Study of ambulatory blood pressure in diabetic children: prediction of early renal insult

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Background: Hypertension is a highly prevalent risk factor for cardiovascular disease in patients with type 1 diabetes mellitus. Elevated blood pressure (BP) promotes the development and progression of microvascular complications, e.g., nephropathy and retinopathy. The purpose of this study was to identify and detect early BP changes in diabetic children and adolescents, aiming for the early prediction of future renal and cardiovascular disease risk during childhood.

Methods and materials: Ambulatory BP monitoring was undertaken for 40 normotensive type 1 diabetic children with mean age of 11.56±2.82 years, and 24 healthy children as control group with matched age and sex. Albumin/creatinine ratio and glycated hemoglobin were tested. BP indices and standard deviation scores were calculated using reference standards. The data were analyzed by SPSS software version 20 using mean and standard deviations for descriptive data. Correlation and regression analysis tests were used to study relations between BP indices and diabetic parameters.

Results: All parameters of BP z-scores were highly significantly increased in diabetic patients compared with controlled group (P<0.0001). The frequency of non-dipping was greater and highly significant in microalbuminuric diabetic patients (P<0.0001). Regression analysis revealed that BP parameters were significantly related to albumin/creatinine ratio, glycated hemoglobin, insulin dose, and body mass index.

Conclusion: Our observation revealed a clear link between the nocturnal BP and microalbuminuria which mandates BP follow-up via ambulatory BP monitoring with therapeutic intervention to prevent renal and cardiovascular diabetic complications in adulthood.

Keywords: ambulatory, blood pressure, diabetic, children, renal

Background
Progression of microvascular complications in type 1 diabetic patients is influenced by arterial hypertension which is a well-recognized risk factor.¹ Type 1 diabetes mellitus (T1DM) is associated with an excess of cardiovascular disease; patients with diabetic nephropathy have a higher risk than those diabetic patients without kidney involvement.²

The diagnosis of hypertension is not an easy task, as one should follow measurement guidelines to decrease any avoidable mistakes thus giving accurate blood pressure (BP) readings.³ In adults, to diagnose hypertension, measurements should be above the known normal levels. In children and adolescents, the task is more difficult as one should follow the percentile levels of BP of each age. Persistent readings of more than 95th percentile is considered hypertension in this age group.⁴

In patients with T1DM, especially the pediatric group, sporadic clinic BP measurement is not reliable. Measuring of BP over a 24-hour period is more convenient and thus a highly valuable and effective tool.⁵ Many studies have now confirmed that BP measured over a 24-hour period is superior to clinic BP measurement.
in predicting future cardiovascular events and target organ
damage.\textsuperscript{6,7} To assess risk, whole daytime and nighttime
ambulatory BP and BP load are used. The calculation of
both systolic and diastolic load threshold is manually and
automatically done. It is considered abnormal if BP loads
are in excess of 25\%–30\%.\textsuperscript{8}

BP will fall at night in normotensive individuals. People
who undergo this normal physiological change are described
as “dippers”.\textsuperscript{9} So if more than 10\% of the diurnal BP values
dropped nocturnally, it is considered a normal phenomenon.
The non-dipping pattern is defined as a blunted decline in the
person’s physiological nocturnal BP drop in whom the BP
remains high, ie, less than 10\% lower than daytime average.\textsuperscript{10}

Heart complications such as ventricular hypertrophy as
well as renal insults with its events of microalbuminuria and
decreased arterial acquiescence are developed in type 1 dia-
betic patients who display normal BP with non-dipping pattern;
moreover, these patients represent a worse outcome.\textsuperscript{11,12}

Surprisingly, there are relatively few data to recognize
whether the changes of BP through the day are repre-
sented in patients with diabetes mellitus as in the normal
population.\textsuperscript{13}

It is known that approximately one third of diabetic
patients will suffer from renal insult an extended time after
onset of diabetes. Clinically detectable diabetic nephropathy
begins with the development of microalbuminuria.\textsuperscript{14} Hyper-
tension and microalbuminuria are considered the major
cardiovascular risk factors in young patients with T1DM.
Many studies have demonstrated that strict control of blood
glucose level and BP significantly reduces the incidence and
progression of diabetic kidney disease.\textsuperscript{15}

\textbf{Aim of study}

The present study was undertaken to characterize type 1
diabetic children and adolescents for detection of subtle BP
abnormalities using ambulatory blood pressure monitoring
(ABPM) and determining its relation to microalbuminuria
and other diabetic parameters.

\textbf{Methods and materials}

The studied groups included 40 patients with T1DM. Their
ages were from 8 to 17 years. All were diagnosed by decreased
level of C-peptide (connecting peptide) with symptoms of
diabetes; they were followed-up in pediatric clinic of Al Ansari
Specialist Hospital. The studied group included 15 males and
25 females. Exclusion criteria were as follows: hypertensive
patients, age above 18 years, receiving medication that
affects BP or kidney such as angiotensin-converting-enzyme
(ACE) inhibitors and other antihypertensive drugs, and other
chronic illness.

Inclusion criteria of diabetic group were children and adoles-
cents aged below 18 years, diabetic patients diagnosed by glucose level, glycated
hemoglobin (HBA\textsubscript{1c}), and C-peptide levels, normotensive by
traditional simple sphygmomanometer method, and no history
of medication such as antihypertensives or ACE inhibitors.

Inclusion criteria of control group were children and adoles-
cents aged below 18 years, normotensive by traditional simple
sphygmomanometer method, no history of medication such
as antihypertensives or ACE inhibitors, and no history of
chronic illness such as diabetes, heart, or kidney diseases.

The control group included 24 children (nine males, 15 females)
of matched age and sex. They were randomly chosen from
children attending outpatient clinics for general checkups and
agreed to participate in this research. The study was approved
by the local ethics committee, and informed consent was
obtained from the parents or legal guardians of participating
children and from children aged above 13 years.

All the studied groups were thoroughly evaluated. Full
history-taking included duration of diabetes in years, dosage
of insulin (units/kg of body weight) weight, height, and body
mass index (BMI). Venous blood for testing HBA\textsubscript{1c} levels
was drawn from all study groups three times within at least
3 months interval, and the normal range was considered
from 4.05\% to 6.05\% according to the Diabetes Control and
Complication Trial. The test was done using COBAS INTE-
GRA 400 (Hoffman-La Roche Ltd., Basel, Switzerland) for
the quantitative determination of percent HBA\textsubscript{1c} following
manufacturer guidelines.

The International Society for Pediatric and Adolescent
Diabetology defined persistent microalbuminuria as albumin
excretion rate of 20–200 mg/min in timed overnight urine
collection in two consecutive urine specimens 4 weeks
apart. They also considered albumin/creatinine ratio of
30–300 mg/g in the morning spot urine sample as positive
for microalbuminuria. In 24 hours urine collection; it is defined
positive if albumin excretion rate is 30–300 mg/24 hours.
In our study, we used albumin/creatinine ratio in the morning
spot urine to study microalbuminuria in our studied groups.

Microalbuminuria was determined from the collected three
separate urine samples with at least 1 month interval. The
patients were asked to avoid physical activity and had to be
afebrile on the day of urine testing. Urinary albumin excre-
tion was measured by the nephelometric method. BP profiles
were compared with albumin/creatinine ratio.

\textbf{Twenty-four hour ABPM}

ABPM was measured by an oscillometric monitor (Win
Pro Model PG MAP; SunTech Medical Inc., Morrisville,
NC, USA) that was validated for children. The monitor was attached to the nondominant arm using an appropriately sized cuff. The application of cuff around the arm should not be too tight or too loose; this was easily done by putting two fingers below the cuff area to ensure correct fit. The children were told that they may resume normal activities but instructed not to participate in strenuous activities or contact sports while wearing the monitor. They were asked to wear comfortable, loose shirts and a belt. The monitor was programmed to measure BP every 20 minutes during the day between 8 am and 10 pm and every 30 minutes during anticipated night sleep time (10 pm and 8 am). A reminder card was given to the volunteers to record their hours of sleep and when exactly they woke up, which was valuable when analyzing their BP values. Adhering to these instructions was a cornerstone for estimation of nocturnal dipping.\(^{16}\) The ABPM recording was considered acceptable when a minimum of one reading per hour for a minimum of 20 hours (including six readings during sleep) was available. Mean daytime, mean nighttime, systolic BP, diastolic BP, and heart rate were calculated.

The night/day systolic BP and diastolic BP ratio was calculated for each patient and those with a ratio higher than 0.9 were classified as non-dippers.\(^{17}\)

The nocturnal dip percentage is defined as more than 10% drop in systolic and diastolic readings and calculated as:\(^{18}\)

\[
\text{Daytime mean BP – Nighttime mean BP} \times 100 \quad (1)
\]

Ambulatory hypertension was considered to exist when the means of total daytime or nighttime systolic or diastolic BP were higher than expected for the 95th percentile of the subject’s age, sex, and height, using standardized tables.\(^{18}\)

We used \(z\)-score formula for BP parameters to normalize our data using the following equation:

\[
\text{\(z\)-score value} = \frac{\text{Patient BP value} - \text{normal BP value}}{\text{SD of normal BP value}} \quad (2)
\]

In the studied groups, BP \(z\)-score >0 means that systolic, diastolic, or mean BP is more than 95th percentile for sex, age, and height.

### Statistical analysis

Statistical analysis was performed using SPSS\(^{\circledR}\) Statistics 20 (IBM Corporation, Armonk, NY, USA). After testing for Gaussian distribution (Kolmogrov–Smirnov), we found our data were nonparametric, and thus we used nonparametric test for comparisons between studied groups (Mann–Whitney). Multiple linear regression analysis was used to identify diabetes-associated risk factors for arterial hypertension. The independent variables which were used to compare with BP profiles were: age in years, total diabetes duration in years, sex, HBA\(_1c\) level, BMI, and the dosage of insulin in units/kg of weight. Statistical results were presented as mean ± standard deviation. In comparison tests, significance was defined by a \(P\)-value less than 0.05 and highly significant if less than 0.01.

### Results

Demographic, descriptive data including that of diabetes and BP profiles and their comparisons between patients and control groups were shown in Table 1. On comparing the data between the two sexes, we found that most of our study parameters with descriptive BP profiles did not differ between the two sexes (Table 2).

HBA\(_1c\), albumin/creatinine ratio, diabetes duration, and insulin dose were positively correlated with all BP parameters including systolic, diastolic, and mean (both nocturnal and diurnal); on the other hand, they were negatively correlated with nocturnal dipping of BP (Table 3).

Multiple regression analysis using age, sex, BMI, albumin/creatinine ratio, HBA\(_1c\), insulin dose, and diabetes duration as independent factors was performed (Table 4). It was found that systolic, diastolic, and mean arterial BP were significantly related to albumin/creatinine ratio, HBA\(_1c\), insulin dose, and BMI. Diabetes duration was significantly associated with increased night systolic BP.

Nocturnal dipping of BP was only associated with albumin/creatinine ratio (Table 5).

### Discussion

In this study, diabetic children showed abnormal BP profiles both systolic and diastolic with significant failure of nocturnal dipping.

Age-related changes in BP regulation were observed in diabetic patients suggesting accelerated vascular ageing.\(^{19}\)

Being a diabetic patient, one is susceptible to cardiovascular complications and this risk increases significantly if one is pre-hypertensive with changes in ambulatory BP readings; this is evidenced in the Strong Heart Study.\(^{20}\) Our study showed a similar conclusion as these “risky events” already began in children and adolescents who suffered from T1DM.

The increased night BP and occurrence of non-dipping is usually accompanied by cardiovascular insults in most patients.

This insult is an outcome of structural changes in arteries and their higher tone.\(^{21}\) Major complications such as stroke...
and infarction of the heart easily occur in non-dippers if compared with normal dippers.22

The studied diabetic children and adolescents had abnormal BP regulation, especially during nighttime which means they may be facing many vascular complications even if they were only recently diagnosed as diabetics. The results regarding diabetic non-dipping during the night corresponds with results of Hermada et al.23 Markuszeuski et al studied the BP changes during 24 hours in T1DM patients. They demonstrated that both nocturnal systolic and diastolic BP were higher in diabetic patients than controls, and the absence of BP drop (non-dippers) was more prevalent in the diabetic group.24 Their result corresponds with this study but disagree with regard to daytime BP, both systolic and diastolic. They found that daytime BP was not significantly different from the control group while this study’s results demonstrated highly significant differences between both groups with regard to daytime systolic and diastolic BPs.

In this study, it was found that BMI was positively correlated with systolic BP both diurnal and nocturnal but had no effect on BP dipping. This result corresponded with that of Axel et al’s findings.25 Also, some researchers demonstrated a significant association between systolic BP and BMI.18

The insulin need is usually increased due to insulin resistance which occurs in obese subjects with a high BMI.26 Uncontrolled diabetic condition for an extended period of time eventually causes vascular disturbances and endothelial damage that can easily lead to changes in BP values and difficulty in its regulation.27

Table 1 Descriptive data and comparison study between studied groups using Mann–Whitney test

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients (n=40)</th>
<th>Controls (n=24)</th>
<th>P (significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>Age in years</td>
<td>11.56</td>
<td>2.82</td>
<td>13.5</td>
</tr>
<tr>
<td>Height z-score</td>
<td>1.41</td>
<td>12.92</td>
<td>1.54</td>
</tr>
<tr>
<td>BMI</td>
<td>19.40</td>
<td>3.04</td>
<td>19.36</td>
</tr>
<tr>
<td>IDDM duration in years</td>
<td>4.64</td>
<td>2.70</td>
<td>0.0</td>
</tr>
<tr>
<td>HbA1c</td>
<td>11.22</td>
<td>1.70</td>
<td>5.00</td>
</tr>
<tr>
<td>Insulin dose units/kg BW</td>
<td>0.99</td>
<td>0.27</td>
<td>0.0</td>
</tr>
<tr>
<td>Albumin/creatinine ratio</td>
<td>42.34</td>
<td>8.673</td>
<td>16.83</td>
</tr>
<tr>
<td>Daytime systolic blood pressure z-score</td>
<td>7.73</td>
<td>1.62</td>
<td>0.0</td>
</tr>
<tr>
<td>Nighttime systolic blood pressure z-score</td>
<td>8.73</td>
<td>0.78</td>
<td>0.0</td>
</tr>
<tr>
<td>Daytime diastolic blood pressure z-score</td>
<td>5.80</td>
<td>0.38</td>
<td>0.0</td>
</tr>
<tr>
<td>Nighttime diastolic blood pressure z-score</td>
<td>9.50</td>
<td>1.95</td>
<td>0.0</td>
</tr>
<tr>
<td>Mean daytime blood pressure z-score</td>
<td>5.22</td>
<td>0.79</td>
<td>0.0</td>
</tr>
<tr>
<td>Mean nighttime blood pressure z-score</td>
<td>6.98</td>
<td>0.67</td>
<td>0.0</td>
</tr>
<tr>
<td>Nocturnal systolic dipping</td>
<td>7.80</td>
<td>4.85</td>
<td>16.12</td>
</tr>
<tr>
<td>Nocturnal diastolic dipping</td>
<td>7.68</td>
<td>4.91</td>
<td>22.46</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; IDDM, insulin dependent diabetes mellitus; HbA1c, glycated hemoglobin; BW, body weight.

Table 2 Comparison study between males and females in the study group by Mann–Whitney test

<table>
<thead>
<tr>
<th>Parameters</th>
<th>P (significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.308</td>
</tr>
<tr>
<td>Height</td>
<td>0.199</td>
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<tr>
<td>BMI</td>
<td>0.685</td>
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<tr>
<td>IDDM duration in years</td>
<td>0.845</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.408</td>
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<tr>
<td>Insulin dose units/kg BW</td>
<td>0.775</td>
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<tr>
<td>Albumin/creatinine ratio</td>
<td>0.685</td>
</tr>
<tr>
<td>Daytime systolic blood pressure z-score</td>
<td>0.663</td>
</tr>
<tr>
<td>Nighttime systolic blood pressure z-score</td>
<td>0.822</td>
</tr>
<tr>
<td>Daytime diastolic blood pressure z-score</td>
<td>0.822</td>
</tr>
<tr>
<td>Nighttime diastolic blood pressure z-score</td>
<td>0.663</td>
</tr>
<tr>
<td>Mean daytime blood pressure z-score</td>
<td>0.641</td>
</tr>
<tr>
<td>Mean nighttime blood pressure z-score</td>
<td>0.641</td>
</tr>
<tr>
<td>Nocturnal systolic dipping</td>
<td>0.916</td>
</tr>
<tr>
<td>Nocturnal diastolic dipping</td>
<td>0.443</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; IDDM, insulin dependent diabetes mellitus; HbA1c, glycated hemoglobin; BW, body weight.
Table 3 Correlation study between blood pressure parameters and studied variables using Spearman test

<table>
<thead>
<tr>
<th>Variables</th>
<th>Daytime systolic blood pressure</th>
<th>Nighttime systolic blood pressure</th>
<th>Daytime diastolic blood pressure</th>
<th>Nighttime diastolic blood pressure</th>
<th>Mean daytime z-score</th>
<th>Mean nighttime z-score</th>
<th>Nocturnal systolic dipping</th>
<th>Nocturnal diastolic dipping</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>z-score r P</td>
<td>z-score r P</td>
<td>z-score r P</td>
<td>z-score r P</td>
<td>z-score r P</td>
<td>z-score r P</td>
<td>z-score r P</td>
<td>z-score r P</td>
</tr>
<tr>
<td>Height</td>
<td>0.052 0.762</td>
<td>-0.305 0.067</td>
<td>-0.205 0.225</td>
<td>-0.186 0.271</td>
<td>-0.198 0.240</td>
<td>-0.418 0.010*</td>
<td>-0.210 0.211</td>
<td>0.149 0.378</td>
</tr>
<tr>
<td>BMI</td>
<td>0.126 0.457</td>
<td>0.249 0.137</td>
<td>0.150 0.375</td>
<td>0.270 0.105</td>
<td>-0.195 0.247</td>
<td>-0.074 0.662</td>
<td>0.075 0.660</td>
<td>0.306 0.065</td>
</tr>
<tr>
<td>IDDM duration</td>
<td>0.961 &lt;0.0001*</td>
<td>0.652 &lt;0.0001*</td>
<td>0.668 &lt;0.0001*</td>
<td>0.858 &lt;0.0001*</td>
<td>0.853 &lt;0.0001*</td>
<td>0.728 &lt;0.0001*</td>
<td>-0.622 &lt;0.0001*</td>
<td>-0.823 &lt;0.0001*</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.732 &lt;0.0001*</td>
<td>0.694 &lt;0.0001*</td>
<td>0.656 &lt;0.0001*</td>
<td>0.793 &lt;0.0001*</td>
<td>0.821 &lt;0.0001*</td>
<td>0.631 &lt;0.0001*</td>
<td>-0.514 0.001*</td>
<td>-0.711 &lt;0.0001*</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>0.788 &lt;0.0001*</td>
<td>0.748 &lt;0.0001*</td>
<td>0.805 &lt;0.0001*</td>
<td>0.754 &lt;0.0001*</td>
<td>0.753 &lt;0.0001*</td>
<td>0.542 &lt;0.0001*</td>
<td>-0.390 0.017*</td>
<td>-0.726 &lt;0.0001*</td>
</tr>
<tr>
<td>Albumin/creatinine ratio</td>
<td>0.776 &lt;0.0001*</td>
<td>0.594 &lt;0.0001*</td>
<td>0.643 &lt;0.0001*</td>
<td>0.0841 &lt;0.0001*</td>
<td>0.800 &lt;0.0001*</td>
<td>0.656 &lt;0.0001*</td>
<td>-0.590 &lt;0.0001*</td>
<td>-0.854 &lt;0.0001*</td>
</tr>
</tbody>
</table>

Notes: *: Spearman correlation; **p<0.05 (statistically significant).
Abbreviations: BMI, body mass index; IDDM, insulin dependent diabetes mellitus; HbA1c, glycated hemoglobin.

1) The rapid proper diagnosis of hypertension in diabetic children using ABPM is often a “wake-up call”, and

Recommendations

The rapid proper diagnosis of hypertension in diabetic children is crucial. It is important to identify and manage the modifiable risk factors that contribute to the development of hypertension in these patients. This includes lifestyle modifications such as dietary changes, physical activity, and weight management. It is also important to monitor blood pressure regularly to track progress and adjust treatment as necessary. 

1c

Ambulatory blood pressure in diabetic children

These findings support the research result that poor glycemic control reflected by elevated HbA1c was significantly associated with elevated systolic and diastolic BP both diurnal and nocturnal. In contrast, some research failed to find any correlation between HbA1c and hypertension in diabetic children. 1c No relation between sex and alterations of BP was demonstrated, unlike Axel et al 11 who found that BP changes are more prevalent in female patients and tend to be observed during puberty and menarche in female patients. The findings by the fact that females tend to be obese during puberty and may be due to the small sample size of this study.
following-up those patients is an opportunity to make lifelong changes that will likely decrease their risk of developing chronic complications and enable vascular directed preventive intervention at the earliest possible time.

2) Further work is required to see if the BP load could be one of the predictive parameters in ABPM in normotensive T1DM children. While using 24-hour ambulatory BP in this study, systolic BP load had been observed to be higher than 40% in most of the diabetic patients which is considered, in hypertensive adult patients, an early prognostic marker for cardiovascular events.

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Disclosure

The authors report no conflict of interest in this work.

References


