Implications of Nocturnal Hypertension in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE—Diabetes is associated with atherogenic risk factors. Hypertension has a major influence on cardiovascular disease in diabetic patients. Ambulatory blood pressure monitoring (ABPM) is useful for identifying nocturnal hypertension. Carotid intima-media thickness (cIMT) is a good measure for identifying subclinical atherosclerosis. This study aimed to evaluate whether nocturnal hypertension affects atherosclerosis in children and adolescents with type 1 diabetes and to investigate the relationship between atherogenic risk factors and cIMT.

RESEARCH DESIGN AND METHODS—ABPM and cIMT were measured in 82 diabetic children and adolescents. We reviewed the hemoglobin A_{1c} levels, 24-h urine microalbumin excretion, lipid profiles, and duration of diabetes. Nocturnal hypertension was defined as hypertension observed only at night.

RESULTS—Forty-three (52%) subjects were hypertensive, and 30 subjects were classified as having nocturnal hypertension. cIMT was higher in the nocturnal hypertensive group than in the normotensive group (0.44 ± 0.03 vs. 0.42 ± 0.04 mm, $P = 0.026$). Among children and adolescents with nonhypertensive blood pressure levels in clinic blood pressure monitoring, cIMT and daytime blood pressure were higher in the nocturnal hypertensive group. All ABPM parameters were significantly related to cIMT in multiple linear regression analysis.

CONCLUSIONS—This study showed significantly increased cIMT and daytime blood pressure in diabetic children and adolescents with nocturnal hypertension. ABPM may be a useful method for detecting the macrovascular complications of type 1 diabetes. Longitudinal studies are needed to find the causes of nocturnal hypertension and to evaluate the effect of nocturnal hypertension on atherosclerosis in type 1 diabetes.

Type 1 diabetes is a risk factor for the development of cardiovascular disease. Patients with diabetes show a 2- to 10-time greater risk of developing atherosclerotic lesions compared with the normal population (1). Although the complications caused by atherosclerosis usually appear in adulthood, atherosclerotic changes at the endothelial level begin in childhood and progress rapidly in the presence of risk factors (2,3). Therefore, early detection and treatment of risk factors for cardiovascular disease related to type 1 diabetes beginning in childhood are important (4).

The prevalence of hypertension is 8% in adolescents between the ages of 12 and 19 years in the U.S. (5), but the prevalence is 73% in children and adolescents with type 2 diabetes and 22% in children and adolescents with type 1 diabetes. These differences suggest that the prevalence of hypertension is significantly higher in young people with either type 1 or type 2 diabetes. A considerable number of patients with type 1 diabetes have two or more additional cardiovascular disease risk factors (6). The need to manage the risks for cardiovascular disease associated with type 1 diabetes should be considered from childhood.

Ambulatory blood pressure monitoring (ABPM), which now is used in the diagnosis of hypertension, can detect and characterize changes in blood pressure during daily activities (7) and is superior to clinical blood pressure monitoring in predicting cardiovascular morbidity and mortality (8). The risk of nephropathy increases in adolescents with type 1 diabetes with elevated nighttime blood pressure, as measured by ABPM (9). For these reasons, ABPM may be recommended for pediatric patients with diabetes (7).

Carotid intima-media thickness (cIMT) measured by vascular ultrasound also is used as a subclinical marker of hypertensive vascular damage (10). In adults, increased cIMT is an indirect indicator of atherosclerosis and is an important predictor of cardiovascular morbidity and mortality (11). In children, cIMT increases in diseases with increased cardiovascular risk, including diabetes (12) and familial hypercholesterolemia (13). However, there are few studies on the effect of night-time blood pressure, measured by ABPM, on atherosclerosis and macrovascular complications in children with type 1 diabetes.

This study was conducted to determine the relationship between nocturnal hypertension and cIMT, a surrogate marker of atherosclerosis, and to search for potential atherogenic risk factors in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

—This study included children and adolescents aged 12–19 years who were diagnosed with type 1 diabetes between January 2009 and March 2010 and who were treated for at least 1 year at the endocrinology clinic of Seoul National University Children's Hospital. Patients who were taking antihypertensive drugs or ACE inhibitors were excluded. A total of 82 patients underwent ABPM and had their cIMT measured. The average of two sphygmomanometer measurements, after the subject had been in a sitting position for at least 5 min, was regarded as the patient's clinic blood pressure.

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Participants with systolic or diastolic blood pressure higher than the 95th percentile for age, sex, and height for Korean children and adolescents (14) were classified as having hypertension. Laboratory test results included 24-h urine microalbumin excretion, lipid profile, and levels of high-sensitivity C-reactive protein and glycosylated hemoglobin A_{1c} (HbA_{1c}). Information on the patients' duration of diabetes, daily insulin dose, height, and weight was collected. The study was conducted according to the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Seoul National University (Seoul, Korea).

ABPM parameters

ABPM was performed using a Tonoport V ambulatory blood pressure system (General Electric, Milwaukee, WI), with a suitably sized cuff around each patient's nondominant arm. The blood pressure system was programmed to measure 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 divide ABPM data into daytime and nocturnal periods.

Hypertension was defined when the daytime or nighttime mean systolic or diastolic blood pressure was higher than the 95th percentile blood pressure of the pediatric norms for ABPM (15). To adjust for sex and height, a blood pressure index was calculated using the following formula: blood pressure index = measured mean systolic or diastolic blood pressure/95th percentile systolic or diastolic blood pressure for sex and height according to the pediatric norms for ABPM (10).

The blood pressure indices were calculated from 24-h, daytime, and nighttime measurements. The night dip in blood pressure was calculated using the following formula: systolic/diastolic night dip = (daytime systolic or diastolic mean blood pressure − nighttime systolic or diastolic mean blood pressure)/daytime systolic or diastolic mean blood pressure (7). Normal dipping is defined as a ≥10% decline in blood pressure.

cIMT

cIMT was measured using a high-resolution B-mode ultrasound (Vivid 7 Dimension; General Electric) and is expressed as mean cIMT. cIMT was defined as the distance between the lumen-intima and media-adventitia borders of the right common carotid artery and was measured 1 cm below the right carotid body while the patient was in a recumbent position with his or her neck tilted slightly to the left. cIMT was measured at least three times, and the average value was used to calculate the mean cIMT. Two experienced sonographers, who did not know the clinical or laboratory information of the study patients, performed the cIMT ultrasounds. The intra- and interobserver variability expressed as coefficients of variation were 5.4 and 5.8% for cIMT, respectively.

Laboratory methods

Blood samples were obtained by venipuncture in the morning after an 8- to 12-h fast. The levels of HbA_{1c}, high-sensitivity C-reactive protein, total cholesterol, LDL cholesterol, and HDL cholesterol were measured. Some patients could not fast for 12 h because of the risk of hypoglycemia; non–HDL cholesterol (total cholesterol minus HDL cholesterol) also was calculated. Total cholesterol, LDL cholesterol, and HDL cholesterol were measured by enzymatic calorimetry. Dyslipidemia was defined when LDL cholesterol was ≥100 mg/dL (2.6 mmol/L) according to the International Society for Pediatric and Adolescent Diabetes guidelines (4) or when HDL cholesterol was <40 mg/dL (1.0 mmol/L), according to the National Cholesterol Education Program Adult Treatment Panel III (16).

The serum or plasma high-sensitivity C-reactive protein levels were measured by latex agglutination, and 24-h urine microalbumin excretion was measured by an immunoturbidimetric assay. Microalbuminuria was diagnosed when the microalbumin excretion was ≥30 mg in two consecutive 24-h urine samples.

Statistics

The data are expressed as means ± SD. All statistical analyses were performed using SPSS 12.0 (SPSS, Inc., Chicago, IL). The mean values were compared between the study groups using the Student *t* test, and frequencies and proportions were compared using the χ^2 test. Univariate associations between the variables in the study were analyzed by calculating the Pearson correlation coefficients. Multiple linear regression analyses were performed to evaluate the multivariate associations between cIMT (dependent variable) and atherosclerotic risk factors (independent variables). A P value <0.05 was considered significant.

RESULTS

Comparison of clinical and laboratory data between the hypertensive and nonhypertensive groups, as classified by ABPM

Basic clinical and laboratory characteristics of participants in the study are summarized in Table 1. Thirty-nine of

Table 1—*Auxological data of the participants*

Characteristics	
N	82
n (male; female)	39:43
Age (years)	15.78 ± 2.06
Mean HbA_{1c} level in the previous year (%)	9.14 ± 1.90
Diabetes duration (years)	7.87 ± 3.82
BMI-SD score	−0.14 ± 0.87
Daily insulin dose (per kg)	0.95 ± 0.32
LDL cholesterol (mg/dL)	96.04 ± 26.12
HDL cholesterol (mg/dL)	63.65 ± 15.50
Non–HDL cholesterol (mg/dL)	110.20 ± 27.05
24-h urine microalbumin (mg/day)	11.69 ± 19.73
Clinical systolic blood pressure (mmHg)	116.90 ± 9.83
Clinical diastolic blood pressure (mmHg)	64.33 ± 7.90
24-h systolic blood pressure mean (mmHg)	117.75 ± 7.40
24-h diastolic blood pressure mean (mmHg)	72.8 ± 5.56
Daytime systolic blood pressure mean (mmHg)	120.79 ± 7.81
Daytime diastolic blood pressure mean (mmHg)	76.29 ± 6.35
Nighttime systolic blood pressure mean (mmHg)	110.98 ± 8.26
Nighttime diastolic blood pressure mean (mmHg)	64.94 ± 5.86
Systolic dip (%)	8.40 ± 4.70
Diastolic dip (%)	14.72 ± 7.41

Data are means ± SD.

82 patients were male (48%), and 43 were female (52%). The mean age of the patients was 15.78 ± 2.06 years. At the start of the study, seven patients had nephropathy, one had neuropathy, and two had retinopathy. Forty-three (52%) patients had daytime or nighttime hypertension (hypertensive group), and 39 (48%) patients showed nonhypertensive blood pressure levels (nonhypertensive group) when classified by ABPM. There were no significant differences between the two groups in age, duration of diabetes, mean HbA_{1c} level for the past year, and LDL cholesterol concentration. However, cIMT was significantly higher in the hypertensive group than in the nonhypertensive group (0.45 ± 0.04 mm vs. 0.42 ± 0.04 mm, $P = 0.004$), and HDL cholesterol concentration was significantly lower in the hypertensive group than in the nonhypertensive group (60.00 ± 13.84 mg/dL vs. 67.67 ± 16.40 mg/dL, $P = 0.026$).

Comparison of clinical and laboratory data between the nocturnal hypertensive and nonhypertensive groups as classified by ABPM

The patients were divided into two groups according to blood pressure measured by ABPM: those who had hypertension only during the night (nocturnal hypertensive group [$n = 32$]) and those with nonhypertensive blood pressure levels (nonhypertensive group [$n = 39$]). cIMT was significantly greater in the nocturnal hypertensive group (0.44 ± 0.03 mm) than in the nonhypertensive group (0.42 ± 0.04 mm) ($P = 0.026$). HDL cholesterol concentration was significantly lower in the nocturnal hypertensive group (60.09 ± 14.81 mg/dL) than in the nonhypertensive group (67.67 ± 16.40 mg/dL) ($P = 0.045$). There were no significant differences in age, sex, daily insulin dose per kilogram, and 24-h urine microalbumin excretion between the two groups.

Comparison of clinical and laboratory data between the nocturnal hypertensive and nonhypertensive groups with an HDL cholesterol concentration ≥40 mg/dL

The results mentioned above suggested that cIMT might be high because of low HDL cholesterol concentrations in the hypertensive and nocturnal hypertensive groups. We classified the patients with an HDL cholesterol concentrations ≥40 mg/dL into two groups: those with hypertension only at night (nocturnal hypertensive group [$n = 30$]) and those with nonhypertensive blood pressure levels (nonhypertensive group [$n = 38$]) (Table 2). Although HDL cholesterol concentrations did not differ significantly between the two groups, cIMT was significantly greater in the nocturnal hypertensive group. The daytime systolic and diastolic mean blood pressure values were within nonhypertensive levels in the two groups but were slightly higher in the nocturnal hypertensive group. After adjusting for age and sex, the daytime systolic blood pressure index still was higher in the nocturnal hypertensive group (0.91 ± 0.04) than in the nonhypertensive group (0.88 ± 0.04) ($P = 0.002$). The daytime diastolic blood pressure index also was higher in the nocturnal hypertensive group (0.90 ± 0.05) than in the nonhypertensive group (0.87 ± 0.06) ($P = 0.031$). The proportions of patients without night dipping were 28 of 30 in the nocturnal hypertensive group and 19 of 38 in the nonhypertensive group ($P < 0.001$). Of seven patients with nephropathy, three had normal blood pressure and four had only nocturnal hypertension; thus, the frequency of microalbuminuria did not differ between the two groups ($P = 0.691$). Dyslipidemia, defined as an LDL cholesterol concentration ≥100 mg/dL, was observed in 17 patients in the nonhypertensive group and in 13 patients in the nocturnal hypertensive group, but the frequency of dyslipidemia did not differ significantly between groups.

Comparison of clinical and laboratory data between the nocturnal hypertensive and nonhypertensive groups in patients with nonhypertensive blood pressure levels in clinic blood pressure monitoring

The patients who had normal blood pressure measured clinically were divided into two groups: those with nocturnal hypertension only when measured by ABPM (nocturnal hypertensive group) and those with nonhypertensive blood pressure levels during ABPM (nonhypertensive group) (Table 3). The cIMT was significantly greater in the nocturnal hypertensive group ($P = 0.030$). Daytime systolic and diastolic blood pressure indices also were significantly higher in the nocturnal hypertensive group ($P = 0.002$ and $P = 0.036$, respectively).

Correlation between cIMT and atherogenic risk factors

cIMT in children and adolescents with type 1 diabetes did not correlate with BMI-SD

Table 2—*Comparison of clinical and laboratory data between the nocturnal hypertensive group and the nonhypertensive group according to HDL cholesterol concentrations ≥40 mg/dL*

	Nocturnal hypertensive group	Nonhypertensive group	*P*
N	30	38	
n (male; female)	13:17	17:21	
Age (years)	15.82 ± 2.00	15.46 ± 2.13	0.473
Age at diagnosis (years)	7.87 ± 3.74	8.09 ± 3.46	0.801
Mean HbA_{1c} level in the previous year (%)	8.89 ± 1.69	9.30 ± 2.13	0.390
Diabetes duration (years)	7.95 ± 3.66	7.36 ± 3.70	0.516
cIMT (mm)	0.44 ± 0.03	0.42 ± 0.04	0.020*
BMI-SD score	−0.03 ± 0.92	−0.24 ± 0.71	0.318
Daily insulin dose (per kg)	0.93 ± 0.31	0.94 ± 0.36	0.917
LDL cholesterol (mg/dL)	94.70 ± 22.28	97.68 ± 24.01	0.598
HDL cholesterol (mg/dL)	61.53 ± 14.15	68.58 ± 15.99	0.056
Non–HDL cholesterol (mg/dL)	109.70 ± 27.70	111.66 ± 25.14	0.764
24-h urine microalbumin (mg/dL)	10.85 ± 11.97	12.03 ± 25.21	0.801
Daytime mean systolic blood pressure (mmHg)	120.83 ± 6.35	116.85 ± 5.50	0.009*
Daytime mean diastolic blood pressure (mmHg)	75.82 ± 4.22	73.41 ± 4.99	0.034*
Daytime mean systolic blood pressure index	0.91 ± 0.04	0.88 ± 0.04	0.002*
Daytime mean diastolic blood pressure index	0.90 ± 0.05	0.87 ± 0.06	0.031*

Data are means ± SD. *$P < 0.05$ by Student *t* test.

Table 3—*Comparison between the nocturnal hypertensive group and the nonhypertensive group in patients with normal blood pressure in clinic blood pressure monitoring*

	Nocturnal hypertensive group	Nonhypertensive group	*P*
N	26	32	
n (male; female)	10:16	13:19	
Age (years)	15.79 ± 2.11	15.46 ± 2.16	0.564
Age at diagnosis (years)	7.49 ± 3.78	8.57 ± 3.38	0.264
Mean HbA_{1c} level in the previous year (%)	8.95 ± 1.76	9.67 ± 2.08	0.163
Diabetes duration (years)	8.29 ± 3.79	6.89 ± 3.57	0.156
cIMT (mm)	0.44 ± 0.03	0.42 ± 0.04	0.030*
BMI-SD score	−0.09 ± 0.97	−0.27 ± 0.76	0.446
Daily insulin dose (per kg)	0.93 ± 0.27	0.95 ± 0.38	0.847
LDL cholesterol (mg/dL)	96.92 ± 22.34	96.69 ± 23.29	0.969
HDL cholesterol (mg/dL)	62.23 ± 18.70	69.19 ± 15.95	0.079
Non–HDL cholesterol (mg/dL)	112.31 ± 27.13	111.81 ± 25.02	0.943
24-h urine microalbumin (mg/day)	11.25 ± 12.70	13.68 ± 27.19	0.656
Daytime mean systolic blood pressure (mmHg)	120.04 ± 5.29	116.23 ± 4.92	0.007*
Daytime mean diastolic blood pressure (mmHg)	75.54 ± 3.79	73.08 ± 4.99	0.038*
Daytime mean systolic blood pressure index	0.91 ± 0.03	0.88 ± 0.04	0.002*
Daytime mean diastolic blood pressure index	0.90 ± 0.04	0.87 ± 0.06	0.036*

Data are means ± SD. *$P < 0.05$ by Student *t* test.

score, LDL cholesterol concentrations, non–HDL cholesterol concentrations, mean HbA_{1c} levels in the previous year, or diabetes duration. In contrast, cIMT correlated positively with several ABPM parameters, including 24-h systolic blood pressure index ($r = 0.454$, $P = 0.001$), 24-h diastolic blood pressure index ($r = 0.389$, $P = 0.001$), daytime systolic index ($r = 0.430$, $P = 0.001$), daytime diastolic index ($r = 0.330$, $P = 0.002$), nighttime systolic blood pressure index ($r = 0.323$, $P = 0.003$), and nighttime diastolic blood pressure index ($r = 0.347$, $P = 0.001$).

The mean yearly HbA_{1c} level correlated with a number of cardiovascular factors, including HDL cholesterol ($r = 0.240$, $P = 0.030$), LDL cholesterol concentrations ($r = 0.248$, $P = 0.025$), and non–HDL cholesterol ($r = 0.350$, $P = 0.001$).The mean yearly HbA_{1c} level did not correlated with cIMT or blood pressure indexes.

After adjusting for atherogenic risk factors (age, BMI-SD score, LDL cholesterol concentrations, mean HbA_{1c} levels in the previous year, and duration of diabetes) in individual multiple linear regression models, all ABPM parameters, including 24-h, daytime, and nighttime systolic and diastolic blood pressure indexes, were significantly related to cIMT in 82 participants included in the study.

CONCLUSIONS—In this study, we defined hypertension according to ABPM criteria. cIMT was greater in the hypertensive group than in the nonhypertensive group. Moreover, cIMT in the nocturnal hypertensive group was greater than in the nonhypertensive group. In addition, all blood pressure indexes were significantly associated with cIMT in multiple linear regression analysis, independent of other atherogenic risk factors.

cIMT is greater in patients with type 1 diabetes compared with normal subjects (12,17). Moreover, cIMT is greater in type 1 diabetic patients with complications such as hypertension or nephropathy than in those without these conditions (12), and cIMT is significantly associated with blood pressure in patients with type 1 diabetes (18). However, these investigations have been conducted using clinic blood pressure measurements, and there are conflicting data on the relationship between cIMT and blood pressure in type 1 diabetes using data from clinic blood pressure monitoring (12,18). To our knowledge, few studies have used ABPM criteria to assess blood pressure in children and adolescents with type 1 diabetes to investigate the relationship between cIMT and hypertension.

Some studies have reported on the relationship between cardiovascular disease and nocturnal hypertension in adults. These studies show that the prognosis for stroke or a cardiac event is poorer in adult patients who exhibit a nocturnal blood pressure rise than in adults who exhibit a daytime blood pressure rise (19,20). Bouhanick et al. (21) showed that an increase in nighttime systolic blood pressure of 10 mmHg increased the occurrence of cardiovascular events by 35% in hypertensive diabetic individuals. However, nocturnal hypertension and its association with cardiovascular disease has not yet been investigated in children with type 1 diabetes. Our finding that a greater cIMT in children and adolescents with type 1 diabetes is accompanied by nocturnal hypertension suggests that nocturnal hypertension influences the development and progression of atherosclerosis in pediatric patients with type 1 diabetes.

Dyslipidemia, one risk factor for atherosclerosis, frequently is associated with diabetes and increases the risk of cardiovascular disease (22). In contrast, we found no significant difference in the mean LDL cholesterol concentrations between the nonhypertensive and nocturnal hypertensive groups and that the proportion of patients with an LDL cholesterol concentration ≥100 mg/dL did not differ between groups (44.7% in the nonhypertensive group and 43.3% in the nocturnal hypertensive group). Otherwise, HDL cholesterol concentration was significantly lower in the hypertensive group classified by ABPM in our study. Low HDL cholesterol concentration also is regarded as an important risk factor for coronary artery disease and is classified as a type of dyslipidemia (23). Krantz et al. (12) found that cIMT correlated negatively with HDL cholesterol concentration but not with LDL/HDL cholesterol concentrations. They suggested that HDL cholesterol concentration correlated negatively with the occurrence and progression of atherosclerosis in pediatric patients with type 1 diabetes. Therefore, to exclude the possibility that a low HDL concentration increased cIMT, only patients who had an HDL cholesterol concentration ≥40 mg/dL were included in the analysis. cIMT still was high in both the hypertensive group and the nocturnal hypertensive group. This result supports the relationship between nocturnal hypertension and atherosclerosis. Schwab et al. (24) investigated the relationship between cIMT and clinic blood pressure but used different measures of cholesterol concentration from those used in our

study to define dyslipidemia. Their results were similar to ours in showing that systolic blood pressure has a greater effect on early atherosclerosis than does dyslipidemia in children with an LDL cholesterol concentrations <100 mg/dL. Additional studies of patients without dyslipidemia according to both criteria (LDL cholesterol concentrations <100 mg/dL and HDL cholesterol concentrations ≥40 mg/dL) are needed to confirm the relationship between nocturnal blood pressure and atherosclerosis.

Poor glycemic control also is a risk factor for atherosclerosis (17). However, in our study, HbA_{1c} level and the duration of diabetes did not differ significantly between the nocturnal hypertensive and nonhypertensive groups. The HbA_{1c} levels in both groups were similarly high. The participants of the study were adolescents, and it is difficult to maintain good metabolic control in this period. In addition, in the Epidemiology of Diabetes Interventions Complications cohort, they suggest that a prolonged time period is needed to show the influence of glycemic control on the progression of atherosclerosis (25). Additional longitudinal studies are needed to investigate the role of a change in HbA_{1c} level has on the progression of atherosclerosis.

We subdivided the nonhypertensive subjects in clinic blood pressure monitoring into nocturnal hypertensive and nonhypertensive groups by ABPM. cIMT was significantly greater in the nocturnal hypertensive group than in the nonhypertensive group. This result suggests that blood pressure measured by ABPM, especially nighttime blood pressure, is more strongly related to end-organ damage than is blood pressure measured in clinic. Although daytime blood pressure measured by ABPM was within the nonhypertensive levels, it was higher in the nocturnal hypertensive group than in the nonhypertensive group. This result suggests that blood pressure may be maintained at a high level at nighttime and daytime in nocturnal hypertensive patients; such elevation may influence end-organ damage.

This is the first study to show a relationship between nighttime blood pressure and cIMT and that nighttime blood pressure may indirectly predict the degree of atherosclerosis in children with type 1 diabetes. Our data underline the importance of monitoring blood pressure, especially nighttime blood pressure, in children and adolescents with type 1 diabetes. To provide early detection and management of risk factors for macrovascular complications, ABPM should be considered in children and adolescents with type 1 diabetes.

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S.H.L. wrote the manuscript and researched data. J.H.K. contributed to the data analysis and discussion. M.J.K. researched data. Y.A.L. reviewed the manuscript. S.W.Y. reviewed and edited the manuscript. C.H.S. contributed to the discussion and reviewed and edited the manuscript.

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