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Effects of circadian blood pressure alterations on the development of microvascular complications in pediatric patients with type 1 diabetes mellitus

1형 당뇨병 청소년에서 일중 혈압 변동이 미세혈관 합병증 발생에 미치는 영향

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이 논문을 의학석사 학위논문으로 제출함

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Abstract

Effects of circadian blood pressure alterations on the development of microvascular complications in pediatric patients with type 1 diabetes mellitus

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The effects of circadian blood pressure (BP) alterations on the development and progression of microvascular complications remain to be determined in type 1 diabetes (T1DM). This study evaluated the effects of circadian BP alterations such as non-dipper hypertension with development of microvascular complications during follow-up of patients with childhood-onset T1DM.

We investigated the medical records of 81 pediatric patients (33 males and 48 females) with T1DM who had received 24-h ambulatory BP monitoring (ABPM) between January 2009 and February 2010 at Seoul National University Children's Hospital. The effects of circadian BP alterations such as non-dipper hypertension on the development of microvascular complications over 8 years of follow-up were evaluated after adjusting for glycemic control and the duration of T1DM.

The mean ages at T1DM diagnosis and ABPM evaluation were 8.0 ± 3.9 and

15.6 ± 2.4 years, respectively. Hypertension (daytime, nighttime, and/or 24-h mean hypertension) was present in 42 (51.9%) patients. The results of 24-h ABPM were categorized into three circadian BP groups: dipper (n = 30, 37.0%), non-dipper normotension (n = 18, 22.2%), and non-dipper hypertension (n = 33, 40.7%). During the 8 years of follow-up after ABPM, microvascular complications occurred in eight patients (diabetic retinopathy [DR] in six, microalbuminuria in three, and both in one), of whom seven had non-dipper BP. Nighttime diastolic BP (standard deviation score: 1.29 ± 1.06 vs. 1.85 ± 0.46), nighttime mean arterial pressure (1.28 ± 1.26 vs. 1.98 ± 0.57), and the hemoglobin A1c level (8.5 ± 1.0% vs. 10.1 ± 0.7%) were significantly higher in patients with DR than in those without DR ($p < 0.05$ for all). Daytime or nighttime BP and presence of dipper BP were not related to microvascular complications, but diabetic microvascular complications were more likely to occur in patients with an older age at diagnosis and higher hemoglobin A1c level. In addition, the risk of developing DR was significantly higher in those of adolescent age at diagnosis. The proportion of patients with DR was significantly higher in those with non-dipper hypertension (83.3%) compared with dipper and non-dipper normotension (0% and 16.7%, respectively; $p = 0.021$). As a predictor of microvascular complications, the hazard ratio of non-dipper hypertension was evaluated using Cox proportional hazards regression analysis; however, the results were not significant.

Glycemic control rather than non-dipper hypertension in childhood is the predominant factor determining DR in T1DM patients. Further research is needed to evaluate the relationship between non-dipper hypertension and microvascular complications.

Keywords: type 1 diabetes, ambulatory blood pressure monitoring, hypertension

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LIST OF ABBREVIATIONS

T1DM	Type 1 diabetes mellitus
DR	Diabetic retinopathy
BP	Blood pressure
AHA	American Heart Association
ABPM	Ambulatory blood pressure monitoring
HbA1c	Glycated hemoglobin A
LDL	Low density lipoprotein
HDL	High density lipoprotein
SDS	Standard deviation score
MAP	Mean arterial pressure
CGM	Continuous glucose monitoring

Introduction

In patients with type 1 diabetes mellitus (T1DM), microvascular complications such as microalbuminuria and diabetic retinopathy (DR) are associated with a significant increase in long-term mortality. It is important to prevent complications via thorough blood sugar management and regular check-ups. Despite the considerable evidence that coexisting hypertension and diabetes increase the risks of development and progression of microvascular complications[1],there is insufficient information on the role of blood pressure (BP) alterations in the progression of microvascular complications in diabetes[2]. Children with T1DM suffer from both sustained and masked hypertension[3]. There are some reports that impaired nighttime BP regulation is associated with microalbuminuria[4] and cardiovascular complications[5] in T1DM. Furthermore, the 2014 American Heart Association statement recommended routine performance of 24-h ambulatory BP monitoring (ABPM) in patients with diabetes mellitus for assessing BP patterns such as blunted dipping or isolated sleep hypertension[6].

In this study, we investigated the factors that affect the occurrence of microvascular complications in childhood-onset T1DM patients. We

also evaluated the effects of circadian BP alterations such as non-dipper hypertension on the development of microvascular complications during an 8-year follow-up of patients with childhood-onset T1DM.

Materials and Methods

Study population

We retrospectively investigated the medical records of 91 T1DM patients who had received 24-hour ABPM in pediatric aged between January, 2009 and February, 2010 at Seoul National University Children's Hospital and were under 19 years of age at the time of evaluation and participated in previous ABPM study conducting in our hospital[5]. Among them, 10 patients were excluded acccording to the exclusion criteria (Figure 1). Therefore, total 81 patients with (33 males and 48 females) who were regularly followed up for 8 years in Seoul National University Children's Hospital outpatient clinic were included. The study was conducted according to the Declaration of Helsinki. The study protocol was approved by the ethics committee of Seoul National University and informed consent was waived in line with approval of Seoul National University Institutional Review Board

(IRB No. H-2007-196-1144).

Clinical and biochemical assessment

Laboratory tests included measurements of glycated hemoglobin A (HbA1c), lipid profile (total cholesterol, triglycerides, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol), 24-h urine microalbumin excretion, albumin-to-creatinine ratio, free thyroxine, thyroid-stimulating hormone, and triiodothyronine. Information on the duration of T1DM, height, weight, and age at diagnosis was collected. The mean HbA1c level over the total T1DM duration was recorded from patient files. Blood samples were obtained by venipuncture the morning after an 8–12 h fast. The levels of HbA1c, lipids, free thyroxine, thyroid-stimulating hormone, and triiodothyronine were measured. Some patients could not fast for 12 h because of the risk of hypoglycemia. Total cholesterol, LDL cholesterol, and HDL cholesterol levels were measured by enzymatic calorimetry. The albumin-to-creatinine ratio (mg/mg) or 24-h urine microalbumin excretion (mg/24 h) was measured in a random urine or 24-h urine sample collected from each subject, respectively, using turbidimetric immunoassay. Height (cm) was measured using the Harpenden stadiometer (Holtain Ltd., Crymych, Wales, UK), and weight (kg) was measured using a digital

scale (150 A; Cas Co. Ltd., Seoul, Korea). Body mass index was calculated as weight (kg) divided by height squared (m^2).The standard deviation score (SDS) for height, weight, and body mass index (BMI) was assigned based on the 2017 Korean National Growth Charts for patients over 2 years old[7].

Definition of microvascular complications

Microvascular complications were evaluated over approximately 8 years of follow-up after the ABPM assessment. Screening for the presence or absence of DR was performed by trained ophthalmologists using direct fundoscopy with mydriasis. The age at first pathological eye examination was defined as age at DR onset. Microalbuminuria was defined as excretion of 30 - 300 mg albumin per 24 h or a spot urine albumin-to-creatinine ratio of 30 - 300 mcg/mg on two of three urine collections.

Blood pressure measurements

The average of two sphygmomanometer measurements conducted in the sitting position for at least 5 min was defined as the clinic BP. ABPM was performed using the Tonoport V ambulatory BP system (General Electric, Milwaukee, WI, USA), with a suitably sized cuff

placed around each patient's nondominant arm. The BP system was programmed to measure BP every 20 min from 8:00 A.M. to 10:00 P.M. and every 30 min from 10:00 P.M. to 8:00 A.M. Self-reported sleep - wake times have been used to classify ABPM data into daytime and nighttime periods. The BP indices were calculated from 24-h, daytime, and nighttime measurements[5]. Systolic and diastolic BPs and mean arterial BP (MAP) were analyzed according to normal values adjusted for sex and height, and their SDSs were calculated[8]. The nighttime dip in BP was calculated using the following formula : systolic or diastolic nighttime dip = (daytime systolic or diastolic mean BP - nighttime systolic or diastolic mean BP)/daytime systolic or diastolic mean BP[5]. Hypertension was defined when the daytime, nighttime, or 24-h mean systolic or diastolic BP was higher than the 95th percentile of the normal pediatric ABPM value, which was adjusted for sex and height[8]. Normal BP was defined as daytime, nighttime, and 24-h systolic and diastolic BP < 95th percentile for age and sex. Non-dipper status was defined as nighttime systolic BP or diastolic BP < 10% of the diurnal mean value. Patients were categorized in to three circadian BP groups : dipper, non-dipper normotension, and non-dipper hypertension.

Statistical analysis

All continuous variables were tested for normality and are presented as the mean ± standard deviation or median with interquartile range. Student's t-test or the Mann - Whitney U test was used to compare continuous variables, and the chi-squared test or Fisher's exact test was used to compare categorical variables between two groups. The Cox proportional hazards model was used to identify the predictors of microvascular complications at 8 years after ABPM evaluation. Event-free survival curves for total microvascular complications, DR, and microalbuminuria were constructed using the Kaplan - Meier method. Multivariate models were adjusted for age at T1DM diagnosis and mean HbA1c level from diagnosis to last follow-up. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 22.0; IBM Corp., Armonk, NY, USA).

Results

1. Characteristics of the study population

The clinical characteristics of the patients with T1DM are given in Table 1. The mean age of the patients was 15.6 ± 2.4 years, mean T1DM duration was 7.5 ± 4.0 years, mean BMI was −0.04 ± 0.86

(SDS), and mean HbA1c level was 8.9 ± 1.5% at the time of ABPM evaluation. Among the 81 patients, 33 were male, and 25 were in puberty. No patient had both microalbuminuria and DR between January 2009 and February 2010.

2. BP profiles

All BP values (SDSs) were elevated (Table 2), especially nighttime systolic BP (1.03 ± 1.26), diastolic BP (1.33 ± 1.04), and MAP (1.33 ± 1.23). All BP profiles (mmHg) are summarized in Table 3. Hypertension (daytime, nighttime, and/or 24-h mean hypertension) was observed in 42 patients (51.9%), daytime hypertension in 18 patients (23.5%), nighttime hypertension in 35 patients (43.2%), and 24-h hypertension in 20 patients (24.7%). Fifty-one patients (62.9%) had non-dipper BP. Using the results of 24-h ABPM, patients were categorized into three circadian BP groups: dipper (n = 30, 37.0%), non-dipper normotension (n = 18, 22.2%), and non-dipper hypertension (n = 33, 40.7%). There were no significant difference among the three groups in terms of age at diagnosis, T1DM duration, sex ratio, puberty status, or mean HbA1c level from T1DM diagnosis to ABPM.

3. After 8 years follow-up (Table 4).

The mean age at follow-up was 23.3 ± 2.6 years, the mean T1DM duration was 15.2 ± 4.2 years, BMI was 22.4 ± 2.9 kg/m^2, and the mean HbA1c level was 8.6 ± 1.1 % (Table 4). Over the 8-year follow-up after ABPM evaluation, microvascular complications occurred in eight patients (DR in six, microalbuminuria in three, and both in one; Fig. 2), seven of whom had non-dipper BP. The mean HbA1c level (from diagnosis to last follow-up) was significantly lower in the DR group than non-DR group (8.5 ± 1.0% vs. 10.1 ± 0.7%; $p < 0.001$; Table 4). The mean clinic systolic BP, nighttime diastolic BP, and MAP were significantly higher in the DR than non-DR groups ($p = 0.049$, 0.033, and 0.017, respectively; Tables 2 and 3). Although not statistically significant, the other BP profiles (clinic diastolic BP and MAP; 24-h systolic BP, diastolic BP, and MAP; daytime systolic BP, diastolic BP, and MAP; and nighttime systolic BP, diastolic BP, and MAP) were also higher in the DR group (Table 2). The proportion of patients with DR was significantly higher in the non-dipper hypertension (83.3%) compared with the dipper and non-dipper normotension groups (0% and 16.7%, respectively; $p = 0.021$). Univariate Cox regression analysis after adjustment for T1DM duration showed that the mean HbA1c level (hazard ratio [HR]: 4.84, 95% confidence interval [CI]: 1.97 - 11.92; $p < 0.001$), age at diagnosis (HR: 1.33, 95% CI: 0.98 - 1.81; $p = 0.07$),

and puberty status at diagnosis (HR: 8.478, 95% CI: 1.095 – 65.666; p = 0.041) were significantly related to the development of microvascular complications (Table 5); none of the BP profiles showed a significant relationship. In a multivariate analysis adjusted for age at diagnosis and mean HbA1c level, neither the BP profile nor presence of dipper BP was related to the development of microvascular complications. Regarding microalbuminuria, the mean HbA1c level (from diagnosis to last follow-up) was significantly higher in the microalbuminuria than non-microalbuminuria group (10.1 ± 0.6% vs. 8.6 ± 1.1%; p = 0.019; Table 4). Unlike DR, the BP profiles were not significantly related to microalbuminuria (Tables 2 and 3). In a univariate Cox regression analysis adjusted for T1DM duration, the mean HbA1c level (HR: 3.78, 95% CI: 1.19 – 12.03; p = 0.024) and age at diagnosis (HR: 1.54, 95% CI: 0.93 – 2.55; p = 0.096), but not puberty status at diagnosis or BP profiles, were significantly related to the development of microalbuminuria (Table 5). In a multivariate analysis adjusted for age at diagnosis and mean HbA1c level, the BP profile and presence of dipper were also not related to the development of microvascular complications. Thus, age at diagnosis, the mean HbA1c level (from T1DM diagnosis to complication development) and puberty status at diagnosis were significantly predictive of the development of DR. For

microalbuminuria, only the mean HbA1c level was significantly predictive.

Table 1. Baseline characteristics of participants

Parameter	Total	Diabetic retinopathy		*p*-value	Microalbuminuria		*p*-value
		No	Yes		No	Yes	
N	81	75	6		78	3	
Sex (% male)	33 (40.7%)	45 (60%)	3 (50%)	0.634	33 (42.3%)	0 (0%)	0.146
Age at diagnosis (years)	8.0 ± 3.9	8.0 ± 4.0	7.9 ± 2.1	0.958	7.9 ± 3.9	9.9 ± 1.9	0.407
Puberty at diagnosis (%)	25 (30.9%)	23 (30.7%)	2 (33.3%)	0.892	23 (29.5%)	2 (66.7%)	0.174
At the time of ABPM evaluation							
Age (years)	15.6 ± 2.4	15.5 ± 2.5	16.5 ± 2.0	0.337	15.5 ± 2.5	16.3 ± 2.1	0.617
Diabetes duration (years)	7.5 ± 4.0	7.5 ± 4.1	8.6 ± 2.9	0.529	7.6 ± 4.1	6.4 ± 3.8	0.619
BMI (kg/m^2, SDS)	-0.0 ± 0.9	-0.0 ± 0.9	-0.1 ± 0.6	0.787	-0.1 ± 0.9	0.9 ± 0.7	0.066
average HbA1c (%)*	8.9 (1.9)**	8.6 (1.6)**	10.1 (1.8)**	0.009	8.8 ± 1.3	12.2 ± 3.2	0.204

N, number; BMI, body mass index. *, Average HbA1c from diagnosis to the time of ABPM evaluation; **, Median (IQR).

Table 2. Blood pressure profiles (SDS) of T1DM patients

		Diabetic retinopathy			Microalbuminuria		
Parameter (SDS)	Total (n=81)	No (n=75)	Yes (n=6)	*p*-value	No (n=78)	Yes (n=3)	*p*-value
24-h sBP	0.63 ± 1.29	0.59 ± 1.30	1.07 ± 1.13	0.362	0.63 ± 1.31	0.53 ± 0.92	0.875
24-h dBP	0.92 ± 1.13	0.91 ± 1.15	1.12 ± 0.83	0.582	0.90 ± 1.14	1.51 ± 0.72	0.273
24-h MAP	0.87 ± 1.28	0.83 ± 1.30	1.35 ± 1.06	0.297	0.85 ± 1.30	1.36 ± 0.89	0.424
daytime sBP	0.40 ± 1.24	0.38 ± 1.24	0.65 ± 1.24	0.625	0.40 ± 1.25	0.24 ± 0.74	0.752
daytime dBP	0.61 ± 1.15	0.62 ± 1.17	0.57 ± 0.97	0.906	0.60 ± 1.16	0.98 ± 0.53	0.342
daytime MAP	0.58 (1.6)*	0.75 ± 1.16	0.81 ± 1.14	0.905	0.75 ± 1.17	0.91 ± 0.64	0.704
nighttime sBP	1.03 ± 1.26	0.98 ± 1.27	1.75 ± 0.81	0.071	1.04 ± 1.26	0.88 ± 1.22	0.845
nighttime dBP	1.33 ± 1.04	1.29 ± 1.06	1.85 ± 0.46	0.031	1.32 ± 1.05	1.74 ± 0.56	0.321
nighttime MAP	1.13 (1.5)*	1.28 ± 1.26	1.98 ± 0.57	0.031	1.32 ± 1.25	1.50 ± 0.92	0.774

SDS, standard deviation score; 24-h, 24 hour; sBP, systolic blood pressure; dBP, diastolic blood pressure; MAP, mean arterial pressure. *, Median (IQR).

Table 3. Blood pressure profiles (mmHg) of T1DM patients

		Diabetic retinopathy			Microalbuminuria		
Parameter (mmHg)	Total (n=81)	No (n=75)	Yes (n=6)	*p*-value	No (n=78)	Yes (n=3)	*p*-value
clinical sBP mean	116.5 ± 9.8	115.8 ± 9.5	125.7 ± 9.4	0.049	116.8 ± 9.8	110.0 ± 5.2	0.139
clinical dBP mean	64.0 ± 8.2	63.8 ± 8.5	67.0 ± 3.4	0.084	63.9 ± 8.2	65.7 ± 10.2	0.799
clinical MAP mean	95.3 ± 3.3	95.1 ± 3.3	97.2 ± 3.0	0.157	95.3 ± 3.4	94.6 ± 1.5	0.511
24-h sBP mean	116.7 (8.9)*	117.5 ± 8.2	118.7 ± 7.2	0.719	116.9 (9.5)*	116.1 (9.4)*	0.432
24-h dBP mean	72.3 ± 6.0	72.2 ± 6.1	72.9 ± 4.4	0.739	72.2 ± 6.1	75.0 ± 3.3	0.272
24-h MAP mean	87.4 ± 6.3	87.3 ± 6.5	88.2 ± 5.0	0.712	87.3 ± 6.4	88.4 ± 3.6	0.673
daytime sBP mean	119.8 (10.8)*	120.7 ± 8.2	120.5 ± 8.7	0.949	120.8 ± 8.3	117.9 ± 4.2	0.353
daytime dBP mean	75.8 ± 6.6	75.9 ± 6.6	75.4 ± 6.1	0.869	75.8 ± 6.6	78.2 ± 3.0	0.293
daytime MAP mean	90.8 ± 6.8	90.8 ± 6.8	90.4 ± 6.7	0.899	90.8 ± 6.9	91.4 ± 3.4	0.778
nighttime sBP mean	110.4 ± 9.3	110.0 ± 9.5	114.8 ± 5.7	0.105	110.5 ± 9.4	107.8 ± 8.1	0.621
nighttime dBP mean	63.9 ± 6.8	63.7 ± 6.9	67.4 ± 3.1	0.033	63.9 ± 6.9	66.3 ± 4.2	0.418
nighttime MAP mean	79.4 ± 7.2	79.1 ± 7.4	83.2 ± 2.9	0.017	79.4 ± 7.3	80.1 ± 5.5	0.839
systolic dip (%)	8.5 ± 5.6	8.8 ± 5.6	4.5 ± 4.3	0.06	8.5 ± 5.6	8.5 ± 6.7	0.989
diastolic dip (%)	15.5 ± 8.2	15.9 ± 8.2	10.2 ± 7.1	0.114	15.5 ± 8.4	15.2 ± 3.8	0.914

sBP, systolic blood pressure; SDS, standard deviation score; dBP, diastolic blood pressure; MAP, mean arterial pressure; 24-h, 24 hour. *, Median (IQR).

Table 4. 8-years follow up characteristics of T1DM patients

Parameter	Total (n=81)	Diabetic retinopathy			Microalbuminuria		
		No (n=75)	Yes (n=6)	*p*-value	No (n=78)	Yes (n=3)	*p*-value
Age (years)	23.3 ± 2.6	24.4 ± 2.8	23.2 ± 2.6	0.111	25.3 ± 3.0	23.6 ± 2.3	0.169
T1DM duration (years)	15.2 ± 4.2	16.4 ± 4.3	14.9 ± 2.9	0.313	17.4 ± 4.5	13.9 ± 2.8	0.100
BMI	21.6 (3.7)*	22.5 ± 2.9	20.0 ± 1.1	0.001	22.4 ± 2.9	21.9 ± 3.4	0.765
Mean HbA1c (%)	8.6 ± 1.1	8.5 ± 1.0	10.1 ± 0.7	<0.001	8.6 ± 1.1	10.1 ± 0.6	0.019
FU duration (years)**	7.7 ± 0.8	8.9 ± 1.8	6.1 ± 1.1	<0.001	8.0 ± 0.1	6.6 ± 0.9	0.118
Age at event (years)***		NA	22.6 ± 2.2		NA	22.9 ± 2.6	
T1DM duration at event (years)***		NA	14.6 ± 2.6		NA	13.0 ± 4.4	
Dipper	30 (37.0%)	30 (40.0%)	0 (0%)		29 (37.1%)	1 (1.2%)	
Non-dipper normotension	18 (22.2%)	17 (22.7%)	1 (16.7%)	0.021	17 (21.8%)	1 (1.2%)	0.774
Non-dipper hypertension	33 (40.7%)	28 (37.3%)	5 (83.3%)		32 (41.0%)	1 (1.2%)	

N, number; BMI, body mass index; FU, follow-up; NA, not available; NHTN, non hypertension; HTN, hypertension. *, Median (IQR);**, from ABPM evaluation to last follow-up about 8years;***, event means development of microvascular complications.

Table 5. Predictors for microvascular complications

	Diabetic retinopathy				Microalbuminuria			
	HR (95%CI)	*p* value	adj. HR**(95%CI)	adj.*p* value	HR (95%CI)	*p* value	adj. HR**(95%CI)	adj.*p* value
Age at diagnosis (years)	1.33 (0.98, 1.81)	0.070			1.54 (0.93, 2.55)	0.096		
Mean HbA1c (%)*	4.84 (1.97, 11.92)	<0.001			3.78 (1.19, 12.03)	0.024		
Puberty at diagnosis	8.478 (1.10, 65.67)	0.041			524.01 (0.00, 2.70)	0.490		
24-h sBP SDS	1.28 (0.69, 2.38)	0.430	1.919 (0.16, 23.13)	0.608	0.91 (0.37, 2.25)	0.845	0.62 (0.12, 3.19)	0.570
24-h dBP SDS	1.13 (0.54, 2.36)	0.739	1.399 (0.38, 5.14)	0.613	1.49 (0.60, 3.66)	0.389	2.36 (0.29, 18.95)	0.420
24-h MAP SDS	1.33 (0.72, 2.45)	0.367	0.974 (0.35, 2.68)	0.960	1.3 (0.56, 3.00)	0.536	1.25 (0.28, 5.59)	0.770
daytime sBP SDS	1.12 (0.59, 2.12)	0.728	0.554 (0.16, 1.90)	0.347	0.86 (0.33, 2.23)	0.759	0.75 (0.16, 3.53)	0.720
daytime dBP SDS	0.89 (0.43, 1.83)	0.751	0.89 (0.30, 2.66)	0.835	1.24 (0.49, 3.13)	0.643	1.91 (0.32, 11.41)	0.478
daytime MAP SDS	0.97 (0.48, 1.95)	0.930	0.731 (0.26, 2.07)	0.555	1.07 (0.40, 2.83)	0.891	1.20 (0.29, 4.99)	0.806
nighttime sBP SDS	1.64 (0.87, 3.09)	0.128	1.064 (0.33, 3.44)	0.917	0.88 (0.34, 2.26)	0.794	0.402 (0.08, 2.14)	0.285
nighttime dBP SDS	1.64 (0.73, 3.67)	0.230	3.207 (0.51, 20.35)	0.216	1.41 (0.46, 4.36)	0.550	0.638 (0.09, 4.46)	0.651
nighttime MAP SDS	1.56 (0.82, 2.97)	0.179	1.63 (0.48, 5.60)	0.437	1.08 (0.43, 2.73)	0.865	0.495 (0.10, 2.67)	0.413

sBP, systolic blood pressure; SDS, standard deviation score; dBP, diastolic blood pressure; MAP, mean arterial pressure.*Average HbA1c from diagnosis to last follow up; **Multivariate analysis with adjusting age at diagnosis and average HbA1c level.

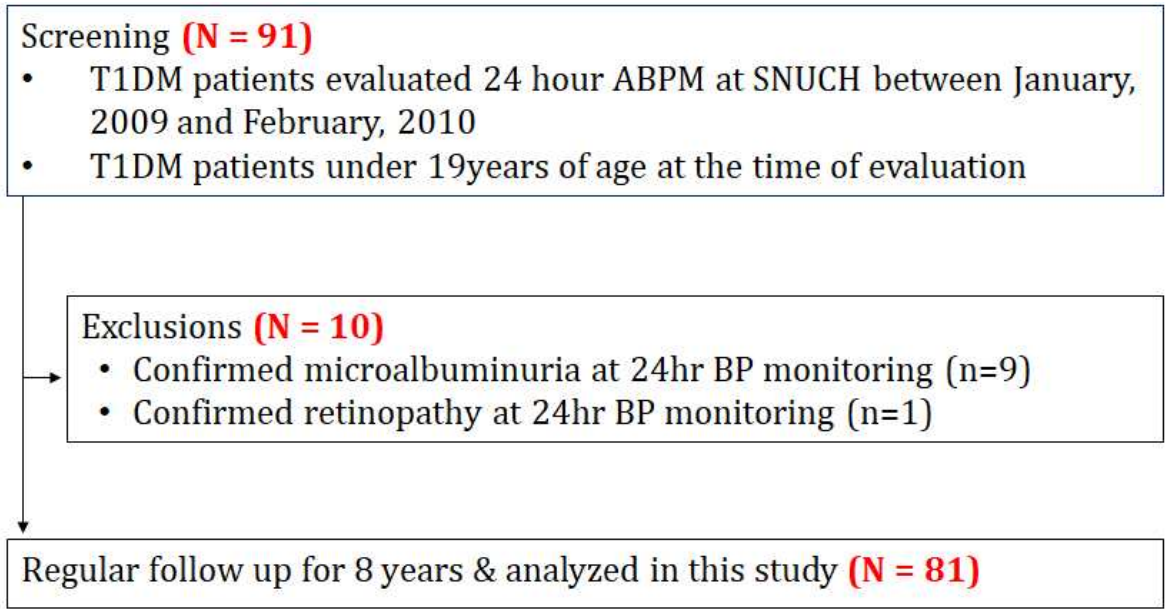

Figure 1. **Patient selection criteria for inclusion in the study.** Among the 91 patients, 9 with microalbuminuria and 1 with DR at the 24-h ABPM evaluation were excluded. Therefore, a total of 81 patients were included in this study.

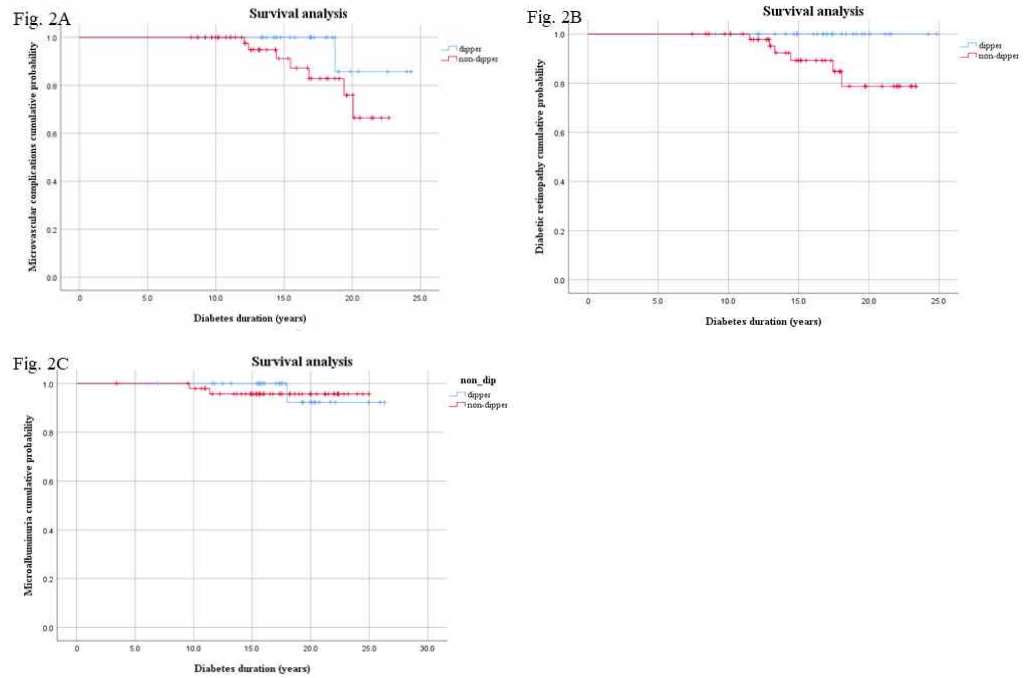

Figure 2. Kaplan - Meier survival curves. Cumulative probabilities of (A) total microvascular complications (microalbuminuria and DR) (p = 0.105), (B) DR (p = 0.038), and (C) microalbuminuria (p = 0.85) according to T1DM duration. Over the 8-year follow-up after ABPM evaluation, microvascular complications occurred in eight patients (DR in six, microalbuminuria in three, and both in one), of whom seven had non-dipper BP.

Discussion

T1DM is potentially associated with serious microvascular and macrovascular complications. Although intensive glycemic control reduces the incidence of microvascular and macrovascular complications, many patients with T1DM still develop complications such as microalbuminuria, neuropathy, and retinopathy, which are specific to diabetes. Hyperglycemia predominantly affects the retina, peripheral nerves, and renal glomeruli, none of which can downregulate glucose uptake in the presence of increased levels of extracellular glucose[9]. Not only hyperglycemia but also the diabetes duration, age, and pubertal stage are critical factors affecting the development of microvascular complications[10]. Several studies reported that impaired BP regulation and increased BP influence the occurrence of microvascular complications in both children and adolescents[4,5,11,12]. The usefulness of BP evaluation using ABPM has been actively investigated in adults, but there have been relatively few studies in children. The prevalence of masked hypertension, a predictor of target organ damage in pediatric patients[13,14], is reportedly 9.5% in youths with T1DM[15]. The 2014 American Heart Association statement recommended ABPM implementation in T1DM patients[6]. Although BP is influenced by age, sex, body size, and ethnicity, particularly in pediatric patients, there have been few ABPM studies in pediatric T1DM patients in Korea. The main findings of this study were identification of the risk factors for microvascular complications, incidence of complications, and BP profiles determined by ABPM in pediatric T1DM patients in Korea.

HbA1c, age at diagnosis, and puberty status at diagnosis were reported to be associated with DR[16]. However, in our study, the only modifiable predictor of

microvascular complications was a high HbA1c level after adjustment for the T1DM duration. In comparisons of the three BP groups (dipper, non-dipper normotension, non-dipper hypertension), the incidence of DR was significantly higher in the non-dipper group than in the dipper group, suggesting that circadian BP changes are associated with microvascular complications. However, high BP, altered circadian BP rhythm, sex, and BMI were not predictors of microvascular complications. Although no association between the BP profile and microvascular complications was found, there was a significant difference in the mean BP between patients with complications and those without complications. These results may have been because of the low incidence of microvascular complications or the long duration from ABPM measurement to complication development. Therefore, further evaluation of the relationships of circadian BP alterations and BP profiles with microvascular complications is needed.

In patients with childhood-onset T1DM, the cumulative prevalence of microalbuminuria is approximately 25–30% at 10 years and 40–60% at 20 years after T1DM diagnosis[17,18]. The prevalence of DR, which causes vision loss, ranged from 50% to 90% at 10 and 20–30 years after T1DM diagnosis, respectively, reported in a study published in 2017[19]. A multicenter study in the United kingdom published in 2019 reported a DR prevalence of 11% and mean diabetes duration of 7.67±3.72 years[20]. In our study, 7.4% of patients were diagnosed with DR, and their mean T1DM duration was 14.6±2.6 years. Only 3.7% of patients were diagnosed with microalbuminuria, and their mean diabetes duration was 13.0±4.4 years; none were diagnosed with macroalbuminuria. The incidence of microvascular complications should be re-examined at a diabetes duration of 20 or 30 years. The incidence of microvascular complications at 10 years was lower in our study compared with previous studies[17,18,19], possibly due

to the management of blood sugar via insulin multi-injection therapy and regular outpatient clinical examinations. The incidence and severity of complications at a diabetes duration of 10 years have decreased in the more recent era of T1DM. Updated projections should be used when informing newly diagnosed individuals of their prognosis and for healthcare cost assessments. Blood sugar management via continuous glucose monitoring (CGM) was introduced in Korea approximately 5 years ago and is now covered by insurance; thus, many patients currently use CGM[21]. Therefore, further research is needed on changes in blood glucose management and in the incidence of microvascular complications after more strict blood glucose control using CGM.

There are no reports on BP levels measured by ABPM in T1DM patients in Korea. The BP profiles of our study population are summarized in Table 2. Usually, the treatment criterion for high BP and the definition of hypertension for the general public are BP > 95th percentile. According to an article published in 2018[16], T1DM patients with BP > 90th percentile should be treated with angiotensin-converting enzyme inhibitors or other BP-lowering agents. The routine performance of 24-h ABPM is recommended in patients with diabetes mellitus to assess BP patterns such as blunted dipping or isolated sleep hypertension[6]. Alterations in circadian BP rhythm have been frequently documented in hypertension, type 2 diabetes mellitus, chronic kidney disease, and sleep apnea syndrome and are generally regarded as a harmful condition[22]. Kilicet al.[23] suggested that individuals with non-dipper normotension are at risk of target organ damage[23]. In this study, no association between BP and the occurrence of microvascular complications was identified. However, the link between BP and microvascular complications in T1DM patients is widely known. Therefore, BP monitoring and strict management using ABPM are needed and

should be evaluated.

This study had some limitations. First, the size of the patient population was small compared with larger studies of type 2 diabetes. Second, as BP was not measured by ABPM at the time of complication development, the degree of complications caused by changes in BP measured by ABPM is unknown. Third, few patients had complications, but there were limitations in analyzing the characteristics of the patients with microvascular complications.

In conclusion, the occurrence of microvascular complications in patients with T1DM has a large impact on quality of life. Several factors that affect the occurrence of microvascular complications have been evaluated, but blood sugar control is very important over the long term, and further research on circadian BP alterations is needed. Therefore, blood sugar monitoring using CGM, BP monitoring using ABPM, and their impacts on disease progression require additional studies.

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국문초록

1형 당뇨 환자에서 미세혈관 합병증의 발생과 진행에 24시간 혈압 변화가 미치는 영향에 대해선 아직 명확히 밝혀진 바가 없다. 본 연구는 소아 청소년기에 1형 당뇨로 진단 된 환자들을 경과관찰 하여, non-dipper와 같은 일중혈압변동이 미세혈관 합병증의 발생에 미치는 영향을 평가하고자 한다.

2009년 1월부터 2010년 2월 까지 서울대학교 어린이 병원에서 소아청소년기에 24시간 활동 혈압을 측정한 81 명의 1형 당뇨 환자 (남자 33명, 여자 48명)의 의무기록을 후향적으로 분석하였다. non-dipper와 같은 일중 혈압 변동이 8년 추적관찰 기간 동안 당뇨병성 미세혈관합병증의 발생에 미치는 영향을 확인하기 위해 혈당조절과 유병기간을 보정 하여 평가하였다.

연구에 참여한 환자들의 평균 1형 당뇨 진단 나이는 8.0 ± 3.9 세, 24시간 활동 혈압 측정당시 나이는 15.6 ± 2.4 세였다. 이들 중 고혈압 (낮, 밤, 24시간 평균)은 42명 (51.9%) 였다. 그리고 이들의 24시간 활동혈압결과로 3 그룹; dipper (n=30, 37.0%), 정상혈압과 non-dipper (n=18, 22.2%), 고혈압과 non-dipper (n=33, 40.7%)으로 나누었다. 24시간 활동 혈압 측정 후 8년 추적관찰 기간 동안, 미세혈관 합병증은 8명 (당뇨병성 망막병증 6명, 미세알부민뇨 3명, 모두 1명) 에서 발생하였고, 그 중 7명은 non-dipper였다. 당뇨병성 망막병증이 발생한 환자들의 밤시간 이완기 혈압 (1.29 ± 1.06 SDS vs. 1.85 ± 0.46 SDS)과 밤시간 평균 동맥압 (1.28 ± 1.26 SDS vs. 1.98 ± 0.57 SDS), 진단 시부터 망막병증이 발생하거나 마지막 추적관찰 기간까지의 당화혈색소 평균 (8.5 ± 1.0 % vs. 10.1 ± 0.7 %)이 망막병증이 발생하지 않은 환자들에 비해 유의 하게 (p<0.05 for all) 높았다. 낮 또는 밤시간 혈압과 dipper의 유무는 미세혈관합병증과 관련이 없었으나, 진단 시 나이가 많을수록, 당화혈색소가 높을수록 당뇨병성 미세혈관합병증이 잘 발생 하였으며, 진단 시 사춘기 인 경우에는 망막병증의 발생 위험이 통계적으로 유의하게 높았다 (p-value < 0.05). ABPM 결과로 분류한 세 그룹을 비교 했을 때, dipper, 정상혈압 non-dipper,

고혈압 non-dipper 순으로 갈수록 당뇨병성 망막병증이 발생 비율이 증가 (0%, 16.7%, 83.3%, p=0.021) 했다. 하지만, 미세혈관합병증 발생 예측 인자로 cox 회귀 분석을 시행 했을 시, non-dipper의 유무는 통계적으로 유의미한 결과는 볼 수 없었다.

이 연구를 통하여 소아청소년기에 진단된 1형 당뇨 환자에서 24시간 혈압 변동 보다 혈당 조절이 당뇨병성 미세혈관합병증 발생에 주로 영향을 미치는 것을 알 수 있었다. 하지만, 혈압과 미세혈관합병증이 관계가 없다고 할 수는 없으며, 추가적인 연구가 필요하다.

주요어: 1형 당뇨, 24시간 활동 혈압 측정, 고혈압

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