Ambulatory blood pressure measurements are related to albumin excretion and are predictive for risk of microalbuminuria in young people with type 1 diabetes

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Abstract

Aims/hypothesis The relationship between BP and microalbuminuria in young people with type 1 diabetes is not completely clear. As microalbuminuria is preceded by a gradual rise in albumin excretion within the normal range, we hypothesised that ambulatory BP (ABP) may be closely related to albumin excretion and progression to microalbuminuria.

Methods ABP monitoring (ABPM) was performed in 509 young people with type 1 diabetes (age median [range]: 15.7 [10.7–22.6] years) followed with annual assessments of three early morning urinary albumin:creatinine ratios (ACRs) and HbA_{1c}. Systolic BP (SBP) and diastolic BP (DBP) and the nocturnal fall in BP were analysed in relation to ACR.

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Results All ABPM variables were significantly related to baseline $\log_{10}$ ACR ($p < 0.001$). After the ABPM evaluation, 287 patients were followed for a median of 2.2 (1.0–5.5) years. ABP at baseline was independently related to mean ACR during follow-up. Nineteen initially normoalbuminuric patients developed microalbuminuria after 2.0 (0.2–4.0) years and their baseline daytime DBP was higher than in normoalbuminuric patients ($p < 0.001$). After adjusting for baseline ACR and HbA_{1c} , there was an 11% increased risk of microalbuminuria for each 1 mmHg increase in daytime DBP. Forty-eight per cent of patients were non-dippers for SBP and 60% for DBP; however, ACR was not different between dippers and non-dippers and there were no differences in the nocturnal fall in BP between normoalbuminuric and future microalbuminuric patients.

Conclusions/interpretation In this cohort of young people with type 1 diabetes, ABP was significantly related to ACR, and daytime DBP was independently associated with progression to microalbuminuria. Increasing albumin excretion, even in the normal range, may be associated with parallel rises in BP.

Keywords Albumin excretion · Ambulatory blood pressure monitoring · Blood pressure · Diabetic nephropathy · Microalbuminuria · Type 1 diabetes · Young people

Abbreviations

ABP	Ambulatory BP
ABPM	Ambulatory BP monitoring
ACR	Albumin:creatinine ratio
DBP	Diastolic BP
HR	Heart rate
NFS	Nephropathy Family Study
SBP	Systolic BP
SDS	Standard deviation score

Introduction

In patients with type 1 diabetes, microalbuminuria represents an important predictor for diabetic nephropathy and cardiovascular disease [1, 2]. Increased arterial BP and the development of microalbuminuria are closely linked [1] and a familial predisposition to hypertension has been associated with the development of microalbuminuria [3]. Furthermore, antihypertensive treatment in patients with microalbuminuria has been shown to reduce albumin excretion and prevent the progression to overt proteinuria [4]. However, the temporal relationship between microalbuminuria and rises in BP has not been clarified. Whereas some studies have shown that increases in BP precede microalbuminuria and could influence its development [5, 6], other studies have not supported this hypothesis and

suggested that the two phenomena could occur together [7, 8] or that BP increases only after the onset of microalbuminuria [9]. A greater understanding of the relationship between BP and microalbuminuria could be of particular relevance for the early identification of patients at risk of complications and the implementation of preventive and therapeutic strategies. However, most of the studies attempting to explore this relationship have been based on office BP [6, 9] and have mainly been conducted in adult populations [6, 8]. Twenty-four hour ambulatory BP (ABP) monitoring (ABPM) presents several advantages over office BP measurements [10, 11]. In particular, it has a better correlation with target organ damage [12] and is more indicative of cardiovascular morbidity and mortality [12]. It permits evaluation of the circadian rhythm of BP, which may also be of significance [10, 11].

Using ABPM, the most common finding in normotensive patients with type 1 diabetes and microalbuminuria has been a blunted decline in BP overnight [13, 14], the so-called ‘non-dipping’ phenomenon. A high prevalence of non-dippers has also been described in normoalbuminuric patients and related to the future development of microalbuminuria [15]. However, significant overlaps in the fall in BP overnight exist between normoalbuminuric and microalbuminuric patients [8, 16]. Therefore, the predictive value of the ‘non-dipping’ phenomenon on future microalbuminuria is not proven.

Microalbuminuria is often preceded by a progressive rise in albumin excretion within the normal range and this has been found to be an important predictor of microalbuminuria and overt diabetic nephropathy [17–21]. Assessing the relationship between albumin excretion and ABP as continuous variables may increase understanding of the role of BP in the pathogenesis of microalbuminuria. We hypothesised that there might be a close relationship between albumin excretion and ABP, even within the normal range, and that ABP might predict the risk of developing microalbuminuria in young people with type 1 diabetes.

Methods

Study population and study design: the Nephropathy Family Study (NFS) cohort The NFS cohort was set up in 2000 as part of the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes Inflammation Laboratory: Genetic Resource Investigating Diabetes study [22]. Between 2000 and 2005, 1,066 patients, aged 10–16 years, who had developed type 1 diabetes before the age of 16 years, were recruited throughout four regions of England (East Anglia, Birmingham, Bristol and Oxford). Patients with insulin-treated diabetes secondary to other pathologies were excluded. Similarly, children with chronic renal disease or

other chronic diseases likely to affect renal function were excluded. The median duration of follow-up is currently 2.6 (interquartile range 1.8–3.7) years.

The longitudinal study schedule comprised annual collection of three consecutive early-morning urine specimens for centralised measurement of albumin:creatinine ratio (ACR) and blood samples for measurements of HbA_{1c}. Annual assessments also included measurements of height and weight.

Twenty-four hour ABPM was performed in a subgroup of 509 children from the NFS cohort and assessed in relation to ACR. In addition, 287 of these patients had at least 1 year follow-up after the ABPM was performed, with at least one set of three consecutive early morning urinary samples for the assessment of ACR, a centralised measurement of HbA_{1c} and clinical data, and in these patients the potential associations between baseline ABP and future changes in ACR were also assessed.

Ethics approval was obtained from the regional ethics committee, with written informed consent from the parents. Children were asked to assent before entering the study.

ABPM ABPM was performed with a portable non-invasive oscillometric recorder (Diasys Integra II, Novacor, France). The validity of this monitor has been previously confirmed [23]. An appropriate cuff size was fitted on the basis of the arm circumference of each patient, and applied on the non-dominant arm. ABPM was performed during a normal day with typical activities but patients were asked to avoid vigorous exercises and to keep their arm relaxed during each daytime inflation. A measurement was automatically repeated if values were outside the following intervals of measurement validity: systolic BP (SBP) <50 mmHg; diastolic BP (DBP) <30 mmHg or >150 mmHg; heart rate (HR) <35 beats per min and >250 beats per min; pulse pressure <10 and >150 mmHg at SBP <120 mmHg and pulse pressure <15 and >150 mmHg at SBP >120 mmHg. Furthermore, all patients were asked to record in a diary the time they went to bed and the time they awoke, as well as exercise periods and the quality of the sleep.

BP readings were obtained at 30 min intervals during the daytime (07:00–22:00 hours) and at 60 min intervals during the night-time (22:00–07:00 hours). At the end of the ABPM, the monitor data were downloaded to a personal computer equipped with DiasySoft software for the analysis of the measurements. All readings taken during 24 h were used to calculate mean 24 h SBP, DBP and HR, whereas mean daytime and night-time SBP, DBP and HR were calculated based on the awake and asleep periods, calculated from diary times. To characterise the circadian BP rhythm, the percentage of nocturnal fall in SBP and DBP was calculated using the formula: [daytime SBP (or DBP)–night-time SBP (or DBP)]/[daytime SBP (or DBP)]×100. Patients were classified as

dippers if their daytime SBP and/or DBP decreased by at least 10% during the night; all other patients were classified as non-dippers [24].

Albumin and creatinine measurements All urine samples were assessed centrally in a single reference laboratory at St Thomas's Hospital, London, UK. Samples were stored at –70°C prior to being analysed. Albumin was measured centrally by a double-antibody ELISA method. The within and in-between assay CV values were 6% and 12%, respectively. Creatinine was initially measured using a modified Jaffe method (Unimate 7; Roche Diagnostic Systems, Rotkreuz, Switzerland) on a Cobas Mira (Roche Diagnostic Systems) automated spectrophotometer (CV was 2% at 2.2 mmol/l) and, more recently, by stable isotope dilution electrospray mass spectrometry–mass spectrometry, as previously reported [25].

HbA_{1c} measurements All samples were analysed centrally in Cambridge on a TOSOH G7 analyser (Tosoh Bioscience, Redditch, UK), using HPLC and absorbance change detection, and DCCT aligned methods. The normal range was 4.9–6.3% and the CV was 4.8% at a level of 5.5%, and 6.6% at a level of 10.1%.

Calculations BMI was calculated as weight/height². Standard deviation scores (SDS) for height, weight and BMI were calculated using the British 1990 Growth Reference and Cole's LMS method [26].

The mean of all HbA_{1c} measurements collected from the time of recruitment into the study until the ABPM assessment was calculated.

ACR was summarised as the geometric mean of three consecutive early morning urine samples and log₁₀ transformed for analyses. Microalbuminuria was defined as an ACR between 3.5 and 35 mg/mmol in male patients and between 4.0 and 47 mg/mmol in female patients in two out of three consecutive early morning urine collections during an annual assessment (corresponding to an overnight albumin excretion rate of 20–200 µg/min and an ACR of 2.4 and 2.2 SD above the geometric mean in normal male and female adolescents [27]). Clinical proteinuria was defined as an ACR >35 mg/mmol in male patients, and >47 mg/mmol in female patients (equivalent to >200 µg/min) [27].

The most recent ACR assessment in relation to the time when ABPM was measured (within the previous 6 months) was used for the initial cross-sectional analyses. Subsequently, we calculated a longitudinally adjusted ACR trait, using all available assessments after ABPM was performed. This was calculated as follows: the geometric mean for each assessment was computed and log₁₀ transformed. Then, in order to exclude the effect of significant determinants of ACR, such as duration of diabetes, sex and glycaemic control, we used a

regression model, where $\log_{10}$ ACR was regressed against these variables and residuals (observed–fitted values) were derived [21]. Finally, the average residual for each patient was calculated and taken as the mean adjusted ACR trait.

BP SDS for 24 h, daytime and night-time SBP and DBP were calculated using the European reference standards [28]. Hypertension was defined as an SDS >1.65, adjusted for sex and height (corresponding to the 95th percentile in a standard normal distribution) [28].

Statistical analyses Data are summarised as means $\pm$ SD or median (interquartile range) unless otherwise specified. Non-normally distributed variables, such as ACR, were $\log_{10}$ transformed before analysis. A one-sample *t* test was used to compare BP variables, expressed as an SDS, with published normative data (mean $0\pm$ SD). Comparisons between different groups were performed by an unpaired *t* test. Comparisons across categories were made using χ^2 or Fisher's exact test. Association between variables was performed by Pearson correlation analysis, and expressed as correlation coefficient *r*, and by multiple regression analysis, and results are expressed as regression coefficient *B* $\pm$ SE or as β coefficients. Cox regression hazard regression analysis was performed to assess the proportional contribution of covariates, and in particular of ABPM variables to the risk of developing microalbuminuria during follow-up. *p* values <0.05 were taken as significant. Given that many tests were undertaken, a stricter more conserva-

tive *p* value of <0.01 was also applied in order to give a more cautious interpretation.

Results

General characteristics of the study population and ABPM data ABPM was performed in 509 young patients with type 1 diabetes (278 male and 231 female). The general characteristics of the study population and for male patients and female patients separately are shown in Table 1. Sixty out of the 509 patients had their ACR in the microalbuminuric range at the time when the ABPM was performed or had presented a transient or intermittent microalbuminuria before the ABPM assessment. These patients were included in the analysis of the relationship between ACR and ABP as this allowed us to have a wider range of ACR to be tested against ABP. However, we excluded these patients for the longitudinal analysis in order not to confound our assessment of the predictive value of ABP on future development of microalbuminuria.

Table 1 shows mean values for 24 h, and daytime and night-time, SBP, DBP and HR as well as the night-time fall for SBP and DBP. In 23 patients, data for the overnight period were incomplete and therefore only readings during the daytime were included in the analysis. None of the patients was on treatment for hypertension at baseline or during follow-up.

Table 1 General characteristics and ABPM of the study group

Characteristics/ABPM	All patients	Male patients	Female patients	<i>p</i> value
<i>n</i>	509	278	231	
Age at assessment (years)	15.8 $\pm$ 2.3	15.8 $\pm$ 2.2	15.7 $\pm$ 2.4	NS
Age at diagnosis (years)	8.9 $\pm$ 3.8	9.0 $\pm$ 3.9	8.8 $\pm$ 3.6	NS
Duration (years)	6.9 $\pm$ 3.8	6.8 $\pm$ 3.9	7.0 $\pm$ 3.7	NS
HbA _{1c} (%)	9.3 $\pm$ 1.6	9.1 $\pm$ 1.6	9.4 $\pm$ 1.7	NS
Insulin (U kg ⁻¹ day ⁻¹)	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.4	NS
Height SDS	0.15 $\pm$ 1.04	0.06 $\pm$ 1.05	0.26 $\pm$ 1.01	0.03
BMI SDS	0.97 $\pm$ 1.15	0.85 $\pm$ 1.13	1.10 $\pm$ 1.16	0.03
ACR (mg/mmol)	0.88 (0.63–1.42)	0.78 (0.78–1.17)	1.00 (0.67–1.80)	<0.001
ABPM ^a				
24 h SBP (mmHg)	114 $\pm$ 10	116 $\pm$ 10	112 $\pm$ 10	<0.001
24 h DBP (mmHg)	72 $\pm$ 7	72 $\pm$ 7	72 $\pm$ 7	NS
24 h HR (beats per min)	83 $\pm$ 11	81 $\pm$ 10	86 $\pm$ 11	<0.001
Day SBP (mmHg)	117 $\pm$ 11	119 $\pm$ 11	115 $\pm$ 10	<0.001
Day DBP (mmHg)	74 $\pm$ 8	74 $\pm$ 8	74 $\pm$ 7	NS
Day HR (beats per min)	88 $\pm$ 12	85 $\pm$ 11	90 $\pm$ 12	<0.001
Night SBP (mmHg)	105 $\pm$ 11	106 $\pm$ 11	103 $\pm$ 10	0.001
Night DBP (mmHg)	67 $\pm$ 8	68 $\pm$ 8	66 $\pm$ 8	0.03
Night HR (beats per min)	70 $\pm$ 10	68 $\pm$ 10	72 $\pm$ 11	<0.001
Non-dippers SBP (%)	235 (48.4)	123 (46.2)	112 (50.9)	NS
Non-dippers DBP (%)	292 (60.1)	172 (64.7)	120 (54.5)	0.03

Data are means $\pm$ SD, median (interquartile range) or *n* (%)

^aDifferences in ABPM variables persisted after adjusting for height and BMI SDS. Data for 24 h and night-time BP are for 486 patients (266 male and 220 female), with complete ABPM readings

p values are for the comparison between male patients and female patients

The evaluation of the BP SDS showed values higher than those in the reference population for DBP, particularly at night (mean $\pm$ SD; 24 h DBP: 0.78 ± 1.24 ; daytime DBP: 0.20 ± 1.33 ; night-time DBP: 1.74 ± 1.19 ; all $p<0.01$), but lower than the reference values for SBP (24 h SBP: -0.18 ± 1.34 , daytime SBP: -0.43 ± 1.38 ; $p<0.01$). No differences were found for night-time SBP (0.10 ± 1.27 , $p>0.05$). The prevalence of hypertension was as follows: 24 h SBP: 8.6%; 24 h DBP: 24.4%; daytime SBP: 5.7%; daytime DBP: 12.9%; night-time SBP: 9.4%; night-time DBP: 48.8%. The prevalence of abnormal BP values was not different in male when compared with female patients (all $p>0.05$).

Relationship between ABP and other variables All potential simple correlations between ABP and age, duration of diabetes, HbA_{1c}, log₁₀ ACR, insulin dose, height SDS and BMI SDS were analysed (Electronic supplementary material [ESM] Table 1). Significant correlations were found between log ACR at the time of ABPM assessment and all ABPM variables (all $p<0.001$). HbA_{1c} was significantly related to DBP ($p<0.01$) but not to SBP. Insulin dose was significantly related to 24 h and daytime SBP and night-time DBP ($p<0.05$). BMI SDS was significantly related to all ABPM variables ($p\leq0.01$). Duration of diabetes was only related to 24 h and daytime DBP ($p<0.01$). All ABPM variables were significantly related to age at assessment ($p<0.01$).

Relationship between ACR and ABP In multivariate analysis, log₁₀ ACR was independently related to all ABP variables ($B\pm$ SE; 24 h SBP: 7.5 ± 1.4 ; 24 h DBP: 4.5 ± 1.0 ; daytime SBP: 8.0 ± 1.5 ; daytime DBP: 4.7 ± 1.1 ; night-time SBP: 7.9 ± 1.5 ; night-time DBP: 4.1 ± 1.1 ; all $p<0.001$), after adjustment for potential confounders, such as age, sex, BMI SDS and HbA_{1c}.

Future microalbuminuric vs normoalbuminuric patients After the ABPM evaluation, 287 patients were followed for at least 1 year (follow-up: median [range]: 2.2 [1.0–5.5] years). The baseline characteristics of these patients were similar to those who did not have follow-up assessments, apart from a slightly younger age (15.3 ± 2.1 vs 16.3 ± 2.3 years), a shorter duration of diabetes (6.2 ± 3.6 vs 7.8 ± 3.9 years) and lower mean HbA_{1c} levels (9.0 ± 1.5 vs $9.6\pm1.7\%$), but there were no differences in ABPM variables.

Daytime SBP ($\beta=0.15$, $p=0.01$) and DBP ($\beta=0.21$, $p<0.001$) and night-time SBP ($\beta=0.18$, $p=0.03$) were significantly related to the adjusted mean ACR values during follow-up (Fig. 1). During this period, out of the 250 patients who were normoalbuminuric at baseline, 19 developed microalbuminuria and they were defined as the ‘future microalbuminuric’ group. For the ‘future microalbuminuric’ group median time to onset of microalbuminuria after the ABPM assessment was 2.0 (0.2–4.0) years. A comparison was performed between

these 19 ‘future microalbuminuric’ patients and the remaining 231 patients who remained normoalbuminuric during follow-up (Table 2). Significant differences between the two groups were found for baseline HbA_{1c} and ACR, both being higher in the ‘future microalbuminuric’ group ($p<0.001$). ‘Future microalbuminuric’ patients had higher 24 h, daytime and night-time DBP than normoalbuminuric patients, but there was no difference in the nocturnal fall in BP between the two groups (Table 2). The differences in 24 h and daytime DBP between the groups persisted also after adjustment for HbA_{1c} and log₁₀ ACR (Table 2).

Cox proportional hazard regression In a Cox proportional regression analysis with the development of microalbuminuria as the outcome variable and years of follow-up after the ABPM assessment as the time variable, for each 1 mmHg increase in daytime DBP, the risk of developing microalbuminuria was 1.11 (95% CI 1.03–1.19), $p=0.005$ (Table 3). In this model, HbA_{1c} and baseline ACR also significantly contributed to the risk of developing microalbuminuria, whereas there was no statistically significant effect of sex, age at diagnosis or duration of diabetes (Table 3). The association between daytime DBP and microalbuminuria persisted also after adjusting for the other ABPM variables ($p=0.002$).

In contrast, when the same analysis was repeated separately for each of the other ABPM variables, there was no statistically significant contribution of them to the risk of developing microalbuminuria.

Dippers vs non-dippers Two hundred and thirty-five (48%) patients were non-dippers for SBP and 292 (60%) were non-dippers for DBP. A comparison between dippers and non-dippers is shown in Table 4.

Dippers and non-dippers were comparable for age, duration of diabetes and BMI SDS. SBP non-dippers had higher HbA_{1c} values when compared with dippers. No differences in log₁₀ ACR were found between dippers and non-dippers, whereas HR variables were significantly different between the two groups.

The fall in SBP and DBP overnight was not related to age, duration of diabetes, HbA_{1c}, log₁₀ ACR, insulin dose, height SDS and BMI SDS (all $p>0.05$). In contrast, it was related to 24 h HR (SBP fall: $r=0.12$, $p=0.01$; DBP fall: $r=0.15$, $p<0.01$) and daytime HR (SBP fall: $r=0.18$, $p<0.01$; DBP fall: $r=0.20$, $p<0.01$). In addition, there was no contribution of the nocturnal fall in BP to the risk of developing microalbuminuria in the Cox model ($p>0.05$).

Discussion

In this population of young people with type 1 diabetes we found a high prevalence of abnormal BP values, particu-

Fig. 1 Relationship between baseline ABPM variables and mean adjusted ACR ($\log_{10}$ scale) during follow-up. ACR was adjusted for duration of diabetes, sex and HbA_{1c} , by calculating residuals, which

were then plotted against ABP. Daytime SBP: $\beta=0.15$ (a); daytime DBP: $\beta=0.21$ (b); night-time SBP: $\beta=0.18$ (c)

early nocturnal DBP. Significant differences between male and female patients were found in several ABP variables and this might be related to the age range of the study population. In fact, although BP tends to increase with age, it is during puberty that the sexual dimorphism emerges [29], and this has been related to an effect of sex hormones and pubertal growth [29].

In the present study, all ABPM variables were significantly related to ACR, both at baseline and during follow-up, and daytime DBP was independently associated with

progression to microalbuminuria. This supports our hypothesis that rises in ACR, even within the normal range, may parallel similar progressive increases in ABP. The associations between ACR and ABP at baseline were not explained by HbA_{1c} or BMI, although both these factors were independent contributors of ABP, in line with the findings of previous studies [24, 30, 31]. Similarly, SBP and DBP were independently associated with future changes in ACR during the subsequent follow-up period. In addition, patients developing microalbuminuria during

Table 2 General characteristics and ABPM variables of normoalbuminuric and future microalbuminuric patients

Characteristic/variable	Normoalbuminuric ($n=231$)	Future microalbuminuric ($n=19$)	p value	Adjusted p value ^a
Sex (M/F)	134/97	8/11	NS	
Age (years)	15.2 $\pm$ 2.1	15.5 $\pm$ 2.2	NS	
Age at diagnosis (years)	9.2 $\pm$ 3.8	9.0 $\pm$ 4.1	NS	
Duration (years)	6.1 $\pm$ 3.6	6.6 $\pm$ 4.0	NS	
BMI SDS	0.94 $\pm$ 1.14	0.72 $\pm$ 1.07	NS	
HbA_{1c} (%)	8.8 $\pm$ 1.4	9.9 $\pm$ 1.7	0.001	
ACR (mg/mmol)	0.78 (0.59–1.13)	1.23 (0.97–2.06)	<0.001	
ACR at last visit (mg/mmol)	0.82 (0.59–1.22)	5.70 (5.05–7.51)	<0.001	
ABP and heart rate				
24 h SBP (mmHg)	113 $\pm$ 10	115 $\pm$ 8	NS	NS
24 h DBP (mmHg)	71 $\pm$ 7	76 $\pm$ 6	0.001	0.03
24 h HR (beats per min)	82 $\pm$ 11	87 $\pm$ 7	0.02	NS
Day SBP (mmHg)	116 $\pm$ 10	119 $\pm$ 8	NS	NS
Day DBP (mmHg)	72 $\pm$ 7	79 $\pm$ 6	<0.001	0.003
Day HR (beats per min)	86 $\pm$ 12	93 $\pm$ 7	0.01	NS
Night SBP (mmHg)	104 $\pm$ 10	107 $\pm$ 14	NS	NS
Night DBP (mmHg)	66 $\pm$ 7	70 $\pm$ 10	0.03	NS
Night HR (beats per min)	69 $\pm$ 10	75 $\pm$ 15	0.02	NS
SBP fall (%)	10.4 $\pm$ 7.6	9.8 $\pm$ 10.2	NS	NS
DBP fall (%)	7.8 $\pm$ 8.7	11.4 $\pm$ 11.5	NS	NS

Data are means $\pm$ SD, median (interquartile range) or %

^a Adjusted for HbA_{1c} and ACR

Table 3 Cox proportional hazard regression for the development of microalbuminuria

Variable	Exp(B) ^a	95% CI	<i>p</i> value
Day DBP (mmHg)	1.11	1.03–1.19	0.005
HbA _{1c} (%)	1.44	1.08–1.92	0.014
ACR (mg/mmol)	2.99	1.82–4.90	<0.001

Time variable is years of follow-up after the ABPM assessment

^aExp(B) is for 1-unit increase in the continuous predictor. Other covariates included in the model, but not statistically significant were: age at diagnosis, sex and duration of diabetes

follow-up had higher daytime DBP at the baseline ABPM assessment compared with patients who remained normoalbuminuric. After adjusting for potential confounders, a 1 mmHg rise in daytime DBP increased the risk of developing microalbuminuria by about 11%. This significant effect of daytime DBP persisted even after adjusting for the other ABPM variables, therefore strengthening its independent and dominant association with the progression to microalbuminuria. In adults, pulse pressure has been found to be a key determinant of cardiovascular events and microvascular complications of diabetes [32–34]. In contrast, we could not find any additional or independent effect of pulse pressure over DBP on urinary albumin excretion

and on the progression to microalbuminuria during follow-up (data not shown). However, this different finding could be related to the younger age of our study participants when compared with that of other populations assessed in previous studies [33].

The results of the present study are in line with previous reports, showing that both SBP and DBP are associated with albumin excretion [16, 35] as well as with changes in renal function, such as a decreased renal plasma flow and GFR [16].

Our findings are also not dissimilar from those reported by Lurbe et al. [15] in a population of 75 adolescents with type 1 diabetes. In fact, in that study, the most relevant finding at the first ABPM measurement, in patients who later manifested microalbuminuria, was a similar increase in daytime DBP. Only 2 years later, when they performed a second ABPM, a marked increase in nocturnal BP, with a blunted night-time BP fall was detected. Increases in DBP during daytime might therefore be one of the first BP alterations in patients at risk of developing microalbuminuria, and appears to represent an important variable to monitor over time.

In our population we also assessed the ‘non-dipping’ phenomenon and found a high prevalence of non-dippers, particularly for DBP. A blunted diurnal BP rhythm has often been reported in patients with type 1 diabetes, with a worsening of this abnormal pattern with progression from

Table 4 Dippers vs non-dippers for SBP and DBP

Characteristic/variable	SBP Dippers	Non-dippers	DBP <i>p</i> value	Dippers	Non-dippers	<i>p</i> value
<i>n</i> (%)	251 (52)	235 (48)		194 (40)	292 (60)	
Age (years)	15.7±2.3	15.8±2.3	NS	15.8±2.4	15.8±2.2	NS
Age at diagnosis (years)	8.8±3.9	9.0±3.7	NS	8.6±3.8	9.1±3.8	NS
Duration (years)	6.9±3.9	6.8±3.8	NS	7.1±3.9	6.7±3.8	NS
HbA _{1c} (%)	9.1±1.6	9.5±1.7	0.02	9.3±1.7	9.4±1.7	NS
Insulin (U kg ⁻¹ day ⁻¹)	1.1±0.3	1.1±0.3	NS	1.1±0.3	1.1±0.4	NS
Height SDS	0.26±1.10	0.06±1.04	0.04	0.23±1.07	0.13±1.04	NS
BMI SDS	0.8±0.9	0.7±1.0	NS	0.8±1.0	0.8±0.9	NS
ACR (mg/mmol)	0.85 (0.62–1.24)	0.92 (0.62–1.65)	NS	0.93 (0.61–1.40)	0.83 (0.63–1.42)	NS
ABP and heart rate						
24 h SBP (mmHg)	115±10	112±10	0.01	115±11	113±9	NS
24 h DBP (mmHg)	72±7	72±7	NS	73±7	71±7	0.001
24 h HR (beats per min)	83±11	82±10	NS	84±11	82±10	0.004
Day SBP (mmHg)	120±11	113±10	<0.001	119±12	115±10	0.001
Day DBP (mmHg)	74±8	73±7	0.02	77±8	71±7	<0.001
Day HR (beats per min)	88±12	86±11	0.04	89±12	86±11	<0.001
Night SBP (mmHg)	101±9	109±11	<0.001	103±11	106±10	0.009
Night DBP (mmHg)	66±7	68±8	0.001	63±7	69±7	<0.001
Night HR (beats per min)	69±9	71±11	0.03	70±10	70±10	NS

Data are means±SD, median (interquartile range) or *n* (%)

microalbuminuria to macroalbuminuria [13]. In type 1 diabetes, autonomic dysfunction, reflected by sympathetic overactivity, and alterations in volume regulation have been suggested as potential mechanisms implicated in the pathogenesis of the blunted diurnal rhythm in BP [36–38]. In line with a previous study [39], we found that the most important factors associated with the nocturnal fall in BP were the HR variables, suggesting a role of autonomic dysfunction.

The ‘non-dipping’ phenomenon is a condition known to be associated in adults with an increased risk of end-organ damage [12, 40, 41] and this finding has generated a lot of interest for the potential relationship with vascular disease. Therefore, the high prevalence of impaired fall in nocturnal BP we found may be clinically significant and be associated with an increased risk for the development and/or progression of microvascular and macrovascular complications. However, we could not find any relationship between albumin excretion and the nocturnal fall in BP. This might be related to the high variability in the BP fall overnight in our study population and therefore to significant overlaps across the range of ACR. This high variability associated with the small number of ‘future microalbuminuric’ patients could have also reduced the power of our study to detect a difference in the nocturnal fall between the normoalbuminuric and ‘future microalbuminuric’ groups. In addition, in the present study, ABPM was performed only once, and therefore we could not assess the reproducibility of the dipping/non-dipping, which appears to be variable [42–44] and lower than that of the absolute daytime and night-time values [42], and this could have influenced the study results.

However, previous reports have highlighted a high percentage of non-dippers already among normoalbuminuric populations with type 1 diabetes [45], wide overlaps between normoalbuminuric and microalbuminuric patients [8, 16] as well as lack of associations between the nocturnal dipping and microalbuminuria after adjusting for potential confounders [8]. Based on these data and those from our study, the ‘non-dipping’ phenomenon does not appear to be predictive of risk of microalbuminuria, but it cannot be excluded that it may still be an important determinant of the rate of progression from microalbuminuria to overt diabetic nephropathy. Future studies, with repeated ABPM assessments and longer term follow-up could help in clarifying this aspect.

In conclusion, in this cohort of young people with type 1 diabetes, ABP was significantly related to ACR, suggesting that increasing albumin excretion, even in the normoalbuminuric range, may be associated with parallel rises in arterial BP. In addition, daytime DBP was independently associated with progression to microalbuminuria during follow-up.

Detecting these alterations in BP could represent an important means for an early identification of patients at

risk, before the clinical manifestation of microalbuminuria, and therefore prompt early implementation of preventive measures.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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