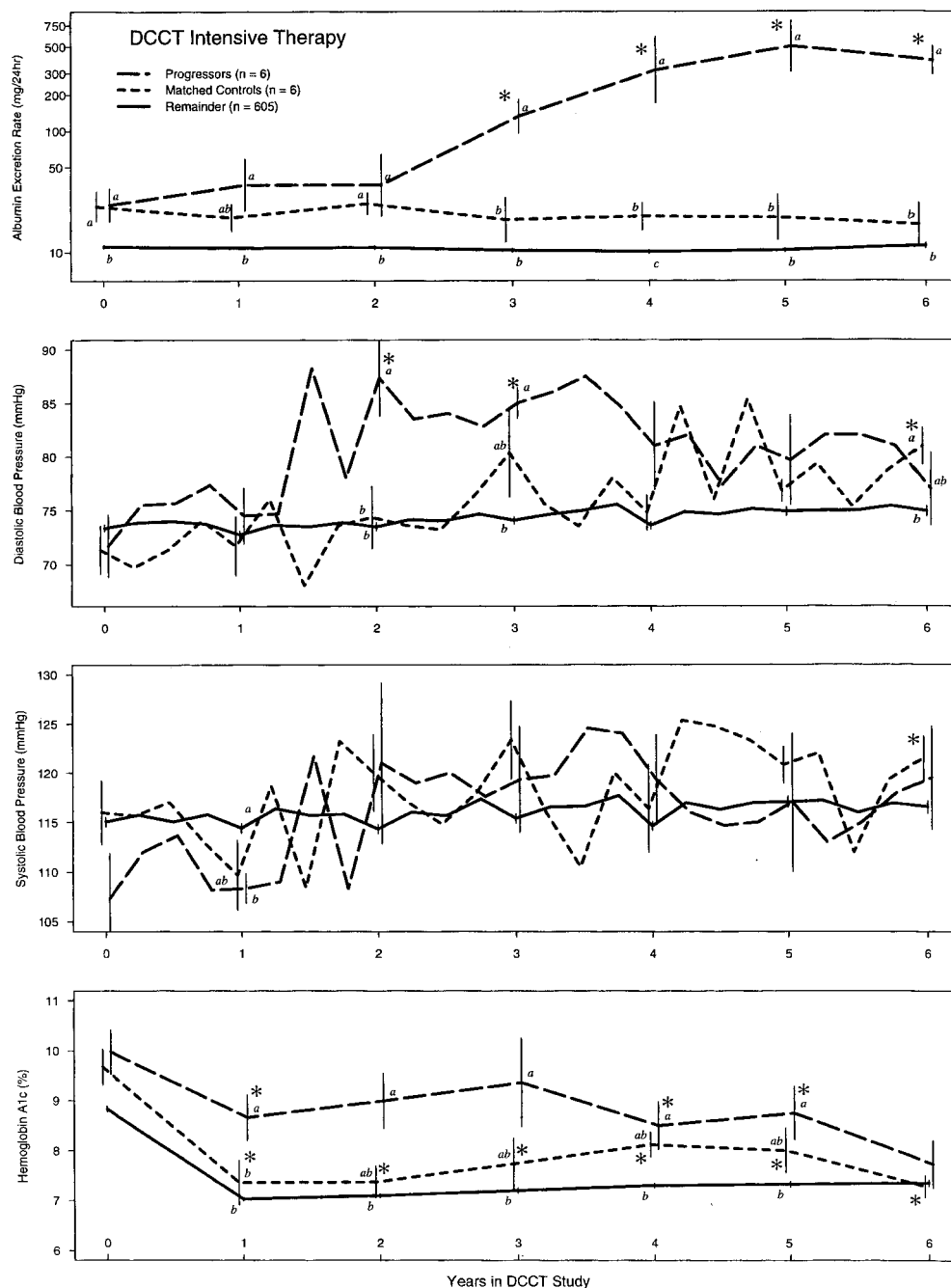


Figure 2. DCCT intensive treatment group: mean albumin excretion rate (mg/24 hr), diastolic and systolic BP (mmHg), and hemoglobin A_{1c} (%), for the 6 progressors, 6 matched controls, and 605 other participants who did not become pregnant during the DCCT. Values for AER are presented on a logarithmic scale. The vertical bars indicate one standard error above and below the mean. Means are compared annually between groups at each year of the DCCT. Where some of the means are significantly different ($P < 0.05$), the means with the same letter are indistinguishable; where there are no letters, the means were not significantly different. Within the progressors and within the matched controls, means were also compared annually to baseline (year 0) levels. Significant change from baseline is indicated with an asterisk (*).

betic nephropathy, the abnormal biochemical environment at an AER of approximately 50 mg/24 h clearly signaled morphometric determined glomerular lesions (15–17). The rise in AER to levels studied here indicated that biochemical, functional, and structural changes of diabetic nephropathy had occurred, usually in advance of increases in DBP. Therefore, albuminuria may synergistically promote the progression of

diabetic nephropathy (27). However, we could not explore this issue limited to measures of renal function in this patient population.

In the conventional treatment group, patients who progressed to diabetic nephropathy exhibited a significant rise in mean AER 1 to 2 yr before rises in diastolic or systolic BP. These findings are in accord with those of Mathiesen *et al.* (11)

Table 3. Summary of DCCT year 6 values for the progressors, matched control subjects, and the remaining members of both DCCT standard and intensive therapy groups who did not become pregnant during the DCCT^a

Parameter	DCCT Standard Therapy Group			DCCT Intensive Therapy Group		
	Progressors	Matched Controls	Remainder	Progressors	Matched Controls	Remainder
Number	21	21	602	6	6	605
Percent ideal body weight	107 (15)	115 (16)	111 (14)	109 (12)	131 (31)	117 (17)
Body mass index	24.0 (3)	25.6 (3)	24.9 (3)	25.9 (3)	29.4 (7)	26.4 (4)
Natural waist-to-hip ratio ^b	0.83 (.11)	0.85 (.07)	0.82 (.08)	0.86 (.06)	0.84 (.07)	0.82 (.10)
Iliac waist-to-hip ratio ^b	0.87 (.10)	0.89 (.06)	0.88 (.06)	0.93 (.05)	0.89 (.07)	0.89 (.08)

^a Numbers are given as means (SD).

^b Measured at participant's final DCCT visit.

and highlight the practical importance of elevated AER, not only as a predictor but likely as an indicator of the presence of diabetic nephropathy in most type 1 diabetic individuals (14–16). In most at-risk patients in the DCCT, these functional changes could be reversed with intensive management; in others, they could not. However, the intensive treatment progressors experienced these increases in reverse order, first DBP then AER at least a year later. Whether this observation indicated alternative pathophysiologic factors underlying the progression of diabetic nephropathy in the intensively treated participants needs more years of observation.

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