

INCREASE IN NOCTURNAL BLOOD PRESSURE AND PROGRESSION TO MICROALBUMINURIA IN TYPE 1 DIABETES

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ABSTRACT

Background Patients with type 1 diabetes mellitus and microalbuminuria often have elevated blood pressure while they are asleep, but it is not known whether the elevation develops concomitantly with microalbuminuria or precedes it.

Methods We monitored 75 adolescents and young adults who had had type 1 diabetes with normal urinary albumin excretion and blood pressure for more than five years. Ambulatory blood-pressure monitoring was used to assess blood pressure at the initial evaluation and about two years later, at which time all subjects had normal urinary albumin excretion. Subsequently, subjects were monitored for the development of microalbuminuria.

Results Microalbuminuria developed in 14 subjects, whereas the other 61 continued to have normal urinary albumin excretion. The mean (\pm SD) systolic pressure during sleep increased significantly in the subjects who ultimately had microalbuminuria (from 109.9 ± 11.3 to 114.9 ± 11.7 mm Hg, $P=0.01$) but not in the subjects with normal albumin excretion (from 106.0 ± 8.8 to 106.4 ± 14.8 mm Hg). The risk of progression to microalbuminuria was examined in relation to the ratio of systolic pressure during sleep to systolic pressure in the daytime. A ratio of 0.9 or lower, used to define a normal fall in nocturnal pressure, had a negative predictive value of 91 percent for the development of microalbuminuria. Moreover, the risk of microalbuminuria was 70 percent lower (95 percent confidence interval, 44 to 110 percent) in subjects with a ratio of 0.9 or less than in those with a ratio higher than 0.9 ($P=0.01$).

Conclusions In persons with type 1 diabetes, an increase in systolic blood pressure during sleep precedes the development of microalbuminuria. In those whose blood pressure during sleep decreases normally, the progression from normal albumin excretion to microalbuminuria appears to be less likely. (N Engl J Med 2002;347:797-805.)

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AMONG persons with type 1 diabetes mellitus who have normal urinary albumin excretion, the prevalence of hypertension, determined on the basis of blood-pressure readings at office visits, is similar to that in the general population.^{1,2} Moreover, when microalbuminuria is detected in persons with type 1 diabetes, indicating the presence of incipient nephropathy, hypertension

is usually absent, whereas persons with type 2 diabetes usually have overt hypertension when microalbuminuria is first detected.²⁻⁴ Thus, if one uses the conventional definition of hypertension, or even the more stringent definition recently proposed for persons with diabetes (i.e., systolic blood pressure that exceeds 129 mm Hg and diastolic blood pressure that exceeds 79 mm Hg),⁵ one must conclude that in persons with type 1 diabetes who are susceptible to kidney disease, hypertension does not develop until microalbuminuria is established.

However, more recent studies with the use of ambulatory blood-pressure monitoring have shown that subjects with type 1 diabetes and microalbuminuria have higher nocturnal blood pressure than either subjects with type 1 diabetes and normal urinary albumin excretion or age-matched controls.⁶⁻¹³ Such studies have shown that persons with type 1 diabetes and incipient nephropathy often have associated nocturnal hypertension.

On the basis of a previous cross-sectional study, we suggested that in persons with type 1 diabetes and incipient nephropathy, nocturnal hypertension may antedate the development of microalbuminuria.⁶ Alternatively, the two conditions may develop concomitantly, as others have suggested.¹³ It is important to determine whether nocturnal hypertension develops before microalbuminuria or at the same time, in view of increasing evidence that the risk of progression to overt nephropathy is strongly influenced by the level of blood pressure, perhaps more than by the degree of glycemic control.¹⁴ If an elevation in blood pressure, manifested as nocturnal hypertension, antedates the development of microalbuminuria, this finding might be useful as a potential marker of nephropathy and might provide a rationale for treating susceptible persons before the onset of microalbuminuria. To address this issue, we performed ambulatory blood-pressure monitoring in a prospective study of adolescents and young adults with type 1 diabetes who had normal

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urinary albumin excretion at the time of enrollment in the study.

METHODS

Subjects and Study Design

We recruited 75 subjects from the pediatrics and diabetes outpatient clinics of Hospital General in Valencia, Spain, and Hospital de Sagunto in Sagunto, Spain, to participate in the study. All the subjects had type 1 diabetes according to the standard criteria of an onset in childhood and insulin dependency. In all subjects, the diagnosis of diabetes had been made at least five years before enrollment. At the time of enrollment, none of the subjects had clinical evidence of diabetic complications, such as proliferative retinopathy, clinical neuropathy, or nephropathy. To be enrolled in the study, subjects had to have normal urinary albumin excretion and normal blood pressure. Normal blood pressure, measured at an office visit, was defined as pressure that was lower than 130/80 mm Hg in adults and less than the 95th percentile for age and sex in adolescents (as reported by the Task Force on Blood Pressure Control in Children).¹⁵ No subjects had ever received antihypertensive therapy. Ambulatory blood-pressure monitoring was performed at intervals of approximately two years as long as urinary albumin excretion remained normal. Subjects were followed prospectively, with measurement of urinary albumin excretion every three months. Those in whom microalbuminuria developed were withdrawn from the study, since they were generally given an angiotensin-converting-enzyme inhibitor as part of standard treatment at that point. Urinary albumin excretion was measured in two separate 24-hour urine specimens with the use of a nephelometric immunoassay (Behring Institute; normal range, 0 to 29 mg per 24 hours). Microalbuminuria was defined as a value for urinary albumin excretion that ranged from 30 to 299 mg per 24 hours, as confirmed by two consecutive measurements less than six months apart.

The study was approved by the committees for the protection of human subjects of Hospital General and Hospital de Sagunto. All participants gave written informed consent. If a subject was younger than 18 years of age, a parent signed the consent form as well.

Blood-Pressure Measurements

At each office visit, blood pressure was measured three times while the subject was seated, after a five-minute rest, with the use of a mercury sphygmomanometer. The first Korotkoff phase was used to signify systolic pressure and the fifth phase to indicate diastolic pressure. The mean of the three readings was recorded as the blood pressure for each office visit. Ambulatory blood-pressure monitoring was performed with a portable oscillometric recorder (Spacelabs 90207). Recording began between 8:30 and 9 a.m. The pressure was measured at 20-minute intervals from 6 a.m. until midnight and at 30-minute intervals from midnight until 6 a.m. The most appropriate cuff was selected from the four sizes supplied by the manufacturer (10 by 13 cm, 13 by 24 cm, 24 by 32 cm, and 32 by 42 cm).

For the purpose of ambulatory blood-pressure monitoring, two different periods were defined. The daytime period included all readings obtained from 8 a.m. until 10 p.m., and the nighttime period included all readings from midnight until 6 a.m. Data from 10 p.m. until midnight and from 6 a.m. until 8 a.m. were not included in the data for the daytime and nighttime periods, respectively, in order to minimize overlaps but were included in the analysis of the 24-hour data. The mean values for all the readings of systolic and diastolic pressure during a daytime or nighttime period were recorded as the systolic and diastolic pressure for that period.^{6,16,17} A value of 0.9 or lower for the ratio of the mean nighttime systolic pressure to the mean daytime systolic pressure was defined as the normal drop in blood pressure during sleep. In a pilot study

of 24 young adults with type 1 diabetes and normal urinary albumin excretion, the reproducibility of this ratio was assessed with the use of the Bland and Altman method, which is an approach based on a graphic technique with calculations.¹⁷ The mean (\pm SD) interval between the two measurements in the pilot study was 10.6 ± 4.6 months. All subjects had normal pressure (daytime, 120.2/74.9 mm Hg; nighttime, 104.6/59.2 mm Hg). The coefficients of repeatability were as follows: daytime systolic pressure, 0.19; daytime diastolic pressure, 0.28; nighttime systolic pressure, 0.17; nighttime diastolic pressure, 0.26; ratio of nighttime to daytime systolic pressure, 0.37; ratio of nighttime to daytime diastolic pressure, 0.33. These relatively low coefficients reflect good reproducibility.¹⁷

Statistical Analysis

We used the Wilcoxon rank-sum test to compare the subjects in whom microalbuminuria developed with those in whom it did not. The associations between several variables and the relative risk of microalbuminuria were calculated with the use of logistic-regression analysis. Positive and negative predictive values were calculated as previously described.¹⁸ We used Kaplan–Meier survival analysis to determine the probability that microalbuminuria would develop in the subjects with a normal fall in nocturnal blood pressure and those without a normal fall in nocturnal pressure, comparing the two groups with the use of the log-rank test. A P value of less than 0.05 (based on the Mann–Whitney test) was considered to indicate statistical significance. The difference in the risk of microalbuminuria between the groups was calculated on the basis of the crude rate of microalbuminuria with the use of SPSS software.¹⁸

RESULTS

Characteristics of the Subjects at Enrollment

At the time of enrollment, urinary albumin excretion was normal in all subjects (mean level, 11.7 ± 13.2 mg per 24 hours). Blood pressure measured at the initial office visit was also normal in all subjects (systolic pressure, 119.9 ± 10.2 mm Hg; diastolic pressure, 75.8 ± 8.8 mm Hg). The mean values for 24-hour ambulatory blood pressure were in the normal range (daytime systolic and diastolic pressure, 119.8 ± 9.1 and 73.4 ± 6.8 mm Hg, respectively; nighttime systolic and diastolic pressure, 106.7 ± 9.2 and 60.1 ± 6.1 mm Hg, respectively).^{6,16}

Urinary Albumin Excretion and Progression to Microalbuminuria

After a mean follow-up of 63.0 ± 9.3 months (range, 23 to 108), microalbuminuria developed in 14 of the 75 subjects (19 percent); urinary albumin excretion in this group increased from 11.6 ± 8.5 to 108.7 ± 85.0 mg per 24 hours ($P < 0.001$) (Fig. 1A) — a conversion rate similar to that reported in other studies.^{19,20} Urinary albumin excretion remained normal in these 14 subjects for a mean of 27.8 ± 16.0 months (range, 9 to 68) after the initial evaluation. In the other 61 subjects (81 percent), microalbuminuria did not develop during a mean follow-up period of 66 ± 21 months (range, 21 to 120) (Fig. 1B). In these subjects, urinary albumin excretion remained within the normal range (from 11.8 ± 7.9 to 14.0 ± 7.8 mg per 24 hours) after more than five years of follow-up (Fig. 1B).

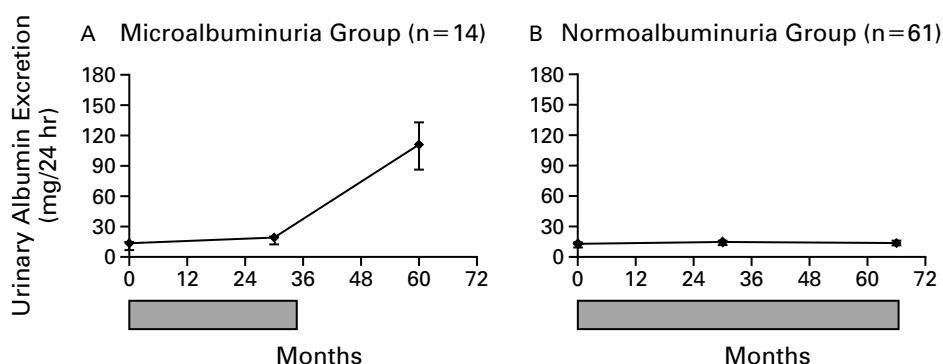


Figure 1. Urinary Albumin Excretion over Time in 75 Subjects with Type 1 Diabetes.

Panel A shows mean urinary albumin values in the 14 subjects in whom microalbuminuria (defined as excretion of 30 to 299 mg per 24 hours) ultimately developed, and Panel B shows values in the 61 subjects in whom urinary albumin excretion remained within the normal range (defined as excretion of less than 30 mg per 24 hours). The bar below each panel indicates the period of normal urinary albumin excretion. I bars indicate standard deviations.

The 14 subjects in whom microalbuminuria ultimately developed are henceforth referred to as the microalbuminuria group, and the 61 subjects in whom urinary albumin excretion remained normal are referred to as the normoalbuminuria group.

Characteristics of the Two Groups

The group of subjects in whom microalbuminuria ultimately developed and the group with normoalbuminuria were similar with respect to age, sex distribution, body-mass index, and base-line urinary albumin excretion (Table 1). The duration of disease, defined by the time elapsed since the diagnosis of diabetes, was shorter in the microalbuminuria group than in the normoalbuminuria group ($P < 0.001$), and the glycosylated hemoglobin level was higher in the microalbuminuria group ($P = 0.01$). The two groups did not differ significantly with regard to either systolic or diastolic pressure, measured in the office (Table 1). Likewise, total cholesterol and triglyceride levels did not differ significantly between the two groups (data not shown). In the course of the study, proliferative retinopathy developed in 5 subjects (1 of 14 in the microalbuminuria group and 4 of 61 in the normoalbuminuria group), but none of the 5 subjects had clinical evidence of neuropathy.

Ambulatory Blood-Pressure Monitoring

At the initial evaluation, the mean systolic pressure during the daytime and nighttime periods did not differ significantly between the microalbuminuria group and the normoalbuminuria group (Table 1). The daytime diastolic pressure was slightly but significantly higher in the microalbuminuria group than in the normoalbuminuria group. The heart rate did not differ

significantly between the two groups during either the daytime or the nighttime period.

At the final evaluation, the systolic and diastolic pressure, measured in the office, also did not differ significantly between the two groups of subjects (Table 1). In contrast, the diastolic pressure during both the daytime period and the nighttime period and the systolic pressure at night were significantly higher in the microalbuminuria group than in the normoalbuminuria group. The heart rate was significantly higher in the microalbuminuria group at night and during the day (Table 1).

In the microalbuminuria group, the nighttime systolic pressure increased from 109.9 ± 11.3 mm Hg at the initial evaluation to 114.9 ± 11.7 mm Hg at the last evaluation ($P = 0.008$), whereas in the normoalbuminuria group it remained essentially unchanged (106.0 ± 8.8 mm Hg at the initial evaluation and 106.4 ± 14.8 mm Hg at the final evaluation) (Fig. 2A). In the microalbuminuria group, diastolic pressure during sleep also increased (from 62.9 ± 7.3 mm Hg initially to 66.4 ± 7.8 mm Hg at the final evaluation), but the increase was not statistically significant ($P = 0.06$). Diastolic pressure during sleep did not change significantly in the normoalbuminuria group (from 59.5 ± 5.7 mm Hg initially to 60.1 ± 6.5 mm Hg). There was little change in the systolic and diastolic pressure during the daytime period in either group (Table 1).

Logistic-regression analysis showed that an increase in nighttime systolic pressure was significantly related to the development of microalbuminuria. For each 5 mm Hg increase in nighttime systolic pressure, the relative risk of microalbuminuria was 1.44 (95 percent confidence interval, 1.03 to 2.02). In the same model, for each 1 percent increase in the glycosylated hemo-

TABLE 1. CHARACTERISTICS OF 75 SUBJECTS WITH TYPE 1 DIABETES, ACCORDING TO WHETHER MICROALBUMINURIA ULTIMATELY DEVELOPED.*

CHARACTERISTIC	INITIAL EVALUATION			FINAL EVALUATION†		
	MICRO-ALBUMINURIA (N=14)	NORMO-ALBUMINURIA (N=61)	P VALUE	MICRO-ALBUMINURIA (N=14)	NORMO-ALBUMINURIA (N=61)	P VALUE
Age (yr)	17.8±2.6	21.7±11.6	0.31	20.1±2.8	24.5±13.3	0.42
Sex (no. of subjects)			0.83			0.83
Male	9	41		9	41	
Female	5	20		5	20	
Body-mass index‡	20.1±4.0	21.4±3.0	0.19	20.3±2.8	21.1±1.6	0.19
Duration of disease (yr)	6.6±1.1	14.2±2.9	<0.001	8.8±1.2	16.9±4.0	<0.001
Urinary albumin excretion (mg/24 hr)	11.6±8.5	11.8±8.0	0.93	16.8±10.3	14.0±7.9	0.37
Glycosylated hemoglobin (%)	10.7±1.7	9.2±1.6	0.01	10.2±2.3	8.4±1.3	<0.001
Office blood pressure (mm Hg)						
Systolic	121.7±10.6	119.3±9.8	0.43	122.3±12.9	117.6±10.7	0.12
Diastolic	77.8±9.3	75.2±8.5	0.36	77.9±9.7	76.1±7.6	0.56
Ambulatory blood pressure and heart rate						
Daytime (8 a.m.–10 p.m.)						
Systolic pressure (mm Hg)	123.1±10.0	119.0±8.8	0.13	124.0±10.3	119.6±7.4	0.17
Diastolic pressure (mm Hg)	76.6±6.8	72.7±6.4	0.02	76.2±4.0	72.7±5.8	0.02
Heart rate (beats/min)	91.1±12.0	84.5±9.4	0.07	91.2±10.5	81.1±11.0	0.007
Nighttime (midnight–6 a.m.)						
Systolic pressure (mm Hg)	109.9±11.3	106.0±8.8	0.16	114.9±11.7	106.4±14.8	0.007
Diastolic pressure (mm Hg)	62.9±7.3	59.5±5.7	0.13	66.4±7.8	60.1±6.5	0.005
Heart rate (beats/min)	70.5±9.9	73.5±12.1	0.48	75.9±11.3	67.5±7.0	0.003

*Plus–minus values are means ±SD.

†The final evaluation was the last evaluation during follow-up in the normoalbuminuria group and the last evaluation before the development of microalbuminuria in the microalbuminuria group.

‡The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

globin level, the relative risk of microalbuminuria was 1.66 (95 percent confidence interval, 1.13 to 2.44).

Progression to Microalbuminuria According to the Ratio of Nighttime to Daytime Pressure

An abnormal pattern of nighttime blood pressure is often described in terms of the ratio of nighttime to daytime pressure.^{6,21,22} We defined an abnormal pattern as a ratio higher than 0.9.^{21,22} At the initial evaluation, 43 of the 75 subjects in our study had a normal pattern of nighttime blood pressure and 32 had an abnormal pattern (Fig. 3). The distribution was similar at the final evaluation, although a change in the pattern was observed in six subjects (from a normal to an abnormal pattern in three subjects and from an abnormal to a normal pattern in the other three). At the initial evaluation, there were no significant differences in daytime systolic or diastolic pressure between subjects with a normal pattern of nighttime pressure and those with an abnormal pattern (daytime systolic pressure, 120.9±10.0 and 118.5±7.38 mm Hg, respectively; P=0.21; daytime diastolic pressure, 74.8±7.08 and 71.8±6.37 mm Hg, respectively; P=0.08). As expected, nighttime blood pressure was higher in the sub-

jects with an abnormal pattern than in those with a normal pattern (nighttime systolic pressure, 112±8.33 mm Hg vs. 102.9±8.04 mm Hg; nighttime diastolic pressure, 63.1±5.28 mm Hg vs. 58.1±5.82 mm Hg; P<0.001 for both comparisons), reflecting the criteria used to define normal and abnormal patterns of nighttime pressure. There were no significant differences between the subjects who had a normal pattern of nocturnal pressure and those who had an abnormal pattern with regard to age (23.3±12.6 and 18.7±8.4 years, respectively; P=0.07), the duration of disease (14.3±7.27 and 13.4±5.07 years, P=0.49), urinary albumin excretion (13.1±14.5 and 13.8±10.8 mg per 24 hours, P=0.52), or the glycosylated hemoglobin level (9.1±1.60 and 9.9±1.80 percent, P=0.14).

Microalbuminuria developed in only 7 of the 43 subjects with a normal pattern of nocturnal blood pressure at the initial evaluation and in only 4 of the 43 with a normal pattern at the final evaluation. As a marker of progression to microalbuminuria, a normal pattern of nocturnal blood pressure had a negative predictive value of 84 percent and 91 percent, respectively, at the initial and final evaluations, indi-

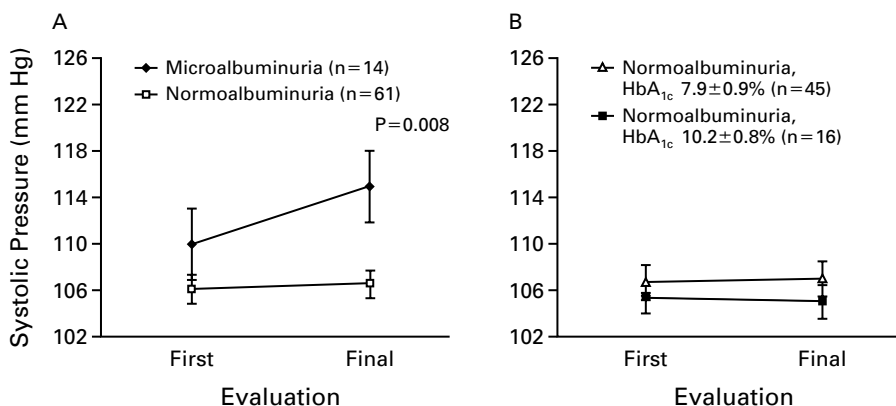


Figure 2. Systolic Blood Pressure during Sleep.

Panel A shows nocturnal systolic pressure in the 14 subjects in whom microalbuminuria ultimately developed and in the 61 subjects in whom urinary albumin excretion remained normal. Panel B shows nocturnal systolic pressure in the normoalbuminuria group according to the mean (\pm SD) level of glycosylated hemoglobin (HbA_{1c}). The final evaluation was the last evaluation during follow-up in the normoalbuminuria group and the last evaluation before the development of microalbuminuria in the microalbuminuria group. I bars indicate standard deviations.

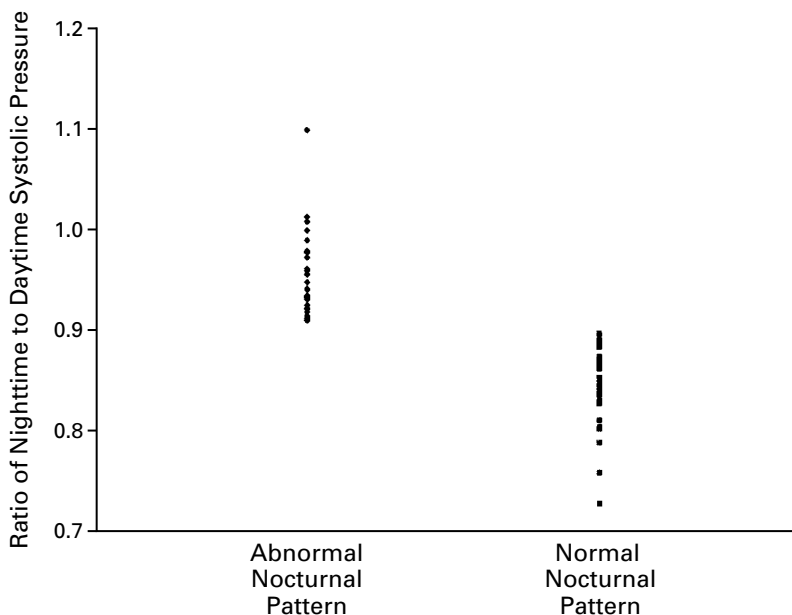


Figure 3. Ratio of Nighttime to Daytime Systolic Blood Pressure at the Initial Evaluation.

A ratio of 0.9 or lower was defined as a normal nocturnal pattern, and a ratio higher than 0.9 as an abnormal nocturnal pattern.

cating a low risk. Microalbuminuria developed in 7 of the 32 subjects classified as having an abnormal pattern of nocturnal pressure at the initial evaluation and in 10 of the 32 classified as having an abnormal pattern at the last evaluation during the period of normal urinary albumin excretion. The positive predictive

value of an abnormal pattern of nocturnal pressure for the progression to microalbuminuria was 22 percent at the initial evaluation and 31 percent at the last evaluation during the period of normoalbuminuria.

Kaplan–Meier analysis showed that the risk of progression to microalbuminuria differed significantly be-

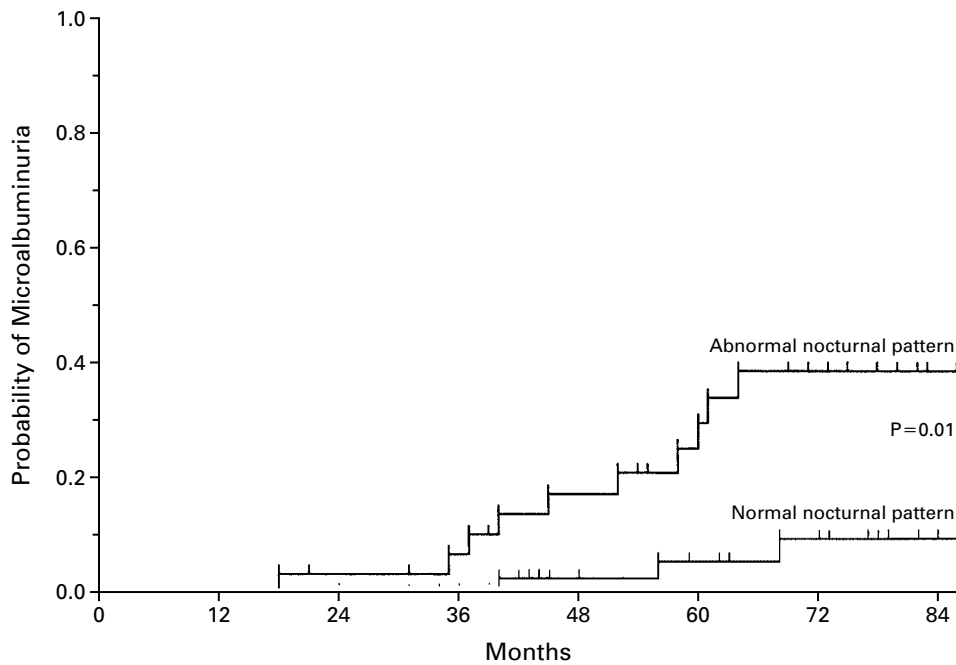


Figure 4. Kaplan–Meier Curves Showing the Probability of Microalbuminuria According to the Pattern of Daytime and Nighttime Systolic Pressure.

The probability of microalbuminuria differed significantly between the two groups ($P=0.01$ by the log-rank test; $\chi^2=6.217$ with 1 df). The risk of microalbuminuria was 70 percent lower in the subjects with a normal nocturnal pattern than in those with an abnormal nocturnal pattern.

tween the subjects with a normal pattern of nocturnal blood pressure and those with an abnormal pattern (Fig. 4). On the basis of the final evaluation, the risk of microalbuminuria in the group of subjects with a normal pattern of nocturnal blood pressure was 70 percent lower than the risk in the group with an abnormal pattern (95 percent confidence interval, 44 to 110 percent).

Subgroup Analysis According to the Glycosylated Hemoglobin Level

At the initial evaluation and during follow-up, glycosylated hemoglobin levels were higher in the subjects in whom microalbuminuria ultimately developed than in those in whom it did not (Table 1). As noted above, logistic-regression analysis indicated that the value for glycosylated hemoglobin was significantly related to the risk of microalbuminuria. Thus, our data confirm the observation that poor glycemic control is a predictor of microalbuminuria.^{19,23}

To address the question of whether poor metabolic control or high nocturnal systolic pressure accounted for the progression to microalbuminuria, we performed a separate analysis of data from ambulatory blood-pressure monitoring in 16 of the 61 subjects

in the normoalbuminuria group; these 16 subjects had levels of glycosylated hemoglobin that were as high as those in the microalbuminuria group (Table 2). In this subgroup of 16 subjects, who were similar in age to the 14 subjects in the microalbuminuria group, urinary albumin excretion at the initial evaluation was in the normal range and was similar to that in the microalbuminuria group (Table 2). The mean values for systolic and diastolic pressure, measured at the initial office visit, were 119.5 ± 9.9 and 75.5 ± 9.2 mm Hg, respectively; the values were nearly the same at the end of the normoalbuminuric period (Table 2). Analysis of data from ambulatory blood-pressure monitoring showed that daytime blood pressure did not differ significantly between this subgroup and the microalbuminuria group. In contrast, systolic pressure during sleep was significantly lower in the subgroup with normoalbuminuria and high glycosylated hemoglobin levels than in the microalbuminuria group (104.9 ± 6.6 vs. 114.9 ± 11.7 mm Hg, $P=0.003$).

Systolic pressure during sleep did not change significantly during the course of the study in the 45 subjects in the normoalbuminuria group who had lower levels of glycosylated hemoglobin (7.9 ± 0.9 percent) (Fig. 2B). Diastolic pressure at night, as well as both

TABLE 2. CHARACTERISTICS OF THE SUBJECTS IN WHOM MICROALBUMINURIA ULTIMATELY DEVELOPED AND THE SUBGROUP OF SUBJECTS WITH NORMOALBUMINURIA AND AN ELEVATED LEVEL OF GLYCOSYLATED HEMOGLOBIN AT THE FINAL EVALUATION.*

VARIABLE	MICROALBUMINURIA (N=14)	NORMOALBUMINURIA, GLYCOSYLATED HEMOGLOBIN >9.5% (N=16)	P VALUE
Age (yr)	20.1±2.8	19.9±10.0	0.33
Sex (no. of subjects)			0.80
Male	9	11	
Female	5	5	
Body-mass index	20.3±2.8	20.3±2.8	0.57
Duration of disease (yr)	8.8±1.2	17.2±4.0	<0.001
Urinary albumin excretion (mg/24 hr)	16.8±10.3	12.3±10.0	0.20
Glycosylated hemoglobin (%)	10.2±2.3	10.2±0.8	0.65
Office blood pressure (mm Hg)			
Systolic	122.3±12.9	118.5±11.6	0.21
Diastolic	77.9±9.7	77.8±8.1	0.48
Ambulatory blood pressure and heart rate			
Daytime (8 a.m.–10 p.m.)			
Systolic pressure (mm Hg)	124.0±10.3	119.2±6.1	0.27
Diastolic pressure (mm Hg)	76.2±4.0	74.2±4.6	0.27
Heart rate (beats/min)	91.2±10.5	84.1±7.9	0.05
Nighttime (midnight–6 a.m.)			
Systolic pressure (mm Hg)	114.9±11.7	104.9±6.6	0.003
Diastolic pressure (mm Hg)	66.4±7.8	61.6±5.7	0.06
Heart rate (beats/min)	75.9±11.3	70.1±5.4	0.10

*For the microalbuminuria group, the final evaluation was the last evaluation before microalbuminuria developed, and for the normoalbuminuria group it was the last evaluation during follow-up. Plus-minus values are means ±SD.

systolic and diastolic blood pressure during the day, did not change significantly in either subgroup of subjects in whom urinary albumin excretion remained normal (data not shown).

DISCUSSION

In this study, which involved a cohort of adolescents and young adults with type 1 diabetes, an increase in blood pressure during sleep, detected by ambulatory blood-pressure monitoring, preceded the development of microalbuminuria. In contrast, in subjects in whom microalbuminuria did not develop during a follow-up period of more than five years, neither nighttime nor daytime blood pressure increased significantly.

Thus, the risk of microalbuminuria, a marker of kidney disease in patients with type 1 diabetes,^{19,23,24} appears to be very low in patients who remain normotensive, as defined not only by normal blood-pressure readings at office visits and during ambulatory daytime monitoring over time but also by the absence of an increase in systolic pressure during sleep. We emphasize these criteria to highlight the fact that neither blood pressure as assessed at office visits nor daytime blood pressure as assessed by ambulatory blood-pressure monitoring changed significantly over time (i.e.,

during the period of normoalbuminuria) in subjects in whom microalbuminuria eventually developed. Thus, an increase in nighttime systolic pressure appears to be the earliest detectable manifestation of altered blood-pressure regulation in patients with type 1 diabetes. Our study documented a temporal relation between an increase in blood pressure and the development of incipient diabetic nephropathy as reflected by microalbuminuria in patients with type 1 diabetes.²⁴

An early increase in nighttime arterial blood pressure may have a key role in the development of diabetic nephropathy. For instance, systemic pressure overload, initially restricted to systolic pressure during sleep, when transmitted to the glomerular circulation, may cause intrarenal hemodynamic changes, leading to microalbuminuria, structural renal damage, or both.

Our findings are in keeping with the concept that a predisposition to essential hypertension increases the risk of diabetic nephropathy. This concept is based on studies showing that the parents of patients with type 1 diabetes and proteinuria have a higher prevalence of hypertension than that in the general population.²⁵⁻²⁷ A different line of evidence that also suggests a common link between a susceptibility to hypertension and diabetic nephropathy among patients with

type 1 diabetes comes from studies showing increased activity of cellular markers such as the sodium–lithium exchanger²⁸ and the sodium–hydrogen exchanger in both subjects with essential hypertension²⁹ and those with type 1 diabetes and nephropathy.³⁰

In accordance with the results of previous studies, our data suggest that the risk of progression to microalbuminuria is influenced by the level of glycosylated hemoglobin.²⁰ Yet microalbuminuria did not develop in a subgroup of subjects with very poor metabolic control in whom blood pressure remained normal. Although poor metabolic control hastens the progression of renal disease,²⁰ nephropathy appears to develop only in susceptible persons with type 1 diabetes.^{31–33} Since subtle but early elevations in blood pressure antedate the development of microalbuminuria, we surmise that, regardless of the level of metabolic control, an elevation in nocturnal blood pressure plays a key part in the development of microalbuminuria in susceptible persons with type 1 diabetes.

Circadian changes in blood pressure can readily be assessed on the basis of the ratio of nighttime to daytime blood pressure.³⁴ In our study, a ratio of 0.9 or lower, reflecting the normal drop in nighttime pressure, had a negative predictive value of 91 percent for progression to microalbuminuria. The potential clinical significance of the nighttime drop in blood pressure is further revealed in the associated 70 percent reduction in the risk of microalbuminuria. Thus, a normal decrease in nocturnal blood pressure is a strong marker of nonprogressive disease.

An evaluation of the risk of nephropathy at an early stage of type 1 diabetes would provide the best basis for choosing therapies designed to prevent the progression to microalbuminuria. The absence of a drop in nocturnal blood pressure has been associated with cardiovascular complications in subjects with essential hypertension^{35,36} and, more recently, in those with type 1 diabetes and overt nephropathy.³⁷ Early documentation of an increase in nocturnal pressure might warrant the use of agents such as angiotensin-converting–enzyme inhibitors or angiotensin II–receptor blockers in a patient with type 1 diabetes. Documentation of normal nocturnal blood pressure, on the other hand, might suggest that there is no need for early therapeutic interventions other than those designed to provide optimal glycemic control.

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