

# Autonomic Dysfunction and Urinary Albumin Excretion Rate Are Associated With an Abnormal Blood Pressure Pattern in Normotensive Normoalbuminuric Type 1 Diabetic Patients

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in normoalbuminuric normotensive type 1 diabetic patients.

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**OBJECTIVE** — To analyze the role of autonomic function and other possible factors associated with a blunted fall in nocturnal blood pressure.

**RESEARCH DESIGN AND METHODS** — A total of 39 normotensive normoalbuminuric type 1 diabetic patients were studied. Glomerular filtration rate ( $^{51}\text{Cr}$ -EDTA technique), extracellular volume ( $^{51}\text{Cr}$ -EDTA distribution volume), and urinary albumin excretion rate (UAER) (by radioimmunoassay) were measured. The subjects' 24-h ambulatory blood pressure and a 24-h electrocardiogram were recorded simultaneously. Heart rate variability was calculated in the time domain for 24 h, in the frequency domain at night, at rest in the supine position, and during tilt. Patients were classified according to diastolic blood pressure (dBp) night/day ratio as dipper patients ( $\leq 0.9$ ) and nondipper patients ( $> 0.9$ ).

**RESULTS** — Nondipper patients presented a higher low-frequency (LF) component (a sympathetic index) and higher LF/high-frequency (HF) ratio during sleep than dipper patients ( $0.29 \pm 0.12$  vs.  $0.19 \pm 0.10$  normalized units [n.u.],  $P = 0.008$ ; and  $0.98 \pm 0.53$  vs.  $0.55 \pm 0.45$  n.u.,  $P = 0.007$ , respectively). At rest, the LF component in nondipper patients ( $0.38 \pm 0.13$  n.u.) was higher than in dipper patients ( $0.27 \pm 0.12$  n.u.,  $P = 0.04$ ). After the tilt, nondipper patients did not show an increase in the LF component ( $P = 0.32$ ), but in dipper patients, the increase was significant ( $P = 0.001$ ). In both groups, tilting promoted a decrease in the HF component (a parasympathetic index). In a stepwise multiple linear regression analysis, the LF component during sleep and the UAER accounted for 24% of the variability in the dBp night/day ratio.

**CONCLUSIONS** — The predominance of sympathetic activity and increased levels of UAER, although within the normal range, are associated with a blunted fall in nocturnal dBp

The absence of a decrease in diastolic blood pressure (dBp) during sleep is associated with a higher degree of target organ damage in normotensive and hypertensive nondiabetic subjects (1). Among diabetic patients, this phenomenon has been described to occur more often in individuals with autonomic neuropathy (2) and with different degrees of diabetic nephropathy (3–5). The reasons why this abnormal pattern of blood pressure is present more frequently in these groups of diabetic patients have not been completely elucidated. An increased extracellular volume (ECV) and nocturnal sympathetic predominance have been proposed as the mechanisms related to such blood pressure abnormalities in patients with diabetic nephropathy and autonomic dysfunction (2,3,6).

We previously reported that, in normoalbuminuric normotensive type 1 diabetic patients without any degree of autonomic dysfunction, according to traditional cardiovascular tests, dBp night/day ratio was associated with an increased glomerular filtration rate (GFR) and an increased ECV (7). Analysis of the factors related to the blunted decline in blood pressure in diabetic patients without advanced chronic complications could elucidate the pathophysiology of this abnormality.

Heart rate variability (HRV) refers to the variations of both instantaneous heart rate and R-R intervals and is usually evaluated by time domain methods and frequency domain methods such as power spectral analysis (PSA) (8). Time domain indexes evaluate the dispersion of the R-R interval around the mean. These indexes are the results of the use of statistical methods on

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**Abbreviations:** CV, coefficient of variation; dBp, diastolic blood pressure; ECG, electrocardiogram; ECV, extracellular volume; GFR, glomerular filtration rate; HF, high frequency; HRV, heart rate variability; LF, low frequency; LF/HF ratio, ratio of power in low-frequency and high-frequency bands; n.u., normalized units; PNN50, the percentage of differences between adjacent R-R intervals  $> 50$  ms; PSA, power spectral analysis; RMSSD, the root mean square of successive differences of adjacent R-R intervals; RRMed, the mean of all R-R intervals; sBP, systolic blood pressure; SDANNi, the SD of the averages of the R-R intervals calculated in 5-min segments; SDNN, the SD of the R-R intervals; SDNNi, the mean of the SD of R-R intervals calculated in 5-min segments; UAER, urinary albumin excretion rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

the measurements of the intervals between successive normal complexes and reflect overall autonomic modulation on the sinus node. PSA evaluates the variance of R-R intervals as a function of frequency and is calculated by mathematical algorithms. The result exhibits 3 main components: very low frequency, low frequency (LF), and high frequency (HF). The significance of the very low frequency component is dubious because its participation in HRV is less well defined. The LF component reflects mainly sympathetic modulation, especially when maneuvers that activate the sympathetic nervous system (e.g., passive tilt) are used (9). The HF component is closely related to respiratory frequency reflecting vagal modulation to the sinus node. The ratio of power in LF/HF bands (LF/HF ratio) can be used as a measure of sympathovagal balance. At rest and during sleep, a predominance of vagal tone and an attenuation in sympathetic outflow is evident in normal individuals (10). This behavior in autonomic modulation has been related to the nocturnal decline in blood pressure (11). Spectral analysis of HRV has been considered to be a useful tool for the assessment of autonomic nervous system function in diabetic patients (12).

The aim of this study was to analyze the role of autonomic function and other possible factors on nocturnal DBP decline in normotensive normoalbuminuric type 1 diabetic patients. For that purpose, HRV was evaluated using 24-h time domain analysis and PSA methods.

## RESEARCH DESIGN AND METHODS

### Patients

A total of 39 type 1 diabetic patients were selected from a cohort of 71 patients who have been followed at the outpatient clinic of the Hospital de Clínicas de Porto Alegre since 1986 (13). The definition of type 1 diabetes was based on World Health Organization criteria (14) (i.e., <40 years of age at onset of diabetes, a previous episode of ketoacidosis or documented ketonuria, and obligatory use of insulin for life maintenance). Patients were included according to the following criteria: diabetes duration >1 year, >18 years of age, ambulatory blood pressure <140/90 mmHg, normoalbuminuria (24-h urinary albumin excretion rate [UAER]  $\leq 20 \mu\text{g}/\text{min}$ ) when measured on at least 2 occasions 3 months apart with sterile urine, normal maximal exercise electro-

cardiogram (ECG), and the absence of renal diseases and autonomic neuropathy (more than 1 abnormal result out of 5 cardiovascular autonomic reflex tests) (15). The proportion of patients with 1 abnormal cardiovascular test was not different ( $P = 0.21$ ) for dipper (29%) and nondipper patients (20%). None of the patients received any drug other than insulin. This study was approved by the ethics committee of the hospital, and informed consent was obtained from all patients.

### Autonomic and blood pressure evaluation

The ECG and the blood pressure recorders were installed simultaneously by the same investigator. The patients received verbal and written instructions to avoid ingesting alcoholic and caffeinated beverages, caffeinated medications, and systemic decongestants; to avoid vigorous exercise; and to avoid wearing elastic stockings 1 day before and on the day of the test. Patients were advised to maintain their usual daily activities and were asked to perform home blood glucose monitoring (before breakfast, lunch, and dinner and at 10:00 P.M. or if hypoglycemia was suspected) and to answer a questionnaire regarding the number of cigarettes smoked and other exceptional activity (extraphysical activity or arguing) on the day of the examination.

For HRV analysis, a 24-h ECG was recorded on cassette tapes using a Cardio-Corder Model 459 (Del Mar Avionics, Irvine, CA) and was analyzed by a cardiologist blinded to the patient's status. Holter recordings were analyzed using a Del Mar Avionics scanner with a Version 750A Innovator with a semiautomatic technique. This program distinguishes normal beats from ectopies and artifacts and builds a time series of normal R-R intervals. Nonsinus beats were eliminated, and for PSA, missing data were interpolated. PSA was computed for periods of 256 s using fast Fourier transformation (16). Only segments free of interpolations were analyzed. Power spectra were quantified by the area in 2 frequency bandwidths: 0.05–0.15 Hz (LF) and 0.15–0.5 Hz (HF). The total power and LF/HF ratio were calculated for each patient. The results were reported in normalized units (n.u.), except for the LF/HF ratio, which was calculated using absolute values (in milliseconds squared). Normalized units denote the relative value of each power component in proportion to the total power minus the very low frequency component.

Expressing the data in normalized units provides a quantitative index of sympathovagal interaction in the modulation of HRV. The following 24-h time domain indexes were also calculated: the mean of all R-R intervals (RRMED), the SD of the R-R intervals (SDNN), the mean of the SD of R-R intervals calculated in 5-min segments (SDNNi), the SD of the averages of the R-R intervals calculated in 5-min segments (SDANNi), the root mean square of successive differences of adjacent R-R intervals (RMSSD), and the percentage of differences between adjacent R-R intervals >50 ms (PNN50).

After coming to the laboratory in the morning, and after the ECG monitoring was started, all patients rested for 15 min in the supine position and underwent a tilt at 90° for 10 min. During the study, the room was kept quiet, and patients were instructed to breathe at their normal respiratory rate. The last 256-s segment of each period (at rest, 5 and 10 min after tilting) was used for PSA. The ECG was continuously recorded during the subsequent 24-h period. During the sleeping period, PSA was evaluated in the 256-s segment close to the lowest heart rate.

The protocol used for the 24-h ambulatory blood pressure measurement (Del Mar Avionics auscultatory technique) was previously described (7). Patients who presented a DBP night/day ratio >0.9 were considered to be nondipper patients. A total of 15 type 1 diabetic patients were classified as nondipper patients, and 24 were classified as dipper patients. Sleep time was recorded as the period between the time when the patient went to bed and the time when the patient woke up in the morning.

### Laboratory methods

GFR was measured by the  $^{51}\text{Cr}$ -EDTA single-injection technique (coefficient of variation [CV] = 12%), the estimated ECV was measured by the distribution volume of  $^{51}\text{Cr}$ -EDTA, and the UAER was measured by radioimmunoassay (DPC, Los Angeles, CA) (inter- and intra-assay CVs were 2.3 and 2.8%, respectively).  $\text{HbA}_{1c}$  was measured by a microchromatographic system (Labtest, Lagoa Santa, Brazil) (normal range 5.3–8.0%).

### Statistical analysis

Student's *t* test and Fisher's exact test were used to compare dipper and nondipper type 1 diabetic patients. The results of the tilt-table test were evaluated by analysis of variance for repeated measures. The rela-

**Table 1—Clinical characteristics of type 1 diabetic patients**

	Dipper patients	Nondipper patients	P
n	24	15	
Age (years)	33.1 ± 7.3 (22–47)	34.3 ± 8.3 (22–51)	0.64
Female/male	12/12	8/7	0.83
Diabetes duration (years)	8.8 ± 4.3 (1–16)	7.5 ± 6.1 (2–20)	0.77
Familial history of hypertension	13	6	0.39
Smokers	4	5	0.42
Ethnicity (black/white)	1/23	2/13	0.67
BMI (kg/m <sup>2</sup> )	23.0 ± 2.8 (18.4–28.7)	23.9 ± 3.8 (18.2–30.2)	0.40
ECG recording on working day	19	9	0.35
Insulin dose (U · kg <sup>-1</sup> · day <sup>-1</sup> )	0.7 ± 0.2 (0.3–1.1)	0.8 ± 0.3 (0.4–1.5)	0.43
Peripheral neuropathy	4	0	0.26
Background retinopathy	5	1	0.46
HbA <sub>1c</sub> (%)	8.3 ± 2.1 (5.0–13.0)	8.3 ± 1.8 (5.2–11.6)	0.99
Home glucose monitoring (mg/dl)	135.6 ± 37.9 (74–250)	153.4 ± 41.2 (80–215)	0.23
GFR (ml · min <sup>-1</sup> · 1.73 m <sup>-2</sup> )	124.8 ± 22.0 (87.0–180.4)	142.0 ± 26.4 (100.4–181.7)	0.03
ECV (l · min <sup>-1</sup> · 1.73 m <sup>-2</sup> )	20.1 ± 3.1 (14.6–26.8)	22.0 ± 3.8 (16.5–30.9)	0.10
Urinary Na (meq/h)	8.0 ± 3.2 (3.6–15.0)	8.8 ± 2.8 (5.5–14.3)	0.47
UAER (μg · min <sup>-1</sup> )	3.8 (0.1–16.5)	7.3 (0.3–15.9)	0.37

Data are n, means ± SD (ranges), or medians (ranges) or number of patients with the characteristic.

tionship between the dBp night/day ratio and other variables was calculated by Pearson's correlation coefficient. Forward stepwise multiple linear regression analysis was carried out to account for the relative contributions of different variables on the dBp night/day ratio. Variables with a *P* value <0.1 in the univariate analysis or with biological relevance for the dBp night/day ratio variation were entered in the model. HRV indexes and UAER were log transformed. Data are means ± SD except for the UAER (medians [ranges]). *P* values <0.05 (2-tailed) were considered to be statistically significant.

## RESULTS

### Clinical and laboratory characteristics

The clinical and laboratory characteristics of the type 1 diabetic patients are shown in Table 1. The GFR was higher in nondipper patients than in dipper patients (*P* = 0.03). The ECV was also higher in nondipper patients but did not reach the conventional level of significance (*P* = 0.10). Nondipper and dipper patients did not differ regarding either the mean nocturnal dose of long-acting insulin (10.3 ± 4.1 and 11.5 ± 6.6 U, respectively, *P* = 0.69) or the number of patients receiving nocturnal insulin (58 and 60%, respectively, *P* = 0.50). By definition, dBp night/day ratio was higher in nondipper

patients than in dipper patients (96 ± 6 and 84 ± 4%, respectively, *P* < 0.001). Systolic blood pressure (sBP) night/day ratio was also higher in nondipper than in dipper patients (90 ± 9 and 81 ± 9%, respectively, *P* = 0.004). Nondipper patients presented higher values of nocturnal sBP (106.0 ± 12.9 mmHg) and nocturnal dBp (73.4 ± 6.0 mmHg) than dipper patients (95.0 ± 12.4 and 65.5 ± 5.9 mmHg, *P* = 0.01 for both analyses). During the day, dipper and nondipper patients presented similar levels of mean sBP (118.0 ± 10.7 and 118.0 ± 12.7 mmHg, respectively) and mean dBp (77.8 ± 6.2 and 76.4 ± 6.3 mmHg, respectively).

### Autonomic evaluation

Time domain HRV indexes (Table 2) were not different when both groups were compared (*P* > 0.05). PSA results are depicted

**Table 2—The 24-h HRV analysis in time domain of type 1 diabetic patients**

	Dipper patients	Nondipper patients	P
n	24	15	—
RRMED (ms)	771.28 ± 98.38	742.27 ± 85.03	0.36
SDNN (ms)	145.01 ± 35.02	144.08 ± 32.12	0.10
PNN50 (%)	10.33 ± 7.88	9.80 ± 7.78	0.71
RMSSD (ms)	20.58 ± 6.48	20.11 ± 7.75	0.68
SDANNi (ms)	134.81 ± 30.31	136.39 ± 34.58	0.93
SDNNi (ms)	59.57 ± 12.87	57.53 ± 14.32	0.61

Data are n or means ± SD.

in Table 3. The LF component and the LF/HF ratio calculated during sleep were higher in the nondipper patients than in dipper patients (*P* = 0.008 and *P* = 0.007, respectively). The nocturnal LF component and the LF/HF ratio presented a significant positive correlation (*r* = 0.66, *P* = 0.008). HF component values during sleep were lower in nondipper patients, but the statistical significance was borderline (*P* = 0.08).

During the day, at rest in supine position immediately before the tilt-table test, the LF component of nondipper patients was higher than that of dipper patients (*P* = 0.04), but the LF/HF ratio and the HF component were similar. In the nondipper group, the LF component did not increase after the tilt-table test (*P* = 0.32), but in dipper patients, it increased significantly after the maneuver (*P* = 0.001). In both groups, the tilt-table test promoted a decrease (*P* = 0.003 for both groups) in the HF component (Table 3).

### Correlations and multiple regression analysis

The univariate analysis revealed a significant correlation between dBp night/day ratio and ECV (*r* = 0.36, *P* = 0.003) and a borderline significant correlation with GFR (*r* = 0.30, *P* = 0.056) and with log UAER (*r* = 0.29, *P* = 0.076). No correlation of the dBp night/day ratio was observed with the LF component during sleep (*r* = 0.18, *P* = 0.17) and with diabetes duration (*r* = 0.08, *P* = 0.62). A stepwise multiple linear regression analysis was performed with the dBp night/day ratio as the dependent variable and the ECV, LF component during sleep, and log UAER as independent variables. dBp night/day ratio was significantly (*R*<sup>2</sup> = 0.24, *F* = 5.79, *P* = 0.007) associated with log UAER (*t* = 2.084, *P* = 0.04) and the LF component (*t* = 2.766, *P* = 0.009) during sleep. ECV was excluded from the model (*t* = 0.106, *P* = 0.106).

**Table 3—PSA (normalized units) of type 1 diabetic patients during sleep and at rest in the supine position during the day after 5 min and 10 min of 90° tilt**

	Dipper patients	Nondipper patients	<i>P</i> between groups	<i>P</i> tilt effect
Sleep				
LF	0.19 ± 0.10	0.29 ± 0.12	0.008	—
HF	0.46 ± 0.19	0.34 ± 0.11	0.08	—
LF/HF ratio	0.55 ± 0.45	0.98 ± 0.53	0.007	—
Tilt				
LF				
Supine	0.27 ± 0.12	0.38 ± 0.13	0.04	0.001 for dipper, 0.32 for nondipper
5 min	0.42 ± 0.13	0.32 ± 0.14		
1 min	0.37 ± 0.16	0.41 ± 0.14		
HF				
Supine	0.15 ± 0.10	0.14 ± 0.06	0.90	0.003 for dipper and nondipper
5 min	0.08 ± 0.05	0.07 ± 0.05		
10 min	0.07 ± 0.06	0.08 ± 0.07		

Data are means ± SD. Tilt effect was analyzed with repeated measures analysis of variance. LF/HF ratio was calculated using absolute values (in milliseconds squared).

**CONCLUSIONS** — The observed results indicate that this sample of nondipper normotensive normoalbuminuric type 1 diabetic patients presents an autonomic dysfunction characterized by sympathetic predominance, especially at night. In nondiabetic individuals, a decrease in sympathetic activity and an increase in vagal influence (LF/HF ratio decreases) occur during sleep, and this rhythm is associated with a decline in blood pressure (11). The observed disruption of the circadian rhythm of sympathovagal activity in our nondipper patients was associated with higher levels in sBP and dBP and with a reduced decline in sBP and dBP levels during the night. To our knowledge, this association has never been described for normoalbuminuric type 1 patients without established autonomic neuropathy.

The parasympathetic function was apparently less compromised in these patients. PNN50 and RMSSD, 2 time domain indexes that reflect parasympathetic activity, were not different when dipper and nondipper patients were compared. The PSA index of parasympathetic activity (the HF component) was also similar in both groups of patients. However, the nocturnal increase in the HF component (HF at sleep minus the diurnal HF before tilting) in nondipper patients ( $0.19 \pm 0.12$  n.u.) tended to be lower than in dipper patients ( $0.29 \pm 0.16$  n.u.,  $P = 0.062$ ). Moreover, because the nocturnal analysis was performed during the period with the lowest heart rate (i.e., a period of greater

parasympathetic activity), minor degrees of parasympathetic dysfunction could not be detected in nondipper patients. These observations together with the expression of PSA results in normalized units (which represent the relative value of each power component [LF and HF] in relation to the total power) suggest that nondipper patients present an autonomic dysfunction during sleep characterized by an absence of the suppression of sympathetic drive and probably by a smaller increase in parasympathetic activity. This is supported by the observation of a higher nocturnal LF/HF ratio (which is an index of sympathovagal balance modulation on the sinus node) in nondipper patients.

During the day, at rest in the supine position, the LF component was also higher in nondipper patients. However, the LF/HF ratio was similar in both groups of patients, which suggests that parasympathetic function during the day was not markedly compromised in nondipper patients. The similar diurnal sBP and dBP levels in dipper and nondipper patients reinforce this lesser degree of autonomic dysfunction during the day.

Parasympathetic activity was also normally suppressed in both dipper and nondipper patients after tilting. Typically, the tilt test induces a decrease in parasympathetic activity and an increase in sympathetic function (9). The 90° tilt used in our study is a strong stimulus for this autonomic adaptation, which is evident from

the almost complete suppression of vagal activity in our patients. A less intense stimulus (e.g., voluntary orthostatism) probably would not have been able to completely suppress the HF component in the nondipper group. In turn, nondipper patients did not present the expected increase in the LF component during the tilt test. The autonomic dysfunction observed in these patients probably makes their sympathetic system less responsive to physiological stimuli such as sleep and orthostatism. Therefore, the data suggest that the autonomic dysfunction of these normoalbuminuric nondipper type 1 diabetic patients is mainly related to a sympathetic predominance during the sleeping period.

Other authors using PSA also observed that the absence of nocturnal blood pressure decline was associated with an increased sympathetic predominance (2,5). This was recently confirmed by Nielsen et al. (6), who reported increased levels of plasma noradrenaline during sleep in type 2 diabetic patients with a minor blood pressure decrease during the night. The increase in sympathetic activity observed by those authors was probably related to established autonomic neuropathy because the study included patients with a longer diabetes duration and abnormal cardiovascular tests. Spallone et al. (2) observed increased nocturnal sympathetic activity in 25 diabetic patients (type 1 and type 2) who did not present a reduction in nocturnal blood pressure. Patients with diabetic nephropathy ( $n = 8$ ) and cardiovascular autonomic neuropathy ( $n = 6$ ) were included. Sleep time in that study was defined as a fixed period from 10:00 P.M. to 8:00 A.M. and not as the actual interval between the moment when the patients went to bed and woke up in the morning. Poulsen et al. (5) reported that normoalbuminuric type 1 diabetic patients at risk for the development of microalbuminuria (UAER levels above the median) also presented abnormalities of sympathovagal balance associated with a blunted nocturnal blood pressure reduction. However, in contrast with our study, these authors observed a reduction in both the HF and LF components. This difference could be related to different maneuvers used to challenge the autonomic system (passive vs. active orthostatism), different criteria to categorize the patients (absence of nocturnal dBP decline vs. UAER above the median), longer diabetes duration (18 years), and probably the presence of a more advanced form of autonomic neuropathy.

In the univariate analysis, the GFR and ECV were significantly associated with the blunted nocturnal decline in blood pressure in normoalbuminuric type 1 diabetic patients, which confirms our previous observation (7). This association was not maintained in the multivariate analysis when the LF component and UAER were included in the model. This means that sympathetic activity and UAER levels, even within the normal range, are stronger predictors of the blunted decline in nocturnal blood pressure in these patients. A significant association of UAER with abnormalities in blood pressure homeostasis was also observed by other authors (5). The sympathetic predominance observed in our patients could be a very early manifestation of autonomic neuropathy that was not detected by bedside cardiovascular tests and by time domain indexes. In fact, some evidence exists that autonomic neuropathy could have a pathogenic role in the development of diabetic nephropathy (17,18), and the absence of sympathetic activity withdrawal during sleep with higher blood pressure levels may impose a burden on the kidneys.

Possible shortcomings of this study were the criterion used to define nondipper patients and the limitation of PSA for independently evaluating sympathetic influences. As far as we know, a standard definition for dipping is not yet available (19), and we believe that the criterion adopted to define nondipper patients is adequate because a greater degree of target organ involvement was observed in hypertensive patients who presented a decreased reduction in DBP during the night (1). Although the LF and HF components evaluate the influences of the autonomic system on the sinus node, their specificity as autonomic markers is incomplete because HRV also depends on other factors. Furthermore, the LF component is also influenced by the parasympathetic system (20,21). However, the passive postural change used in this study allows a better evaluation of sympathetic influence on HRV (9).

The design of the present study does not allow us to assert whether a causal relationship exists among autonomic dysfunction, UAER levels, and dBP abnormalities. Only long-term prospective studies will be able to establish the putative role of these blood pressure and sympathetic abnormalities in the future development of diabetic nephropathy.

In conclusion, predominance of sympathetic activity and increased UAER levels, even within the normoalbuminuric range, were independently associated with abnormal blood pressure homeostasis and may represent very early abnormalities in diabetic patients at increased risk for the future development of diabetic nephropathy.

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